A multi-modal application of magnetic resonance imaging (MRI) techniques to identify and quantify brain abnormalities in retired professional football players

A multi-modal application of magnetic resonance imaging (MRI) techniques to identify and quantify brain abnormalities in retired professional football players

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Lay Abstract

Clinical concussion assessment has a limited ability to identify brain injury location and severity. Therefore, there is a need for more advanced diagnostic tools to provide meaningful, objective information to concussion patients and clinicians. The work presented in this thesis aimed to assess brain health using magnetic resonance imaging (MRI) techniques of retired professional football players with a complex history of concussions and repetitive sub-concussive impacts. Our research found concussion-related functional and cerebral blood flow brain abnormalities past that of normal aging, but minimal white matter damage, present in the retired athletes that also correlated with clinically testable health metrics such as motor speed, emotional well-being, and pain. Through personalized subject-specific analyses, this work provides further evidence of the effects of concussions later in life.

Abstract

High contact sports put athletes at a higher risk of sustaining a concussion. This work focused on assessing regional brain health in aging, retired Canadian Football League (rCFL) players years to decades after retirement. Advanced, quantitative magnetic resonance imaging (MRI) techniques were implemented to identify and quantify microstructural brain white matter damage, cognitive functional signal characteristics (fractal dimension (FD) and amplitude of low frequency fluctuations (ALFF) and fractional ALFF (fALFF)), and cerebral blood flow (CBF) dysregulation.

Due to the high reproducibility of diffusion tensor imaging (DTI) and resting state functional MRI (rsfMRI), a Z-scoring approach exploring outliers relative to a large normative dataset was implemented to examine each rCFL subject individually. However, arterial spin labelling (ASL) data is more sensitive to scanner inconsistencies, therefore a group-wise analysis was performed with the CBF and ASL spatial coefficient of variance (ASL sCoV) data.

Minimal microstructural damage was detected in the rCFL subjects, but a substantial amount of functional and CBF abnormalities were present. The FD was significantly reduced in 48 of 91 regions-of-interest (ROIs) examined, and the four rCFL subjects with the highest number of abnormal ROIs all exhibited worse motor speed, social functioning and general health scores than the other rCFL subjects. Furthermore, the ALFF analysis identified the cerebellum, parietal lobe ROIs, and central sub-cortical ROIs to be consistently abnormal. Finally, the temporal occipital fusiform cortex, superior parietal gyrus, caudate nucleus, and the cerebellum were significantly abnormal bilaterally based on CBF and ASL sCoV values, which also correlated with worse physical functioning and elevated daily chronic pain.

This work adds to the growing literature that brain changes are present later in life that may be related to concussions and repetitive sub-concussive head impacts sustained years earlier. Several consistently damaged ROIs also correlated with adverse clinical presentations to indicate areas of future research.

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I must also thank my parents, Nancy and Rob, for fueling my passion for sport. Your dedication and support of my athletic endeavours enabled my interest and pursuit of sport-related research, which I am hopeful will support other athletes to come.

Last and certainly not least I must acknowledge my partner, Adrienne. Your unconditional support, love, and patience made this all possible for me. You are a wonderful force of nature and you inspire me to be a better person everyday.

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Abbreviation List

(ALFF) – amplitude of low-frequency fluctuations
(BDI-II) – Beck Depression Inventory-II
(BOLD) – blood-oxygen level dependent
(CBF) – cerebral blood flow
(CEI) – cognitive efficiency index
(CFL) – Canadian Football League
(CN) – caudate nucleus
(dMRI) – diffusion magnetic resonance imaging
(DTI) – diffusion tensor imaging
(EFAT) – energy and fatigue
(EH) – emotional health
(EWB) – emotional well-being
(FA) – fractional anisotropy
(fALFF) – fractional amplitude of low-frequency fluctuations
(FD) – fractal dimension
(fSPGR) – fast spoiled gradient
(GH) – general health
(GM) – grey matter
(IB) – injury burden
(IC) – impulse control
(ImPACT) – Immediate Post-concussion Assessment and Cognitive Testing
(IR) – inversion-recovery
(MNI) – Montreal Neurological Institute
(MRI) – magnetic resonance imaging
(MS) – motor speed
(NPC) – number of previously diagnosed concussions
(PCASL) – pseudo-continuous arterial spin labelling
(PCSS) – Post-Concussion Symptom Scale
(PHF) – physical functioning
(PHH) – physical health
(rCFL) – retired Canadian Football League

(ROI) – region-of-interest
(rsfMRI) – resting state functional magnetic resonance imaging
(RT) – reaction time
(sCoV) – spatial coefficient of variance
(SF-36) – Short Form 36 Survey Instrument
(SPG) – superior parietal gyrus
(SI) – symmetry index
(SOFU) – social functioning
(SRC) – sport-related concussion
(TE) – echo time
(TFCE) – threshold free cluster enhancement
(TI) – inversion time
(TOFC) – temporal occipital fusiform cortex
(TR) – repetition time
(VBM) – verbal memory
(VIM) – visual memory
(YSLC) – number of years since last concussion

Declaration of Authorship

I, Ethan Danielli, declare that this thesis titled, "A multi-modal application of magnetic resonance imaging (MRI) techniques to identify and quantify brain abnormalities in retired professional football players" and the work presented in it are my own. I confirm that:

- Chapter 1: This chapter was written, exclusively by Ethan Danielli, and edited, by Ethan Danielli and Dr. Michael D. Noseworthy, to introduce relevant background information about the forthcoming chapters and the thesis in general.
- Chapter 2: This review chapter was written and edited by Ethan Danielli to provide detailed information about regional human brain anatomy and functions, and those brain regions' connection to post-concussion symptoms. This chapter was partially written in collaboration with the co-author Nicholas Simard, and was also edited by Nicholas Simard and Dr. Michael D. Noseworthy.
- Chapter 3: This first research project chapter was written by Ethan Danielli as the first author of this work published in the journal *Brain Disorders*. The work presented in this chapter was organized, written and edited where the data was curated, statistically analyzed, interpreted by Ethan Danielli. Processing and correction of the DTI and rsfMRI data was performed by Nicholas Simard, while manuscript editing was performed by Ethan Danielli, Dr. Michael D. Noseworthy, Nicholas Simard, Dr. Bhanu Sharma, and Mitchell Doughty.

- Chapter 4: This second research project chapter was initiated, written and edited by Ethan Danielli where the data was curated, statistically analyzed and interpreted by Ethan Danielli. The work in this chapter was submitted to the journal *MAGMA* for publication. Processing of the ASL data was performed by Beatriz Padrela and Mathijs Dijsselhof, while ASL expertise and manuscript editing was performed by Beatriz Padrela, Mathijs Dijsselhof, Henk-Jan Mutsaerts, and Jan Petr. Dr. Lawrence C. Mbuagbaw is a biostatistician who assisted with the statistical analysis of this project. Finally, Dr. Michael D. Noseworthy was the lead investigator and contributed to project initiation, statistical analyses, funding acquisition, and manuscript editing.

- Chapter 5: This third research chapter was a project that contained data curation, processing, analysis, interpretation, and writing and editing of the manuscript by Ethan Danielli. Dr. Bhanu Sharma and Cameron Nowikow were involved in data processing of the rsfMRI data in CONN and statistical analyses. Manuscript editing was performed by Ethan Danielli, Dr. Bhanu Sharma, Cameron Nowikow, and Dr. Michael D. Noseworthy.

- Chapter 6: This final chapter was written exclusively by Ethan Danielli, and was edited by Ethan Danielli and Dr. Michael D. Noseworthy. This sixth chapter outlined the overall conclusions of the work presented in this thesis, the main findings, and future directions for this research.

Chapter 1

Introduction

1.1 Concussion overview

Concussion is a leading cause of emergency room visits for both youth and adults (Hon et al. 2019; Taylor et al. 2017). Without requiring a loss of consciousness, a concussion can be caused by an impact to the head, neck or body that transmits forces to the brain (McCrory et al. 2017). Concussions can cause a range of physical, cognitive, emotional, and sleep related symptoms (Danielli et al. 2020; Kontos et al. 2012). Most adults recover in 10-14 days, however, about 10% of adults who sustain a concussion have symptoms lasting longer than one month (McCrory et al. 2017). Especially in the athlete population, many concussions go untreated and undiagnosed (Kroshus et al. 2017; Meehan et al. 2013), which unfortunately puts athletes at a greater risk of more serious brain damage if they return to sport prior to recovery and sustain a second concussion in close succession (Lazaridis et al. 2019; Prins et al. 2013).

Athletes of all sports are susceptible to acquiring injuries, however, athletes of high contact sports such as American-style football, ice hockey, rugby, and wrestling have an increased likelihood of sustaining a concussion (Black et al. 2017; Zuckerman et al. 2015). Specifically for football, there has been mounting evidence surrounding the effects of concussions and sub-concussive head impacts on players (Lancaster et al. 2018; Mustafi et al. 2017), where athletes without a concussion diagnosis or post-concussion symptoms are exhibiting microstructural (Schneider et al. 2019) and functional abnormalities (Talavage et al. 2014). Recent

studies have also identified certain playing positions to be associated with either high frequency, low magnitude head impacts or low frequency, high magnitude head impacts (Baugh et al. 2015; Karton et al. 2020). A major challenge for athletes, clinicians, family members and researchers is the lack of a standardized and unbiased concussion diagnosis tool. There are tests that can assess post-concussion symptoms, sensory feedback, and cognition; however, they are limited by subjective patient self-reporting (Dziemianowicz et al. 2012) and inconsistencies in clinician interpretation (Stern et al. 2017; Stoller et al. 2014). Even routine clinical computed tomography and magnetic resonance imaging (MRI) scans fail to identify concussion-related brain damage (Chamard and Lichtenstein 2018; Rose et al. 2017).

1.2 Diffusion tensor imaging

Although not implemented in clinical concussion practice, there are advanced MRI techniques used in research that have shown the microstructural, functional and perfusion alterations that concussions can cause. The biomechanical forces transmitted to the brain during a concussive event can cause sheering and tearing of white matter structures that produces diffuse axonal injuries (Smith et al. 2003). Such white matter injuries following a concussion can be examined using diffusion MRI (dMRI) techniques such as diffusion tensor imaging (DTI) (Asken et al. 2018), where the diffusion of water in an environment is characterized based on the restriction of water diffusion (Assaf and Cohen 2000). Of the four scalar DTI metrics, concussions have been shown to cause a decrease in fractional anisotropy and axial diffusivity, and an increase in mean diffusivity and radial diffusivity (Adler et al. 2018; Lancaster et al. 2016). These changes have also been found in retired athletes later in life, where the changes exceed that of normal aging (Churchill et al. 2017a; Multani et al. 2016; Wright et al. 2021).

1.3 Functional magnetic resonance imaging

As a compliment to dMRI, functional MRI (fMRI) is a technique that is used to assess grey matter activity based on the blood-oxygen level dependent (BOLD)

signal (Ogawa et al. 1990). The BOLD signal is based on the paramagnetic differences between oxygenated and deoxygenated blood, where active brain regions will have a greater BOLD signal due to increased blood flow, blood volume and cellular metabolism (Ogawa et al. 1990). By using resting state fMRI (rsfMRI), an individual's brain can be assessed based on highly researched underlying functional networks (Yang et al. 2020), or by estimating BOLD signal complexity through the use of statistical fractals (Dona et al. 2017; Ziukelis et al. 2022). An alternative and less researched rsfMRI analysis method is exploring the spontaneous nature of the amplitude of low frequency fluctuations (ALFF) (0.01 – 0.08Hz) in the BOLD signal, indicative of neuronal brain activity, that may be missed through network mapping (Biswal et al. 1995; Mantini et al. 2007; Zou et al. 2008).

1.4 Arterial spin labelling

Finally, arterial spin labeling (ASL) is a non-invasive MRI technique that can measure cerebral blood flow (CBF) by magnetically labeling inherent water molecules in blood and directly measuring microvascular perfusion (Hernandez-Garcia et al. 2019; Jezzard et al. 2018). It has been shown that a history of concussions can lead to a global decrease in CBF (Wang et al. 2020); however, there also appears to be regional hypo- and hyperperfusion in retired professional football players (Hart et al. 2013). As a possible supplement to CBF, a novel metric ASL spatial coefficient of variance (sCoV) has been shown to be an alternative tool to non-invasively assess blood flow and perfusion in the brain that may be a more reliable metric than CBF in patients with impaired or damaged cerebrovasculature and reduce inter-subject physiological and whole-brain differences because it is normalized to the mean CBF (Mutsaerts et al. 2017). Our research applied the novel metric of ASL sCoV on a regional basis for the first time to determine if ASL sCoV could be used on smaller, focal brain regions.

1.5 Common MRI analysis methods to assess concussions in research

The work presented in this thesis provides evidence of concussion-related brain abnormalities present in retired professional football players through the implementation of personalized analysis and novel quantitative methodology. The majority of concussion research is analyzed at a group-wise level. However, each concussion is unique to the individual and to the complex biomechanical forces that caused the injury. Thus, subject-specific analyses were applied using large normative datasets and Z-scoring of DTI and rsfMRI metrics. Furthermore, there has been extensive research on concussion-related functional abnormalities to brain networks such as the default mode network (DMN) (Horn et al. 2014; Liu et al. 2018) and functional connectivity mapping (Churchill et al. 2017b; Sihag et al. 2020). However, fractal complexity and ALFF of the BOLD signal have not been implemented in a retired, aging athlete sample with a history of concussions and sub-concussive head impacts. Thus, DMN and functional connectivity analyses were done to determine if the retired football players used in this research exhibited results consistent with previously published literature, thus allowing us to move beyond these techniques to explore potentially more informative metrics. In alignment with literature (Horn et al. 2014), the preliminary seed-to-voxel network analysis of the DMN found bilateral hypoactive nodes in the medial, inferior aspect of the parietal lobes close to the precuneus and the posterior cingulate cortex (Figure 1.1). Functional connectivity mapping found numerous areas of increased functional connections between frontal, temporal, parietal and occipital lobes, with many areas of regionally decreased activity within the cerebellum, and from the cerebellum to adjacent regions (Figures 1.2 & 1.3). These findings confirmed our expectations for these more common analysis techniques to help validate our implementation of novel methods.

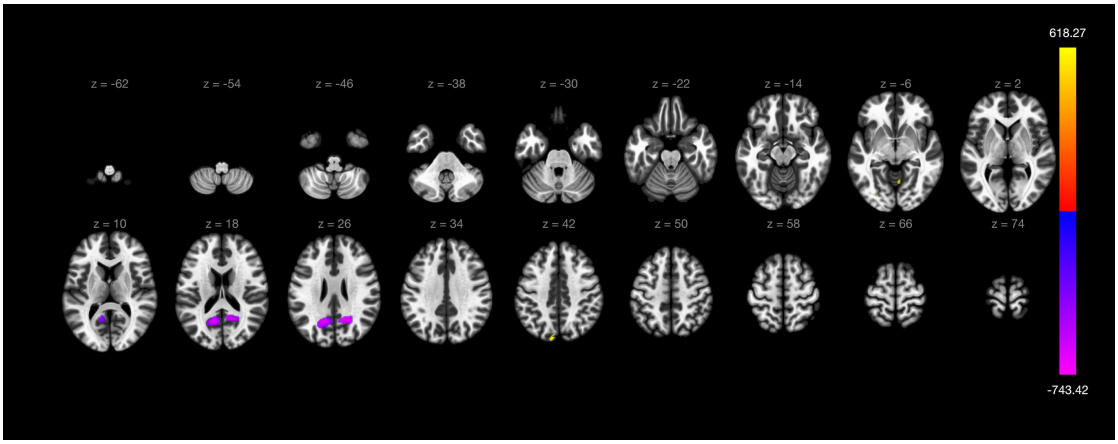

FIGURE 1.1: Results from the preliminary seed-to-voxel Default Mode Network (DMN) correlation analysis to determine significantly different clusters between the retired Canadian Football League (CFL) subjects and the healthy control dataset based on threshold free cluster enhancement (TFCE). Four seeds with equal weighting were used (medial prefrontal cortex, left lateral parietal, right lateral parietal, and precuneus) and 10,000 TFCE simulations were performed. There were large bilateral nodes of hypo-activity (coloured purple) near the precuneus region of the brain.

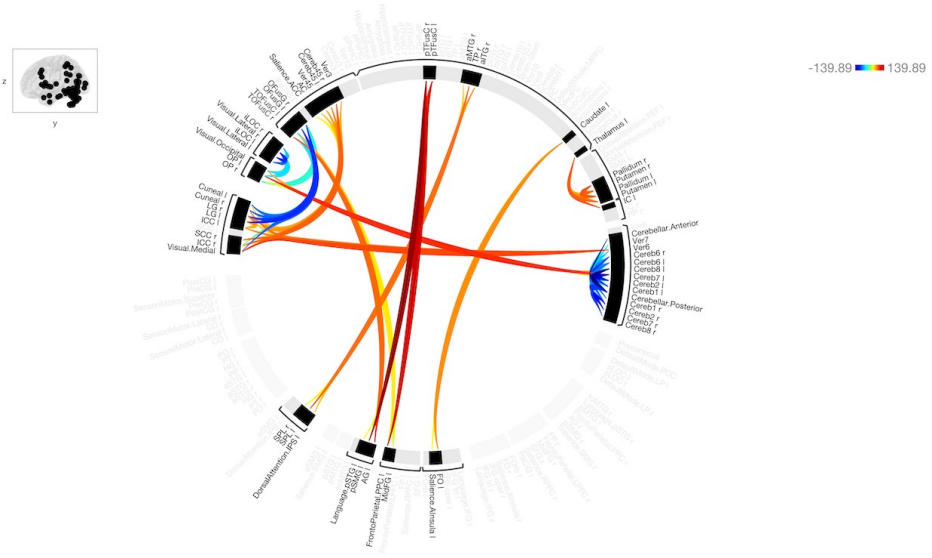

FIGURE 1.2: A region-of-interest (ROI) functional connectivity map from the preliminary ROI-to-ROI functional connectivity analysis of the Default Mode Network (DMN). This shows significantly correlated positive and negative co-activation of ROIs within the retired Canadian Football League (CFL) subjects relative to the healthy control dataset based on threshold free cluster enhancement (TFCE). Ten thousand TFCE simulations were performed. There were many positive connections (coloured red) across the cerebral cortex, and many negative connections (coloured blue) within the cerebellum and its adjacent ROIs.

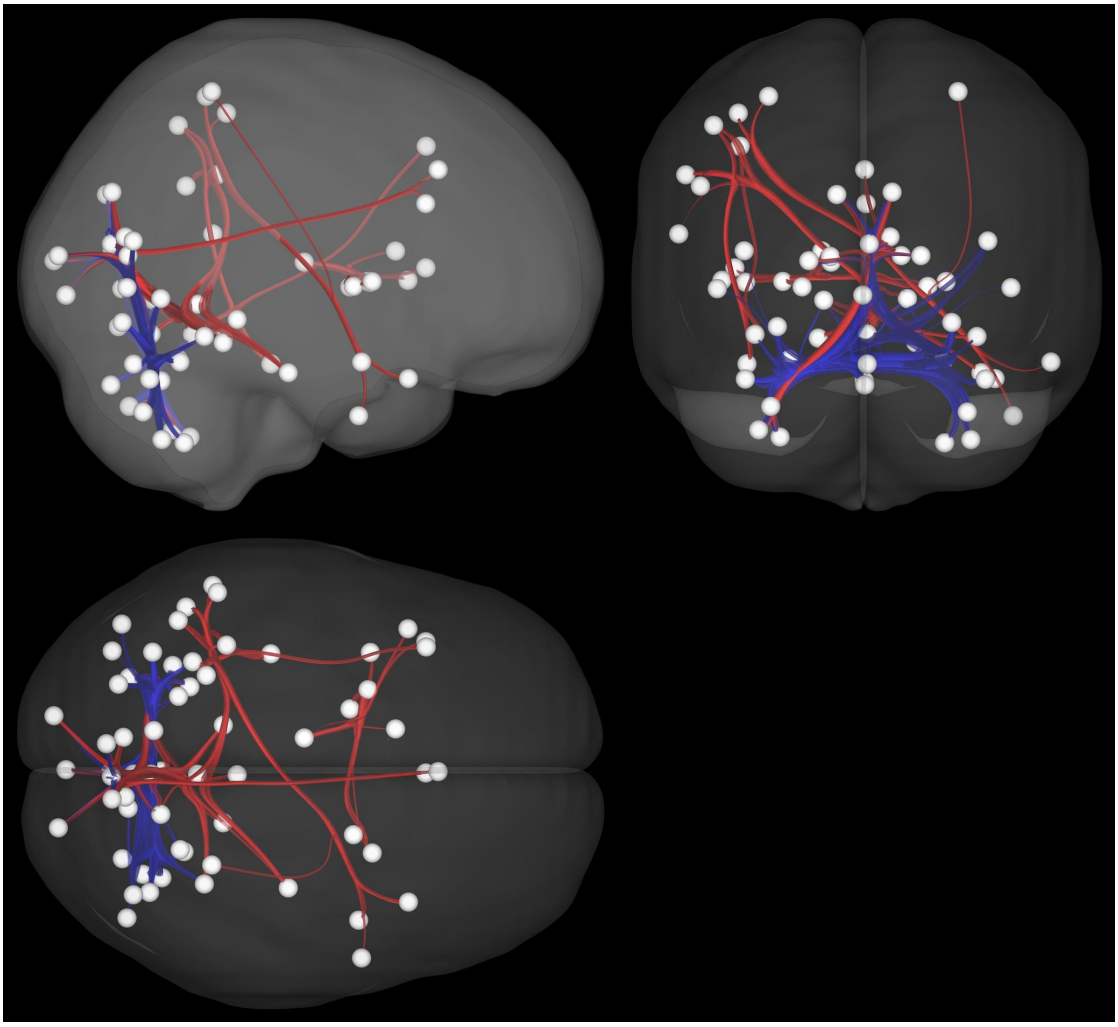

FIGURE 1.3: A region-of-interest (ROI) functional connectivity graphic showing significant ROI correlations from the preliminary ROI-to-ROI functional connectivity analysis of the Default Mode Network (DMN). Here retired Canadian Football League (CFL) subjects were compared to a healthy control dataset based on threshold free cluster enhancement (TFCE). Ten thousand TFCE simulations were performed. There were many positive connections (coloured red) across the cerebral cortex, and many negative connections (coloured blue) within the cerebellum and its adjacent ROIs. Each ROI is indicated by a white sphere. This figures shows the significant functional connections from the right (top left), anterior (top right), and superior (bottom) perspectives.

1.6 Thesis objectives and hypotheses

This thesis was separated into three research projects to examine the same sample of subjects, but is preceded by a non-exhaustive review of important grey and white matter brain regions in relation to their brain anatomical location, and associated normal function, and associated post-concussion symptoms. A foundational understanding of brain anatomy provides essential context to the application of MRI analyses, where without that knowledge significant findings can be identified without considering physical and/or functional relationships with other parts of the brain. The review in Chapter 2, to the best of our knowledge, is the first to compile such an extensive collection of brain regions and connect each ROI to concussion-related symptoms. This could be of substantial clinical importance for concussion rehabilitation to be able to perform personalized concussion assessments and more confidently connect clinically presenting post-concussion symptoms to specific, regional brain damage. Chapter 3 covers subject-specific, regional analysis of the DTI scalar metric fractional anisotropy (FA) and rsfMRI BOLD signal fractal dimensionality using Z-scoring. Following this, Chapter 4 contains group-wise analysis of CBF and ASL sCoV between retired football players and a set of healthy age- and sex-matched controls. Next, Chapter 5 is composed of the novel application of ALFF and fALFF to our sample of retired football players. Finally, Chapter 6 concludes this work with a summary of the main findings and outlining future directions for this research.

The purpose of this body of work was to implement novel subject-specific MRI analyses to identify and quantify regional brain abnormalities present in retired professional athletes with a history of concussive and sub-concussive head impacts. It was hypothesized that concussion-related brain damage would be exhibited as regionally decreased fractional anisotropy, decreased BOLD signal complexity, and region specific increased and decreased CBF and ALFF. As all the rCFL subjects will have had unique brain injuries over their professional careers, it was hypothesized that each former player would have distinctive brain differences, relative to healthy controls. However, from these results, we hypothesized that certain brain regions are likely to be more vulnerable to concussive injuries and as such will appear more frequently as abnormal based on personalized scoring.

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Chapter 2

The anatomy and function of major brain regions

2.1 Overview

2.1.1 Context of the chapter

The human brain is an exceptionally complex organ that is comprised of billions of neurons. Therefore, when a traumatic event such as concussion occurs, cognitive, physical, and behavioural impairments are the common outcome. Each concussion is unique in the sense that the magnitude of biomechanical forces, and the direction, rotation and source of those forces, is different for each concussive event. This helps to explain the unpredictable nature of post-concussion symptoms that can arise and resolve. The purpose of this narrative review is to connect the anatomical location, healthy function, and associated post-concussion symptoms of some major cerebral gray and white matter brain regions and the cerebellum. As a non-exhaustive description of post-concussion symptoms nor comprehensive inclusion of all brain regions, we have aimed to amalgamate the research performed for specific brain regions into a single article in order to clarify and enhance concussion assessment. The current status of concussion diagnosis is highly subjective and primarily based on subject-reporting, and so this review may be able to provide a connection between brain anatomy and the clinical presentation of concussions for the purposes of enhancing medical imaging assessments. By explaining anatomical

relevance in terms of clinical concussion symptom presentation, an increased understanding of concussions may also be achieved to improve concussion recognition and diagnosis.

2.1.2 Declaration statement

Ethan Danielli, as first author, was involved in the review conceptualization and direction, writing the majority of the original draft, and revisions to the final manuscript. Nicholas Simard, as second author and another PhD candidate with Dr. Noseworthy, was involved in the review conceptualization and direction and writing sections of the original draft. Dr. Michael D. Noseworthy, as the corresponding author and primary investigator of our research group, was involved in the study conceptualization, funding acquisition, supervision, and revisions to the final manuscript.

This review article has been prepared for publication in a peer-reviewed journal with clinical authority and relevance for both concussion and MRI research.

2.2 A review of brain regions and associated post-concussion symptoms

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2.3 Introduction

The field of concussion awareness, prevention, and mitigation is constantly growing. As a result, the exact links between anatomical and physiological changes post-concussion are still evolving. In order to improve concussion diagnosis and personalize treatment, it is important to first understand brain structures and their respective functions. This review briefly describes concussion diagnosis, but the main focus is on brain anatomy and the relationship of specific brain regions to post-concussion symptoms. The human brain is an exceptionally complex organ that comprises billions of neurons (Bartheld et al. 2016). Our brain consists of a large cerebrum, with left and right hemispheres made up of four lobes (frontal, temporal, parietal, and occipital)(Forstmann and Wagenmakers 2015) and the cerebellum (latin for "little brain")(Schmahmann et al. 2019). The cerebrum can be separated into two primary tissue sections, grey matter and white matter. Grey matter is the tissue that contains the neuronal cell bodies, dendrites, glial cells, axons, and synapses that produces neuronal signals, and are found in the cortical, sub-cortical and cerebellar areas (Forstmann and Wagenmakers 2015). Conversely, white matter contains myelinated and unmyelinated neuronal axons, which are the physical connection between neuronal cell bodies that transmit the neuronal signals efficiently between grey matter regions (Forstmann and Wagenmakers 2015). The cerebellum is an immensely folded brain region, segmented from the cerebrum, that is involved in all aspects of neurocognition (Schmahmann et al. 2019).

2.3.1 Concussion definition

Concussions are unlike many other sport-related injuries because the brain is such a complicated and adaptable organ. Due to the unpredictable onset and resolution of various symptoms, concussions are complex neurological and behavioural injuries that can have various acute and chronic complications (McCrory et al. 2017). A concussion is caused by a blow to the head, neck or body that results in the brain becoming injured by resultant propagating forces and does not necessarily involve a loss of consciousness (McCrory et al. 2017). The forces applied to the brain during concussive events can produce serious shearing and tearing of tissues that trigger a cascade of neurometabolic changes (Giza and Hovda 2014).

These structural, functional, and physiological brain alterations manifest uniquely in each individual, where most adults who sustain a concussion recover within 10-14 days (90%), however many people have symptoms persisting longer than a month (Hon et al. 2019; McCrory et al. 2017; Zuckerman et al. 2012). Concussions are mainly caused by motor vehicle accidents, falls, assaults, and sports (Cassidy et al. 2004; Hon et al. 2019).

2.3.2 Clinical concussion diagnosis

The diagnosis of a concussion is primarily based on patient's reporting their symptoms, but could include further testing if more serious brain damage is suspected (Hon et al. 2019). Despite efforts to improve concussion recognition and management protocols (DeMatteo et al. 2015; McCrory et al. 2017), diagnosis can still be highly variable due to the subjectivity of patient self-reporting, varying concussion assessment guidelines, and clinician interpretation (Stoller et al. 2014). Some of the tests used to diagnose concussions can be self-administered, while some must be administered by a trained clinician (Broglio et al. 2018; Dziemianowicz et al. 2012). Commonly used concussion diagnosis tests include Immediate Post-Concussion Assessment and Cognition Tool (ImPACT)(Lovell 2006), Sport-related Concussion Assessment Tool – 5th Edition (SCAT5)(Echemendia et al. 2017), CogSport (Collie et al. 2003), the Post-Concussion Symptom Scale (Kontos et al. 2012b), and the Rivermead Post-Concussion Symptoms Questionnaire (Potter et al. 2006).

Although symptom-based diagnosis and recovery tracking remains the clinical gold standard, structural computed tomography (CT) and magnetic resonance imaging (MRI) scans are used to rule out skull fractures and brain bleeding in more serious concussion and traumatic brain injury cases (Chamard and Lichtenstein 2018). However, advances in MRI have provided powerful insights into brain function following a concussion using safe, non-invasive, objective, and reproducible methods. Routine clinical 3-dimensional T1-weighted and T2-weighted MRI scan protocols fail to identify any concussion-related damage, but scan techniques used in research such as diffusion MRI (dMRI), functional MRI (fMRI), MR spectroscopy (MRS), and arterial spin labeling (ASL) have all been shown

to identify microstructural, functional, metabolic, and tissue perfusion alterations, respectively, in acute and chronic concussion patients (Chamard and Lichtenstein 2018; Danielli et al. 2020). Instead of MRI being limited to ruling out serious brain bleeding and skull fractures, symptom-based testing can be supplemented by highly sensitive MRI techniques. Unfortunately, these more advanced MRI techniques provide extensive information but are not yet implemented for clinical concussion diagnoses.

2.3.3 Post-concussion symptoms

A range of acute and chronic symptoms can occur in the days following a concussion, but symptom resolution and determining a complete recovery timeline is difficult and highly unpredictable. The range of post-concussion symptoms highlight the heterogeneity of concussive brain injuries. In general, post-concussion symptoms fall into four different categories of physical, emotional, cognition, and sleep related symptoms (Danielli et al. 2020; Kontos et al. 2012b; McCrory et al. 2017).

Physical post-concussion symptoms can include headaches, nausea, vomiting, balance problems, visual problems, dizziness, light-headedness, fatigue, sensitivity to light, sensitivity to noise, sensory numbness, and tingling. Emotional post-concussion symptoms can include irritability, sadness, feeling hopeless, nervousness, anxiousness, emotional numbness, and feeling more emotional. Cognitive post-concussion symptoms can include feeling "slow," feeling "foggy," difficulty concentrating, difficulty remembering, confusion, and repetitive speech. Finally, sleep related post-concussion symptoms can include trouble falling asleep, sleeping more or less than usual, and drowsiness. The variety of post-concussion symptoms clearly indicate how a range of brain regions could be implicated during a single concussive injury, and why damage to specific brain regions may explain patient-specific symptoms.

2.4 Regional brain anatomy and associated post-concussion symptoms

The brain has been the subject of extensive research, typically conducted as anatomical dissection, histology, and medical imaging, but also as cell/tissue culture and biochemical/genetic assays, that have allowed for an ever-improving understanding of normal and pathological brain function. This review focuses on 15 cerebral grey matter (Figure 2.1 & Table 2.1) and 10 cerebral white matter brain regions (Figure 2.2 & Table 2.2) that are physically large and have been shown in the literature to have important and specific functional relevance to concussions. The cerebellum and its subdivisions (Figure 2.3 & Table 2.3) were also examined to discuss its involvement in post-concussion symptoms, emphasize the influence it has over neurocognitive function, and encourage increased clinical and research attention to this important but often overlooked part of the human brain. These regions will be discussed in terms of their location within the human brain, their healthy functional involvement, and common alterations found post-concussion expressed as physical, cognitive, emotional, or sleep-related symptoms.

2.4.1 Grey matter brain regions

Amygdala

The amygdala is a symmetric deep brain structure that comprises a group of neurons located anterior to the hippocampus (Figure 2.1). It is almond-shaped and sub-divided into the centromedial, laterobasal, and superficial groups (Tortora and Derrickson 2017). The main role of the amygdala involves emotional and cognitive processing linked to the limbic system (Heilbronner and Haber 2014; Kollias 2009; Steele and Lawrie 2004). Emotional responses related to pain, incoming threats, reward-related activities, empathy, personal importance/significance, and facial expressions are all governed by the amygdala (Bubb et al. 2018; Comes-Fayos et al. 2018; Olson et al. 2015; Waller et al. 2017). Moreover, the amygdala has been noted to play roles in social attention, social responses, salience tagging, interpreting visual signals, tactile learning, explicit memory, and implicit learning (Stephani et al. 2011; Tortora and Derrickson 2017).

Damage to the amygdala can lead to deficits in emotional processing, emotional learning, and memory, which can be further manifested in autism spectrum disorder, psychopathy, and loss of the "cognitive control" system in adolescents (Dalton et al. 2005; Kleinhans et al. 2009; Nacewicz et al. 2006; Steinberg 2010; Von Der Heide et al. 2013; Waller et al. 2017)(Table 2.1). Furthermore, sensitivity to fearful facial expressions, fear conditioning to social responses, alterations in vigilance, reduced self-motivation, and deficits in socio-emotional function can be caused by a damaged amygdala (Schmahmann and Pandya 2006; Tortora and Derrickson 2017; Waller et al. 2017).

Anterior intra-parietal sulcus

The anterior intra-parietal sulcus is a deep groove that occupies the antero-lateral bank of the intraparietal sulcus and spans the surface of the parietal lobe (Tortora and Derrickson 2017)(Figure 2.1). The anterior intra-parietal sulcus is further subdivided in three zones (hlP1, hlP2, and hlP3) based on cytoarchitecture (Colby et al. 1988; Scheperjans et al. 2008). Regions hlP1 and hlP2 are situated in the lateral wall of the anterior intra-parietal sulcus, while the hlP3 region lies more medial and has a distinctly different laminar pattern (Scheperjans et al. 2008). The anterior intra-parietal sulcus communicates with the cingulum (Bubb et al. 2018), superior longitudinal fasciculus (Ramayya et al. 2010), sensory and motor cortices (Anwander et al. 2007; Graziano and Cooke 2006), insula (Burks et al. 2017), the temporal (Anwander et al. 2007) and occipital lobes (Prado et al. 2005), and neighbouring parietal structures such as the inferior and superior parietal lobules (Burks et al. 2017; Scheperjans et al. 2008).

The anterior intra-parietal sulcus mainly contributes to visuomotor functions including finger manipulation (Graziano and Cooke 2006; Ramayya et al. 2010), tactility (Avillac et al. 2005), eye movements (Graziano and Cooke 2006; Prado et al. 2005), vestibular and egocentric attention (Chen et al. 2018), auditory co-ordinate location (Bremmer et al. 2001), and hierarchical structure processing (Anwander et al. 2007). The anterior intra-parietal sulcus also plays a role in manipulating objects with responsiveness to size, shape, and surfaces of specific

geometries (Murata et al. 2000; Shikata et al. 2003), temporal relations with regards to grasping (Murata et al. 2000), memorizing geometry (Murata et al. 2000), coordinated defensive movements (Aziz-Zadeh et al. 2006; Iacoboni and Dapretto 2006), and writing-related functions (Sugihara et al. 2006). Visual-dominant neurons, found only in the anterior intra-parietal sulcus, activated differently with respect to ambient light levels (Grefkes and Fink 2005; Iacoboni and Dapretto 2006). Damage to the anterior intra-parietal sulcus primarily manifests in a reduced ability to manipulate objects (Grefkes et al. 2004; Leiguarda and Marsden 2000) such as ideomotor apraxia (Binkofski et al. 1998; Leiguarda and Marsden 2000), reduced grip (Glover 2004; Leiguarda and Marsden 2000), reduced tactile sensitivity (Longo et al. 2010; Shikata et al. 2003), an inability to grasp objects (Grefkes and Fink 2005; Leiguarda and Marsden 2000; Murata et al. 2000), difficulty visualizing object rotation (Wolbers et al. 2007), spatial neglect (Schotten et al. 2005; Kravitz et al. 2011; Shinoura et al. 2009), and autotopagnosia (Longo et al. 2010)(Table 2.1). Other symptoms could include sensitivity to light (Grefkes and Fink 2005; Shikata et al. 2003) and optic ataxia (Perenin and Vighetto 1988).

Broca's area

This area resides in the inferior and lateral aspect of the frontal lobe in the dominant, and typically left, hemisphere (Broca 1861)(Figure 2.1). Broca's area is the language processing area and is fundamentally involved in the motor aspect of speech (Broca 1861). Neurological signals generated from Broca's area help initiate the movement of musculature in the throat, mouth, and tongue to produce meaningful sounds and initiate complex speech (Tortora and Derrickson 2017). This area is the neural mechanism for language and plays vital roles in word decoding, language production, phonology, articulation, ensuring proper grammar and is associated with all language related tasks (Maldonado et al. 2011; Motomura et al. 2014; Tortora and Derrickson 2017; Von Der Heide et al. 2013). Structurally, Broca's area can be subdivided into two parts, Brodmann's Area (BA) 44 and BA45, and the arcuate fasciculus pathway links Wernicke's area to Broca's area to produce the complete motor and sensory aspects of language and speech (Bernal and Ardila 2009; Maldonado et al. 2011).

Damage to Broca's area includes, but is not limited to, conduction aphasia, difficulty initiating speech, effortful speech production, difficulty forming sentences, impairment in speech melody, poor articulation, semantic and phonemic paraphasia, slurring, production of telegraphic sentences, abnormal grammatical forms, omitting the ending of words, and auditory hallucinations (Alexander et al. 1990; Bernal and Ardila 2009; Broca 1861; Maldonado et al. 2011; Rizzolatti et al. 1998; Tortora and Derrickson 2017)(Table 2.1). The overall absence in auditory comprehension can also lead to a reduced ability to imitate other people's spoken word and difficulties with reading and writing (Rizzolatti et al. 1998; Tortora and Derrickson 2017).

Hippocampus

The hippocampus is a symmetrically elongated brain region that lies deep near the brain's hemispheric midline but has lateral extensions to the temporal lobe (Figure 2.1). Subdivisions of the hippocampus include the cornu ammonis, dentate gyrus, entorhinal cortex, and the subiculum which exhibit specific roles in brain function (Tortora and Derrickson 2017). For example, the entorhinal cortex facilitates learning, memory, emotion, and social behaviour (Douet and Chang 2015; Schmahmann and Pandya 2006), whereas the subiculum focuses on episodic memory functions (Vann and Aggleton 2004). The hippocampi are a central node that connects with the temporal (Saur et al. 2008), parietal (Metzler-Baddeley et al. 2012), and frontal lobes (Bubb et al. 2018; Douet and Chang 2015), and more specifically to the premotor cortex (Weissman-Fogel et al. 2010), medial geniculate bodies (Winer and Lee 2007), mammillary bodies (Douet and Chang 2015; Bubb et al. 2018), and other deep brain structures in the diencephalon (Adolphs 2010; Bubb et al. 2018; Tortora and Derrickson 2017). The thalamus, hypothalamus, amygdala, and fornix also have key hippocampal connections to comprise the limbic system and enable memory facilitation (Schmahmann and Pandya 2006; Winer and Lee 2007). Furthermore, important white matter structures such as the cingulum (Bubb et al. 2018; Hyde et al. 2013), uncinate fasciculus (Metzler-Baddeley et al. 2012; Schmahmann and Pandya 2006), and corticospinal tract (Saur et al. 2008) facilitate other functions of the hippocampus.

The main role of the hippocampi is to execute every aspect of memory (Bubb et al. 2018; Hyde et al. 2013; Von Der Heide et al. 2013), but other vital roles include learning new tasks (Tortora and Derrickson 2017), understanding verbal and spatial cues (Spiers and Maguire 2007; Tortora and Derrickson 2017; Wolbers et al. 2007), emotions (Douet and Chang 2015; Rolls 1998; Schmahmann and Pandya 2006; Spunt and Lieberman 2012), motivation (Schmahmann and Pandya 2006), egocentric and allocentric coding (Elliott et al. 2000; Wilber et al. 2014), and executive function (Bubb et al. 2018).

Damage to the hippocampus often manifests in a variety of memory impairments (Metzler-Baddeley et al. 2011; Rudebeck et al. 2009) affecting verbal (Tortora and Derrickson 2017), spatial (Petrides 1985; Tortora and Derrickson 2017), and episodic (Bubb et al. 2018; Douet and Chang 2015; Tortora and Derrickson 2017) memory function (Table 2.1). Furthermore, hippocampal atrophy due to aging (Fjell et al. 2020), concussions (June et al. 2020), and chronic stress (Olson et al. 2015) can produce cascading cell loss and gliosis (Nacewicz et al. 2006), myopathy, weakness, fatigue, bone decalcification and neural degeneration (Melzack 2005). Among other conditions, the sustained degradation of the hippocampus has been shown to cause Alzheimer's Disease (Uysal and Ozturk 2020), anterograde amnesia (Gilboa et al. 2006), mild cognitive impairment (Fletcher et al. 2013; Goukasian et al. 2019), depression (Wu et al. 2018), and anxiety disorders (Ahmed-Leitao et al. 2019). Hippocampal lesions have also been shown to impair social conditioning (Petrides 1985), certain motor tasks (Petrides 1985), learning (Tortora and Derrickson 2017), and emotional regulation (Hyde et al. 2013; Petrides 1985), while also causing painful visceral and laryngeal sensations (Isnard et al. 2004). Fortunately, bilateral communication between hemispheric hippocampi, along with memory training, have been shown to initiate compensatory neuroplastic processes (Bubb et al. 2018) to diminish impairments caused by pathology (Vann and Aggleton 2004).

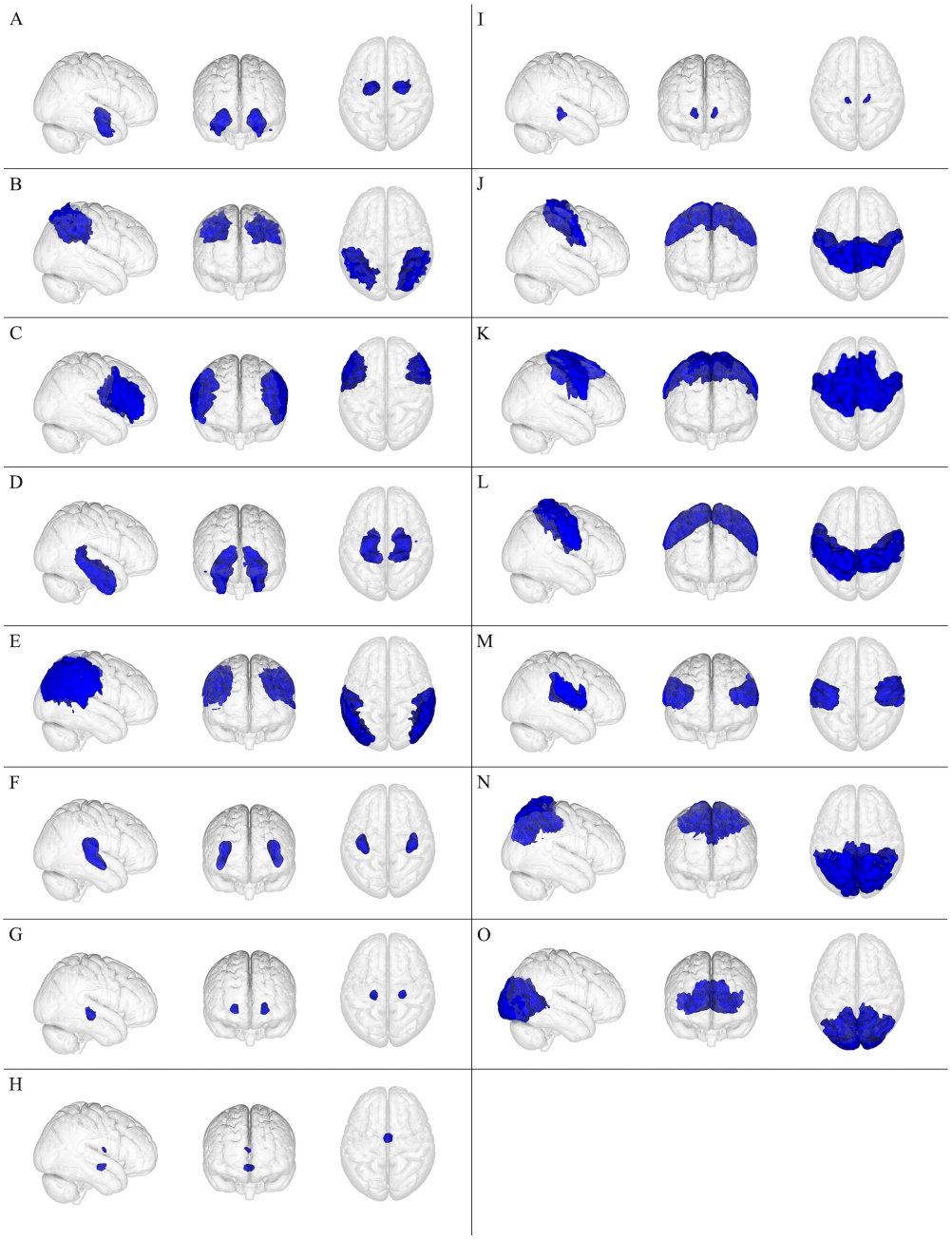

FIGURE 2.1: Grey matter brain regions (coloured blue) relevant to concussion-related damage that is organized as (A to O): (A) amygdala, (B) anterior intra-parietal sulcus, (C) Broca's area, (D) hippocampus, (E) inferior parietal lobule, (F) insula, (G) lateral geniculate body, (H) mamillary body, (I) medial geniculate body, (J) premotor cortex, (K) primary motor cortex, (L) primary somatosensory cortex, (M) secondary somatosensory cortex, (N) superior parietal lobule, and (O) visual cortex. These brain regions are overlayed onto the MNI152 1mm standard space T1-weighted brain from the (left to right) right sagittal, anterior frontal, and superior axial perspectives. These brain regions were from the Juelich Histological atlas (Eickhoff et al. 2005; Eickhoff et al. 2006a; Eickhoff et al. 2007a).

Inferior parietal lobule

The inferior parietal lobule is a large symmetric lobule (i.e., grouping) of gray matter neurons that create the inferior aspect of the parietal lobe (Tortora and Derrickson 2017)(Figure 2.1). The inferior parietal lobule is also considered part of the upswing of the long, deep arcuate intra-parietal sulcus behind the lower postcentral gyrus which then slashes posteriorly across the convex surface of the parietal lobe (Tortora and Derrickson 2017). The inferior parietal lobule can be further separated into 3 subregions based on cytoarchitecture into the anterior, middle and posterior subdivisions (Ruschel et al. 2014). The connectivity of the inferior parietal lobule with all major semantic areas of the brain lends itself to communicate with aspects of the temporal lobe (Meteyard et al. 2012; Schmahmann and Pandya 2006), occipital lobe (Fadiga et al. 2009), cerebellum (Leiguarda and Marsden 2000), neighbouring superior and anterior intraparietal lobules (Bubb et al. 2018; Motomura et al. 2014; Schmahmann and Pandya 2006), sensory and motor cortices (Meteyard et al. 2012; Ramayya et al. 2010; Schmahmann and Pandya 2006), deep brain structures such as the insula (Faillenot 1997), amygdala (Comes-Fayos et al. 2018), medial geniculate bodies (Tanaka et al. 1991), and hippocampus (Heilbronner and Haber 2014). Additionally, white matter bundles like the arcuate fasciculus (Herbet et al. 2014), cingulum (Bubb et al. 2018; Schmahmann and Pandya 2006), and superior longitudinal fasciculus (Martino et al. 2013; Schmahmann and Pandya 2006) form long U-shaped fibers (Maldonado et al. 2011) that connect Broca and Wernicke's area to facilitate the left inferior parietal lobule's contribution to language (Coslett and Schwartz 2018; Schmahmann and Pandya 2006).

Overall, the inferior parietal lobule interfaces with several areas of information convergence to facilitate a variety of sensorimotor and behaviour-related actions (Binder et al. 2009; Burks et al. 2017). Visuospatial navigation is primarily carried out by the inferior parietal lobule, which plays roles in visuomotor mechanisms (Ramayya et al. 2010; Solomon and Lo 2022; Vallar et al. 2014), velocity/timing information (Harrington et al. 1998), grasping (Ramayya et al. 2010), and complex tool-use (Ramayya et al. 2010). Bilaterally, the inferior parietal lobule also plays roles in sound perception (Fadiga et al. 2009), auditory memory (Alain

et al. 2008), saccadic eye movements (Talanow et al. 2020), egocentric decision-making (Iacoboni and Dapretto 2006), and emotional empathy (Comes-Fayos et al. 2018). The left inferior parietal lobule is involved in speech and language processing (Coslett and Schwartz 2018) and reading and writing (Motomura et al. 2014), while the right inferior parietal lobule is responsible for natural handwriting tempo (Bonzano et al. 2021).

Damage to the inferior parietal lobules generally causes reduced visuospatial and motor control abilities (Burks et al. 2017; Buxbaum 2001; Hyde et al. 2013; Maldonado et al. 2011), auditory agnosia (Griffiths 2002), increased egocentric or allocentric behaviour (Chen et al. 2018), and language deficits (Coslett and Schwartz 2018)(Table 2.1). Damage to the inferior parietal lobule is also related to speech pathology and shown to cause phonemic paraphasias (Maldonado et al. 2011), dysgraphia causing difficulties in reading and writing (Burks et al. 2017; Dejerine 1914; Motomura et al. 2014), disrupted phonological processing, and speech arrest (Maldonado et al. 2011).

Insula

The insula is a large triangular region that lies deep to the lateral cerebral fissure under the parietal and frontal lobes and transitions to form the temporal lobes (Centanni et al. 2021; Tortora and Derrickson 2017)(Figure 2.1). The insula is cytoarchitectonically distinguishable from surrounding brain regions by lamination patterns and degrees of granularity (Centanni et al. 2021; Stephani et al. 2011; Taylor et al. 2009). The insula can be subdivided into 3 main subregions known as the anterior granular, posterior granular, and intermediate dysgranular cortices (Centanni et al. 2021; Stephani et al. 2011; Taylor et al. 2009). The anterior and posterior granular cortices are a central node within the limbic, frontal, and auditory pathways (Stephani et al. 2011; Taylor et al. 2009); whereas the intermediate dysgranual cortex mainly facilitates vestibular and somatic sensations (Duffau et al. 2003a). Apart from its subdivisions, the insula's unique anatomical position allows for communication with many brain regions including the larger frontal, temporal, and occipital lobes (Centanni et al. 2021; Wu et al. 2016), and with more distinct structures such as the amygdala (Schmahmann and

Pandya 2006), thalamus (Sarubbo et al. 2013), auditory cortex (Heath and Jones 2013), somatosensory cortices (Stephani et al. 2011), motor cortices (Uddin et al. 2010), medial geniculate nucleus (Heath and Jones 2013), midbrain (Duffau et al. 2001), Broca's area (Cantalupo and Hopkins 2001), and hippocampus (Schmahmann and Pandya 2006), and has other connections to the cerebellum (Sarubbo et al. 2013). White matter bundles connected to the insula also consist of the cingulum (Sarubbo et al. 2013; Schmahmann and Pandya 2006), corpus callosum (Winer et al. 1998), and arcuate fasciculus (Bernal and Ardila 2009).

Given its multiple communication pathways, the insular system carries out a variety of somatic and motor functions, and is involved with emotional behaviours (Centanni et al. 2021). Sensorially, the insula interprets contralateral, and occasionally ipsilateral (Penfield and Faulk 1955), tactility (Schmahmann and Pandya 2006; Stephani et al. 2011) with regard to feelings of warmth (Brooks et al. 2005; Craig 2009; Stephani et al. 2011), vibration (Francis et al. 2000), and paresthesia (Tortora and Derrickson 2017). Processing information for auditory (Heath and Jones 2013), taste (Isnard et al. 2004; Stephani et al. 2011), and pain (Brenner et al. 2021; Makovac et al. 2020; Stephani et al. 2011) stimuli are also insular somatosensory functions. For assistance with the motor cortex, the insula also helps facilitate speech production (Duffau et al. 2000; Duffau et al. 2001; Duffau et al. 2003a; Isnard et al. 2004), gastric motility (Brenner et al. 2021; Stephani et al. 2011; Wang et al. 2008), patterned motor movements (Ruben et al. 2001; Schmahmann and Pandya 2006), cardiovascular function (Abboud et al. 2006; Stephani et al. 2011), and has important autonomic inputs to afferent vagal nerve fibers (Pollatos et al. 2007). Lastly, the insula may allow the production of the appropriate emotional responses to stimuli (Caruana et al. 2011) and connect feelings with decision-making (Centanni et al. 2021; Damasio et al. 2013). Emotions such as empathy (Iacoboni and Dapretto 2006), body awareness (Hyde et al. 2013; Stephani et al. 2011), decision-making tasks (Craig 2009; Stephani et al. 2011), and disgust (Dolensek et al. 2020; Stephani et al. 2011) all have insular involvement.

Pathology associated with the insula is often characterized by spontaneous somatosensory sensations that cause discomfort and pain along with a series of other impairments (Table 2.1). Somatosensory discomfort can include warmth

and thermal sensitivity, violent and painful electric current sensations in the face, mouth, and upper limbs, abdominal heaviness, and difficulty breathing (Isnard et al. 2004; Stephani et al. 2011). As the insula forms part of a central pain pathway (Burton et al. 1993), patients with insular lesions often suffer from pseudothalamic syndrome (Burton and Jones 1976; Critchley et al. 2004), painful paresthesias (Stephani et al. 2011), nociceptive sensitivity, analgesia/hyperalgesia (Burton and Jones 1976) and overall difficulties processing pain (Birklein et al. 2005; Stephani et al. 2011). Diverse impairments are also caused by insular pathology such as auditory impairments (Isnard et al. 2004) including hearing loss (Tanaka et al. 1991), auditory agnosia (Taniwaki et al. 2000), and auditory hallucinations (Woo et al. 2014), olfactory impairments (Tortora and Derrickson 2017; Von Der Heide et al. 2013), gustatory impairments causing unpleasant and metallic tastes (Stephani et al. 2011), alterations in gastro-intestinal movement/motility and tone (Penfield and Faulk 1955), and deficits in discriminating size, texture, and shape of objects (Disbrow et al. 2000). Moreover, speech-related problems can manifest as conduction aphasia (Bernal and Ardila 2009; Fadiga et al. 2009), effortful speech, articulation impairments, semantic and phonemic paraphasias, telegraphic sentences, abnormal grammatical form, and dysphonic and dysarthric speech (Isnard et al. 2004; Stephani et al. 2011). Other symptoms that have been noted due to insular damage include mental confusion (Penfield and Faulk 1955), short-term memory deficits (Bernal and Ardila 2009), and nausea (Longo et al. 2010). Isnard et al. (2004) also found that patients with insular lesions could suffer from hypersalivation, clonic jerks in the arm or face, anxiety, compulsive swallowing, and impaired consciousness (Isnard et al. 2004). Untreated insular damage could lead to empathy or emotional deficits (Hyde et al. 2013), disruptive behaviour disorders in adolescents (Fahim et al. 2011; Hyde et al. 2013), depression in adults (Drevets 2000; Steele and Lawrie 2004), anxiety (Baur et al. 2013) and substance abuse (Fedota et al. 2018).

Lateral geniculate body

The lateral geniculate bodies, also referred to as the lateral geniculate nuclei, are a pair of dense, symmetric neurons that lie directly lateral to the medial geniculate bodies (Liu et al. 2019)(Figure 2.1). The lateral geniculate bodies play a

significant role in relaying visual impulses from the retina by integrating pathways from the optic radiation, optic nerve, Meyer's loop, corpus callosum, brainstem, occipital cortex, and other visual related nodes (Kollias 2009; Liu et al. 2019). The lateral geniculate bodies are also considered to have a large thalamic component and thus are a first stage at which feedback signals affect visual processing (Jones 2012; O'Connor et al. 2002). The thalamic connection to the lateral geniculate bodies governs selective attention control related to visual inputs (Liu et al. 2019).

Pathology associated with the lateral geniculate bodies is characterized by an overall loss of visual experience, lack of visual awareness, and a reduced ability to understand visual inputs (Liu et al. 2019; Schmid et al. 2010)(Table 2.1). In addition, due to the link to selective attention, lateral geniculate body damage can also produce blindsight in particular areas and lead to difficulty concentrating on visual objects (Cowey 2010; Liu et al. 2019; Schmid et al. 2010).

Mamillary body

The mamillary bodies are a pair of spherical structures within the inferior hypothalamus in the midline of the brain that lie directly adjacent to the rostral-anterior aspect of the brainstem (Douet and Chang 2015; Tagliamonte et al. 2015)(Figure 2.1). The mamillary bodies are part of the Papez circuit, which facilitates memory and emotion (Douet and Chang 2015; Kollias 2009). The mamillary bodies are particularly correlated with long-term memory function, word recognition, recall of episodic information, spatial processing, and the ability to understand olfactory inputs (Bubb et al. 2018; Tsivilis et al. 2008; Vann and Nelson 2015).

Damage to the mamillary bodies can lead to a variety of memory, olfactory, and spatial deficits, however, because it is considered a relay station in the Papez circuit, the bodies can often undergo atrophy due to damage in its other connecting nodes such as the amygdala, fornix, hippocampus, and thalamus (Kollias 2009; Meys et al. 2022)(Table 2.1). The function of these structures have also been associated with dementia, epilepsy, schizophrenia, amnesia, and the loss of smell and/or the inability to process or understand the sense of smell (Kollias 2009; Tsivilis et al. 2008; Vann and Nelson 2015).

Medial geniculate body

The medial geniculate bodies, often referred to as the medial geniculate nuclei, are a pair of symmetric structures that lie directly adjacent to the brainstem and medial to the lateral geniculate nuclei (Winer 1984; Winer et al. 2005)(Figure 2.1). The medial geniculate bodies can be subdivided into ventral (Sherman and Guillery 1998), dorsal and medial (Vasquez-Lopez et al. 2017). Connections from the medial geniculate bodies to the inferior colliculus and the auditory cortex also form pathways to create a detailed associations for speech and sound (Vasquez-Lopez et al. 2017). The medial geniculate bodies are mainly responsible for relaying auditory impulses or sounds from the ear to the temporal lobe of the cerebrum via the acoustic radiation and the thalamus (Maffei et al. 2019a; Vasquez-Lopez et al. 2017).

Auditory frequencies processed in the medial geniculate bodies are organized such that complex and higher-order sounds are processed with the neuronally denser lemniscal pathway that integrates auditory and multisensory information, whereas secondary sounds, such as sharp responses to tones, are processed by less neuron rich regions (Winer et al. 2005). The extralemniscal pathway then processes responses to basic tones (Maffei et al. 2019a; Woo et al. 2014). The medial geniculate bodies have also been known to facilitate the efficient transmission of auditory linguistic signals in speech to preserve and perceive environmental sounds (Shivashankar et al. 2001). Pathology associated with the medial geniculate body is generalized auditory agnosia and a reduced ability to understand auditory inputs (Maffei et al. 2017; Winer et al. 2005)(Table 2.1).

Premotor cortex

The premotor cortex spans a substantial portion of the frontal lobe and lies directly anterior to the primary motor cortex (Tortora and Derrickson 2017)(Figure 2.1). The premotor cortex can be subdivided into ventral and dorsal regions and interacts with the primary motor cortex, corticospinal tract, colliculi projections, acoustic radiation, auditory cortex, basal ganglia, cerebellum, and the limbic system to generate and plan motor movements (Sarubbo et al. 2013; Tortora and Derrickson 2017). Information from multimodal sensory inputs is sent to

the premotor cortex where spatial coordinates are transformed into an appropriate visuo-motor 3D representation of space for the primary motor cortex to convert abstract goals into planned motor actions (O'Shea et al. 2007; Sarubbo et al. 2013). The premotor cortex is therefore utilized in precise, fine-motor hand movements (Grefkes and Fink 2005; O'Shea et al. 2007; Schmahmann and Pandya 2006). The premotor cortex also combines tactile, visuospatial, proprioceptive, and cognitive information to carry out specialized tasks (Burks et al. 2017; Iacoboni and Dapretto 2006; Leiguarda and Marsden 2000; O'Shea et al. 2007; Ramayya et al. 2010; Schmahmann and Pandya 2006; Winer and Lee 2007). Studies have further shown that the premotor cortex plays roles in particular social behaviours such as language and articulation processes (Burks et al. 2017; Iacoboni and Dapretto 2006), writing tasks (Motomura et al. 2014), music cognition (Woo et al. 2014), early phases of learning (Leiguarda and Marsden 2000), imitation and empathy (Iacoboni and Dapretto 2006), understanding intentions and actions (Herbet et al. 2014), vigilance (Borst and Gelder 2022), and motivation (Rizzolatti et al. 1998).

Pathology associated with the premotor cortex mainly manifests in reduced motor control which can cause difficulties in chewing and performing facial expressions (Tortora and Derrickson 2017), performing coordinated movements (Leiguarda and Marsden 2000), learning a new skilled movement (Leiguarda and Marsden 2000), and ideomotor apraxia (Rothi and Heilman 2014). Premotor cortex damage can also effect precise hand movements, errors in limb position and trajectory, and praxis in hand and finger movements (Leiguarda and Marsden 2000). Due to its involvement with speech, premotor pathology can also cause hearing impairments (Woo et al. 2014), complete speech arrest (Maldonado et al. 2011), articulatory disturbances (Duffau et al. 2003b), anarthria or dysarthria (Duffau et al. 2003a; Maldonado et al. 2011), and in severe cases can lead to Pick's disease (Leiguarda and Marsden 2000)(Table 2.1). It is also important to note that significant cross-talk occurs between the bilateral premotor cortices and the ipsilateral primary motor cortex in which symptoms can sometimes be expressed (Leiguarda and Marsden 2000).

Primary motor cortex

The primary motor cortex is located on the superior aspect of the frontal lobe, anterior to the central sulcus and the primary somatosensory cortex, and is directly posterior to the premotor cortex (Tortora and Derrickson 2017)(Figure 2.1). Similar to the premotor cortex, the primary motor cortex is closely connected to the premotor cortex, somatosensory cortex, thalamus, hippocampus, corpus callosum, and brainstem to effectively perform motor movements (Iacoboni and Dapretto 2006; Meier et al. 2008; Tortora and Derrickson 2017). Closely linked by proximity and functional communication to the somatosensory homunculus (Muret et al. 2022; Penfield and Boldrey 1937; Thompson et al. 2017), the primary motor cortex is also organized somatotopically where specific zones are responsible for directing the action of specific groups of muscles, joints and limbs (Meier et al. 2008). The organization of the primary motor cortex begins inferolaterally with the tongue, continuing superiorly in the order of lips, squinting, and fingers, with zones for the wrist, forearm and elbow interspersed on the superolateral aspect of the primary motor cortex, with the lower limb and foot zone located on the superomedial aspect (Meier et al. 2008; Tortora and Derrickson 2017).

Regarding function, the primary motor cortex is responsible for the execution of voluntary bodily movement. Once a specific motor task has been decided upon, a "blueprint" for the motor task is sent to the spinal cord or to the cranial nerves for task execution (Meier et al. 2008; Tortora and Derrickson 2017). Information from the primary motor cortex is transmitted through the brainstem's pyramidal desiccations to the contralateral corticospinal tract (i.e., motor plans for the right arm are generated by the left primary motor cortex) (Meier et al. 2008; Tortora and Derrickson 2017). To ensure proper coordination, the primary motor cortex also incorporates important sensory feedback through touch, proprioception, autonomic functions, pain, temperature, strength of muscle contractions, and audiovisual inputs (Sarubbo et al. 2013; Thompson et al. 2017). Apart from directly controlling movements, the primary motor cortex is also involved in writing tasks (Motomura et al. 2014), executive control (Kana et al. 2014; Moayedi et al. 2015), imitation (Iacoboni and Dapretto 2006), and early phases of learning (Leiguarda and Marsden 2000).

Pathology associated with the primary motor cortex traditionally follows loss of function in contralateral muscles, muscle weakness, and reduced motor skills and muscle selectivity (Buetefisch et al. 2018; Lang and Schieber 2004). Other pathological symptoms can include impairments to gait, balance, and skilled movements, muscle paresis, muscle atrophy (Leiguarda and Marsden 2000; Tortora and Derrickson 2017), facial palsy, spasticity, and hearing loss (Kumar et al. 2014; Woo et al. 2014)(Table 2.1). Similar to the premotor cortex, the primary motor cortex also exhibits cross talk between hemispheres, therefore, subtle abnormalities in ipsilateral limbs may also be present (Leiguarda and Marsden 2000). However, if injuries persist, limb-kinetic apraxia can develop into corticobasal degeneration and further into Pick's disease (Fukui et al. 1996; Leiguarda and Marsden 2000). Fortunately, the primary motor cortex is highly adaptive and has shown high capacity for plasticity during injury recovery (Stoeckel and Binkofski 2010; Tamura et al. 2019).

Primary somatosensory cortex

The primary somatosensory cortex is a large brain region that is symmetric and directly posterior to the primary motor cortex and the central gyrus (Tortora and Derrickson 2017)(Figure 2.1). The primary somatosensory cortex can be further subdivided into four cytoarchitectonic areas arranged from anterior to posterior termed Brodmann areas BA3a, BA3b, BA1, and BA2 that connect to other brain structures to process all sensory sensations of the human body (Brodmann 1909; Tortora and Derrickson 2017).

Mechanoreceptive somatosensory inputs from the primary sensory areas including the visual, auditory, vestibular, and other nervous systems send information through the spinal cord to the primary somatosensory cortex to contextualize sensory information to aid future motor-based decisions (Stephani et al. 2011; Tortora and Derrickson 2017). The primary somatosensory cortex is therefore processing the sensory information for proprioception (Chen et al. 2018; Leiguarda and Marsden 2000; Rizzolatti et al. 1998; Tortora and Derrickson 2017), vision (Colby et al. 1988; Rizzolatti et al. 1998), motor control (Borich et al. 2015), regulating cortical excitability (Longo et al. 2010), involuntary movement activation

(Sakata et al. 1995), working memory (Tortora and Derrickson 2017), fast perceptual learning (Pleger et al. 2003), and pain (Bushnell et al. 1999; Casey et al. 1994; Flor et al. 1997). Like the primary motor cortex, the primary somatosensory cortex is organized somatotopically in discrete zones, described by the somatosensory homunculus (Muret et al. 2022; Penfield and Boldrey 1937). Furthermore, each subdivision has been demonstrated to have complete maps of the contralateral body surface (Muret et al. 2022). Neuroplasticity and cortical reorganization is present in the primary somatosensory cortex (Dinse and Merzenich 2002; Pleger et al. 2001), which indicates that cortical maps are in a constant state of fluctuation (Pleger et al. 2003) and that neural representation is dependent on triggered stimuli (Longo et al. 2010).

Damage to the primary somatosensory cortex can cause an overall reduction in sensory input and interpretation, which can manifest as reduced tactile ability, poor grip, and object manipulation, uncoordinated finger movements (Tortora and Derrickson 2017), an impaired recognition of facial expressions (Longo et al. 2010; Pitcher et al. 2008), and praxic errors involving orientation, limb coordination, motor control (Borich et al. 2015; Leiguarda and Marsden 2000)(Table 2.1). Discomfort and pain are also commonly elicited as paresthesia, pins and needles, numbness, tingling, and warmth affecting the lips, cheek, face, tongue, upper limbs, and lower limbs (Isnard et al. 2004; Singh et al. 2020; Stephani et al. 2011). Additionally, deficits in pain processing occur where pain can be generated sporadically (Melzack 2005) or create phantom limb pain (Longo et al. 2010).

Secondary somatosensory cortex

The secondary somatosensory cortex is another large brain region that is symmetric and lies directly posterior to the primary somatosensory cortex on the superior aspect of the parietal lobe (Tortora and Derrickson 2017)(Figure 2.1). Similar to the primary somatosensory cortex, the secondary somatosensory cortex can be further subdivided into four based on their cytoarchitecture and functional differences: Operculum (OP) 1 (lateral dorsal), OP2 (posterior ventral), OP3 (anterior ventral), and OP4 (anterior)(Eickhoff et al. 2006b; Eickhoff et al. 2007b).

The secondary somatosensory cortex carries out similar sensory processing functions as the primary somatosensory cortex (Chen et al. 2018; Leiguarda and Marsden 2000; Ruben et al. 2001; Tortora and Derrickson 2017). Also similar to the primary somatosensory cortex, the secondary cortex is organized inferolaterally to superomedially in a somatotopic form in the order of face, hands, trunk, legs (Eickhoff et al. 2007b; Ruben et al. 2001). The secondary somatosensory cortex sets itself apart in the ability to localize the origin of somatic sensations and communication with the parietal cortex (Scheperjans et al. 2008) and limbic system (Melzack 2005). Moreover, the localization abilities are attributed to enlargements of representation maps (Dinse et al. 2003; Pleger et al. 2001; Pleger et al. 2003) and less consistent somatotopic organization (Del Gratta et al. 2002; Disbrow et al. 2000; Ruben et al. 2001), where variability in activation improves discrimination abilities (Pleger et al. 2003; Romo et al. 2002).

Damage to the secondary somatosensory cortex often manifests in reduced psychophysical performance (Pleger et al. 2003), reduced tactile sensitivity, memory problems (Tortora and Derrickson 2017), phantom limb pain (Guo et al. 2019; Pleger et al. 2003), and praxic errors (Leiguarda and Marsden 2000)(Table 2.1). However, pathology is predominantly presented as diverse and unpleasant sensations of paresthesiae, pins and needles, numbness, tingling, electrical current, warmth, electric discharge, and pain in the lips, cheek, face, tongue, upper and lower limbs, neck, and torso (Grefkes and Fink 2005; Isnard et al. 2004; Stephani et al. 2011; Tortora and Derrickson 2017). Fortunately, the secondary somatosensory cortex is known to have strong cortical reorganization abilities that drive plastic changes, along with similar contralateral somatotopy to reduce effects due to pathology (Disbrow et al. 2000; Pleger et al. 2003; Ruben et al. 2001).

Superior parietal lobule

The superior parietal lobule is a large symmetric brain region on the superior aspect of the parietal lobe and is situated directly superior to the intra-parietal sulcus (Wang et al. 2015)(Figure 2.1). The superior parietal lobule can be further subdivided in 5 subregions (Wang et al. 2015). The main function of the superior parietal lobule is to integrate multimodal somatosensory and visual inputs to create

specific motor movements, and is thus highly connected to motor and sensory brain regions (Tortora and Derrickson 2017; Wang et al. 2015). In addition to motor and sensory integration, the superior parietal lobule plays a role in egocentric tasks (Lester and Dassonville 2014; Rosenbaum et al. 2004), emotion-relevant behaviour (Hyde et al. 2013; Spunt and Lieberman 2012), and auditory association (Molholm et al. 2006; Mørch-Johnsen et al. 2018).

Damage to the superior parietal lobule mainly manifests in visuospatial navigation impairments (Vallar et al. 2014; Wolbers et al. 2007) causing a variety of praxic errors (Leiguarda and Marsden 2000; Motomura et al. 2014), particularly in the dark (Leiguarda and Marsden 2000), such as apraxic dysgraphia (Burks et al. 2017), autotopagnosia (Leiguarda and Marsden 2000; Longo et al. 2010), poor balance (Scheperjans et al. 2008) and poor posture (Leiguarda and Marsden 2000)(Table 2.1). Superior parietal lobule pathology has also been shown to reduce attention spans in youth (Hyde et al. 2013) and is strongly correlated with pathology attributed to the inferior parietal lobe (Burks et al. 2017).

Visual cortex

The visual cortex is a large region of the cerebral cortex that covers much of the occipital lobe (Tortora and Derrickson 2017)(Figure 2.1). More specifically, the primary visual cortex is located at the most posterior point of the occipital lobe, which is medial and close to the longitudinal fissure (Tortora and Derrickson 2017). The secondary and association visual areas cover most of the remaining aspects of the occipital lobe, which are superolateral to the primary visual cortex (Tortora and Derrickson 2017). Based on the description provided by Purves et al. (2013), the visual cortex can be separated into eight different brain regions, where V1 is the primary visual cortex and V2 is the secondary visual cortex, while V3, V3a, V4, ventral posterior (VP), middle temporal (MT), and middle superior temporal (MST) comprise the remaining association visual areas (Purves et al. 2013). The calcarine sulcus runs transversely through the primary visual cortex, the secondary visual cortex wraps around the primary visual cortex, V3 and V3a are superior to the secondary visual cortex, and VP and V4 are inferior to it (Purves et al. 2013). The MT and MST regions are small and slightly separated

from the other visual cortex regions, found on the inferior, lateral aspects of the occipital lobe (Purves et al. 2013).

In general, the visual cortex is responsible for receiving, processing, and interpreting visual information that travels from the retina, along the optic nerve, passing through the thalamus, and arriving at the primary visual cortex (Tortora and Derrickson 2017). This includes the processing of colour, brightness, shape and motion captured with the visual sensory system (Purves et al. 2013). Visual information is also processed on the contralateral side of the brain than the eye is. The cortical visual regions of V3A, MT and MST are involved in motion perceptions (Ozdemir and Black 2005; Purves et al. 2013; Tootell et al. 1997), whereas V4 is involved with colour interpretation and processing (Ozdemir and Black 2005; Purves et al. 2013)(Table 2.1).

TABLE 2.1: A summary of 15 grey matter brain regions and their associated functions and concussion-related symptoms.

Brain region	**Associated functions**	**Concussion-related symptoms**
Amygdala	- Emotional processing and learning - Memory - Fearfulness sensitivity - Self-motivation - Socio-emotional function	- Trouble falling asleep - Loss of sleep - Irritability - Sadness - Nervousness - More emotional - Feeling "slow" or "foggy" - Difficulty concentrating - Difficulty remembering
Anterior intra-parietal sulcus	- Visuomotor functions - Finger manipulation - Tactility - Eye movements - Vestibular and egocentric attention - Auditory coordinate location - Hierarchical structure processing - Memorizing geometry - Affected by light levels	- Light sensitivity - Irritability - Numbness - Feeling "slow" - Visual problems

Broca's area	- Language processing - Motor control with speech	- Noise sensitivity - Irritability - More emotional - Feeling "slow" or "foggy" - Difficulty concentrating - Difficulty remembering - Speech impairment
Hippocampus	- Every aspect of memory - Learning new tasks - Understanding verbal and spatial cues - Emotion - Motivation - Executive function	- Headache - Balance problems - Irritability - More emotional - Visual problems - Difficulty remembering
Inferior parietal lobule	- Visuospatial navigation - Sound perception - Auditory memory - Saccadic eye movements - Egocentric decision-making - Emotional empathy - Speech and language processing - Reading and writing	- Headache - Balance problems - Dizziness - Light sensitivity - Noise sensitivity - Irritability - Sadness - Nervousness - More emotional - Numbness - Feeling "slow" or "foggy" - Difficulty concentrating - Difficulty remembering - Visual problems
Insula	- Somatic, motor, and emotion - Tactility - Auditory - Taste - Pain - Speech production - Gastric motility - Patterned motor movements - Cardiovascular function - Decision-making tasks	- Nausea - Vomiting - Dizziness - Noise sensitivity - Fatigue - Trouble falling asleep - Excessive sleep - Loss of sleep - Drowsiness - Irritability - More emotional - Numbness
Lateral geniculate body	- Relay of visual inputs	- Balance problems - Dizziness - Drowsiness - Light sensitivity - Difficulty concentrating - Visual problems

Mamillary body	- Memory - Olfactory - Inability to understand smells - Spatial abilities	- Headache - Irritability - Loss of smell
Medial geniculate body	- Auditory processing - Speech comprehension	- Headache - Dizziness - Noise sensitivity - Difficulty concentrating - Difficulty remembering
Premotor cortex	- Generate and plan motor movements - Proprioception and spatial awareness - Fine and gross motor coordination	- Headache - Nausea - Balance problems - Dizziness - Fatigue - Trouble falling asleep - Excessive sleep - Drowsiness - Irritability - Numbness - Feeling "slow" - Movement impairments
Primary motor cortex	- Motor control - Movement execution - Sensory feedback	- Headache - Nausea - Balance problems - Dizziness - Fatigue - Trouble falling asleep - Excessive sleep - Loss of sleep - Drowsiness - Irritability - Numbness - Feeling "slow" - Movement impairments
Primary somatosensory cortex	- Interpretation of all sensory information - Distinct localization of where sensory input originated	- Headache - Nausea - Balance problems - Dizziness - Fatigue - Drowsiness - Light sensitivity - Noise sensitivity - Irritability - Numbness - Trouble falling sleep - Visual problems

Secondary somatosensory cortex	- Secondary processing and interpretation of sensory information	- Headache - Nausea - Balance problems - Dizziness - Fatigue - Drowsiness - Light sensitivity - Noise sensitivity - Irritability - Numbness - Trouble falling sleep - Visual problems
Superior parietal lobule	- Somatosensory and visual interpretation for specific motor movements - Egocentric tasks - Emotion-relevant behaviour - Auditory association	- Headache - Balance problems - Dizziness - Fatigue - Light sensitivity - Trouble falling asleep - Numbness - Visual problems
Visual cortex	- Processing of all visual information - Colours, shapes, motion, and light	- Headache - Nausea - Vomiting - Balance problems - Dizziness - Fatigue - Trouble falling asleep - Drowsiness - Light sensitivity - Feeling "foggy" - Difficulty concentrating - Visual problems

2.4.2 White matter brain regions

Acoustic radiation

The acoustic radiation is a white matter tract that originates at the medial geniculate nucleus of the thalamus and travels anterior and lateral towards the primary auditory cortex on transverse temporal gyri of the temporal lobe (Maffei et al. 2019b; Maffei et al. 2019a)(Figure 2.2). It is essential to transmitting auditory information from the thalamus to the temporal cortex and is therefore essential to auditory and language comprehension (Berman et al. 2013; Maffei et al. 2019a; Rademacher et al. 2002).

Damage to the acoustic radiation could lead to a range of auditory impairments (Table 2.2). Studies have shown that damage to the acoustic radiation is associated with hearing and language disorders, auditory processing deficits, and decreased speech comprehension (Maffei et al. 2019a). More serious damage could lead to cortical (central) deafness (Griffiths 2002; Taniwaki et al. 2000), environmental sound agnosia, total auditory agnosia of all sounds (Taniwaki et al. 2000), or verbal deafness (word agnosia)(Maffei et al. 2017; Shivashankar et al. 2001). Additionally, it is possible for an individual to experience auditory hallucinations (i.e., the experience of hearing music in the absence of any external stimuli)(Woo et al. 2014) or tinnitus (Koops et al. 2021). Language impairments may be more likely if an injury occurs to the left acoustic radiation as research has shown a more substantial acoustic radiation asymmetry and predicted that the more developed left acoustic radiation may be due to language processing being located in the left hemisphere (Berman et al. 2013).

Callosal body

The callosal body, also known as the corpus callosum, is a large commissural tract that connects the left and right hemispheres by way of more than 200 million nerve fibers (Aboitiz et al. 1992; Luders et al. 2010)(Figure 2.2). The callosal body resides in the center of the brain and connects with and crosses many other white matter tracts (Kollias 2009; Luders et al. 2010). The corpus callosum can

be subdivided into anterior, middle, and posterior sections respectively named the genu, body and splenium of the corpus callosum (Pietrasik et al. 2020).

Due to its substantial inter-hemispheric connection, the callosal body is essential to most facets of cognitive function. Therefore, injury to this important white matter structure could cause a wide range of cognitive and neurological complications. These could include visual, motor, visuospatial perception, information processing speed and ability, moral reasoning, tactile and somatosensory perception, behaviour, higher cognitive functions, and learning bimanual tasks (Frederiksen 2013; Kollias 2009; Luders et al. 2010; Knaap and Ham 2011)(Table 2.2).

Cingulum

The cingulum, also referred to as the cingulum bundle, is a substantial white matter structure that nearly forms a complete circle within the medial cortex (Bubb et al. 2018)(Figure 2.2). From a sagittal perspective of either hemisphere, the cingulum encircles the corpus callosum with connections to the orbito-frontal regions before posteriorly traveling anterior to the body of the corpus callosum towards the occipital lobe, and then diving inferiorly and anteriorly towards the temporal pole (Bubb et al. 2018; Shah et al. 2012).

As a result of its structure, the cingulum is highly connected to various brain regions and has been linked to have important roles in executive control (Metzler-Baddeley et al. 2012), attention (Chiang et al. 2016), and episodic memory (Bubb et al. 2018; Koenig et al. 2015; Metzler-Baddeley et al. 2011; Ray et al. 2015)(Table 2.2). Additionally, the cingulum has also been linked to pain sensation processing (Bubb et al. 2018; Melzack 2005) and the development of psychosis or schizophrenic behaviour (Pan et al. 2021), obsessive compulsive (Ballantine et al. 1987; Bubb et al. 2018), anxiety (Sindermann et al. 2021), and depression disorders (Bhatia et al. 2018; Chahal et al. 2022). This is of interest specific to post-concussion assessment because anxiety and depression commonly occur following concussions (Kontos et al. 2012a; Rapoport et al. 2003).

Corticospinal tract

The corticospinal tracts are well documented bilateral white matter structures that descend from the motor cortex, travel through the medullary pyramid in the brainstem, and then cross to continue descending contralaterally down the spinal cord to the dorsolateral funiculus (Schieber 2007)(Figure 2.2). Thus, the left and right corticospinal tracts travel contralaterally within the spinal cord.

The corticospinal tracts are essential to motor control including spinal reflexes and motor neuron control (Welniarz et al. 2017). Thus, one of the primary deficits associated with impairment of this region is reduced voluntary motor control (Carper et al. 2015; Jang 2014)(Table 2.2). With a concussion, injury to the corticospinal tracts could affect motor control from the neck down. Injury to the corticospinal tracts, within the brain or spinal cord, could also lead to ipsilaterally impaired proprioception, paralysis, or decreased muscle tone, spasticity, power production, and mass (Shams and Arain 2019; Van Wittenberghe and Peterson 2019).

Fornix

The fornix is a thin, arched white matter structure within the medial aspect of the cerebral hemispheres (Douet and Chang 2015; Senova et al. 2020)(Figure 2.2). Due to the arched structure, the fornix can be separated into several sections including the alveus, subiculum, fimbria, crura, body, and columns (Senova et al. 2020). The fornix is a major hippocampal output tract and resultantly travels from the medial temporal lobe regions, where the alveus is formed medially to the inferior aspect of the temporal horn of the lateral ventricle (Senova et al. 2020). The alveus bundles together to form the fimbria, which curves posteriorly and superiorly, before forming the crura that curves anteriorly and superiorly (Douet and Chang 2015; Senova et al. 2020). The forneal crura travel underneath the splenium of the corpus callosum and project to connect to each other to form the structure known as the dorsal hippocampal commissure (Douet and Chang 2015; Senova et al. 2020). The crura come together and form the forneal body, which arches superior to the thalamus, and travels anteriorly before splitting, at the

anterior commissure, into the left and right columns that descend into the anterior forebrain (Douet and Chang 2015; Senova et al. 2020).

As the primary white matter structure connected to the hippocampus, the fornix is closely related to memory and learning capabilities. Thus, damage to the fornix could involve decreased episodic memory function, learning capabilities, and attention impairment (Douet and Chang 2015; Senova et al. 2020)(Table 2.2). Several concussion and mild traumatic brain injury studies have found decreased fornix microstructural integrity and volume following injury that was correlated with injury severity (Jang et al. 2018b; Kinnunen et al. 2011; Tomaiuolo 2004). Furthermore, atrophy of the fornix has been linked to several neurodegenerative diseases such as Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis, epilepsy, and schizophrenia (Douet and Chang 2015).

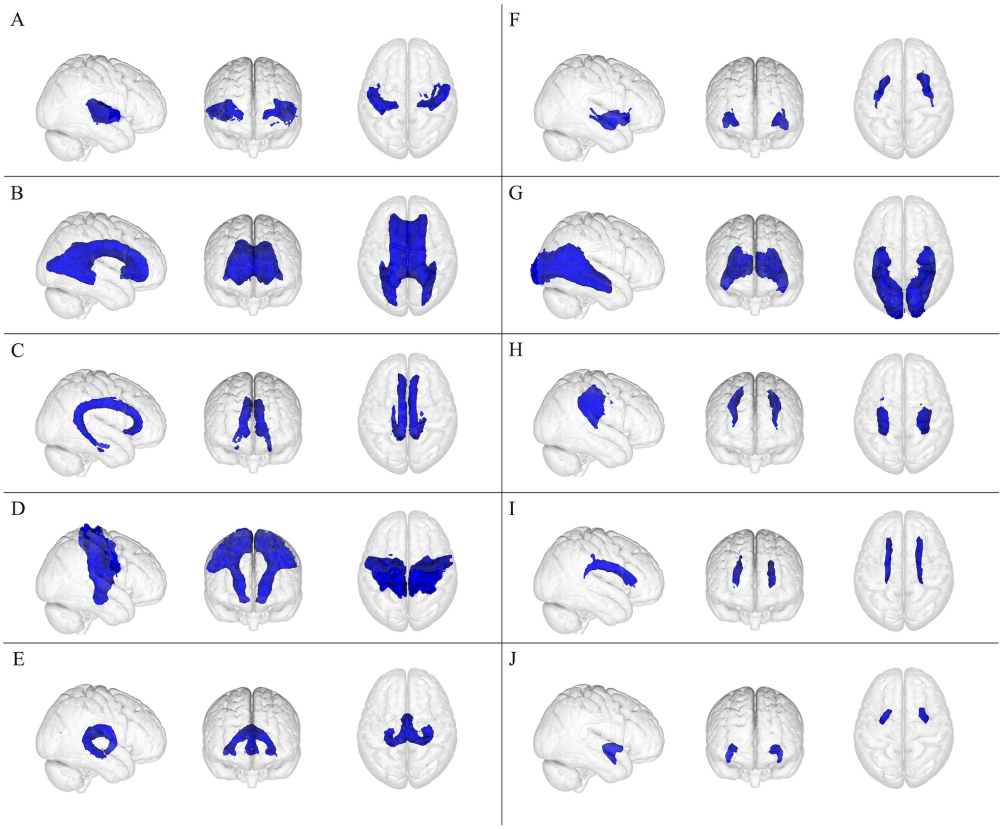

FIGURE 2.2: White matter brain regions (coloured blue) relevant to concussion-related damage that is organized as (A to J): (A) acoustic radiation, (B) callosal body, (C) cingulum, (D) corticospinal tract, (E) fornix, (F) inferior occipito-frontal fascicle, (G) optic radiation, (H) superior longitudinal fascicle, (I) superior occipito-frontal fascicle, and (J) uncinate fascicle. These brain regions are overlayed onto the MNI152 1mm standard space T1-weighted brain from the (left to right) right sagittal, anterior frontal, and superior axial perspectives. These brain regions were from the Juelich Histological atlas (Eickhoff et al. 2005; Eickhoff et al. 2006a; Eickhoff et al. 2007a) and the JHU DTI-based white matter atlases (Hua et al. 2008; Mori et al. 2005; Wakana et al. 2007).

Inferior occipito-frontal fascicle

The inferior occipito-frontal fascicle is one of the long and highly connected white matter bundles in the human brain, however, its distinction from other white matter structures has been a point of controversy for decades (Benedictis et al. 2021; Makris et al. 2007)(Figure 2.2). Fortunately, the evolution of diffusion magnetic resonance imaging (dMRI) has recently allowed for highly detailed fiber tracking of the inferior occipito-frontal fascicle that can be corroborated with cadaveric brain dissections (Makris et al. 2007; Palejwala et al. 2020; Wu et al. 2016). The posterior aspect of the inferior occipito-frontal fascicle originates in the

lateral, inferior portion of the occipital lobe and travels through the occipital lobe lateral to the ventricle horns (Palejwala et al. 2020; Wu et al. 2016). The tract remains lateral through the temporal lobe before veering medially into the anterior portion of the insular short gyri, and terminating anteriorly in the orbitofrontal cortex (Palejwala et al. 2020; Wu et al. 2016).

Based on its anterior-to-posterior anatomical structure, the inferior occipito-frontal fascicle is associated in many important functions that can involve anatomically distant regions (Wu et al. 2016). Furthermore, dMRI studies have found the inferior occipito-frontal fascicle to be specifically involved in various tasks. Due to its anterior connections within the frontal lobe, Brodmann's Area (BA) 10, the inferior occipito-frontal fascicle is associated with many complex cognitive functions such as social cognition, episodic memory, attention, and multitasking (Moayedi et al. 2015; Wu et al. 2016)(Table 2.2). Obsessive compulsive disorder, and its associated behvioural-cognitive flexibility, executive function and decision-making deficits, has been linked to the inferior occipito-frontal fascicle's connection of the frontal lobe with the temporal and occipital lobes (Garibotto et al. 2010; Lawrence et al. 2009; Wu et al. 2016). Additionally, the fronto-temporal fiber section of the inferior occipito-frontal fascicle is associated with language and hearing, where the left region connects to Broca-Wernicke language centers (Duffau et al. 2014) and has been shown to be effected with auditory verbal hallucinations in individuals with schizophrenia (Oestreich et al. 2016). Finally, there has been some evidence of the inferior occipito-frontal fascicle being implicated with visual conceptualization and recognition (Sarubbo et al. 2013).

Optic radiation

The optic radiation is a vital white matter tract responsible for transmitting visual information from the eye to the visual cortex in the occipital lobe (Dayan et al. 2015)(Figure 2.2). The optic radiation is a hook-shaped white matter structure that originates at the lateral geniculate nucleus, a transfer point in the thalamus receiving visual information from the optic tracts, and terminates in the primary visual cortices in the occipital lobe (Dayan et al. 2015).

The visual information transmitted to the primary visual cortex via the optic radiation is contralateral to the eyes. Thus, the main deficit associated with optic radiation damage is visual impairment (Jang et al. 2018a). An injury to the optic radiation can lead to decreased visual field and light perception (Brahm et al. 2009; Suchoff et al. 2008), and reduced retinal function (Lennartsson et al. 2018) which can cause vision related post-concussion symptoms including light sensitivity (Table 2.2).

Superior longitudinal fascicle

The superior longitudinal fascicle is another large white matter structure that due to its many branches and tracts has left researchers and clinicians with some ambiguity surrounding its exact anatomy (Nakajima et al. 2020)(Figure 2.2). Generally, the superior longitudinal fascicle connects most cortical regions of the parietal lobe to the frontal lobe, with some temporal connections as well (Nakajima et al. 2020). Due to the numerous names associated with the tracts and segments of the superior longitudinal fascicle, one recent study (Nakajima et al. 2020) proposed a simplified naming convention separating the superior longitudinal fascicle into four segments named as dorsal, ventral, posterior and arcuate fasciculus segments (Nakajima et al. 2020; Panesar et al. 2019; Schotten et al. 2012; Wang et al. 2016). The dorsal segment would be what has been previously referred to as the superior longitudinal II, the ventral segment to the arcuate fasciculus anterior and superior longitudinal fascicle III, the posterior segment to the arcuate fasciculus posterior and temporoparietal segment of the superior longitudinal fascicle, and the arcuate fasciculus to the arcuate fasciculus or the arcuate fasciculus long segment (Nakajima et al. 2020). The dorsal segment originates in the inferior parietal lobe and terminates in the superior and middle frontal gyri, while the ventral segment also originates in the inferior parietal lobe, slightly anterior and inferior to the dorsal segment, and terminates in the middle and inferior frontal gyri (Nakajima et al. 2020). The posterior segment originates in the superior, middle and inferior temporal gyri and terminates within the inferior and superior parietal areas (Nakajima et al. 2020). Finally, the arcuate fasciculus segment originates across the superior, middle and inferior temporal gyri before traveling posteriorly and arcing around

the Sylvian fissure and insula to terminate anteriorly in the posterior aspects of the inferior and middle frontal gyri (Nakajima et al. 2020).

Based on the four segment naming convention proposed by Nakajima et al. (2020), each segment can be related to specific cognitive functions related to the cortical regions it connects (Nakajima et al. 2020)(Table 2.2). As proposed by Nakajima et al. (2020) and based on previous literature, the function of each superior longitudinal fasciculus segment can be classified bilaterally or hemisphere-specific (Nakajima et al. 2020). The dorsal segment is involved in visuospatial attention in the right hemisphere and bilaterally in motor control, the ventral segment is involved in attention and social cognition in the right hemisphere, language, auditory comprehension and articulation processing in the left hemisphere, and motor control bilaterally, the posterior segment is involved in auditory and visuospatial comprehension in the right hemisphere and auditory comprehension, reading and lexical access in the left hemisphere, and the arcuate fasciculus is involved in social cognition and visuospatial cognition in the right hemisphere and phonological language processing in the left hemisphere (Nakajima et al. 2020).

Superior occipito-frontal fascicle

The superior occipito-frontal fascicle is a long association white matter tract that connects the frontal and occipital cortices (Figure 2.2). The tract travels parallel to the corticospinal tracts and corpus callosum between the corticospinal tracts and the lateral ventricles, and inferiorly to the corpus callosum (Bürgel et al. 2006; Liu et al. 2020). Anterior and posterior to the corpus callosum, the superior occipito-frontal fascicle projects superiorly (Liu et al. 2020).

Due to the location, length and connection of the frontal and occipital cortices, the superior occipito-frontal fascicle is associated with several functions. A study of 90 awake glioma craniotomy patients found that the superior occipto-frontal fascicle had mapping points associated with specific characteristics for speech disorder (27.2%), motor disorder (24.7%), language disorder (16.1%), sensory disorder (15%), and several other functions with less distinction (Liu et al. 2020). The study also found that the superior occipito-frontal fascicle was positively associated with the visual field, visuospatial cognition, and spatial working memory

(Liu et al. 2020). Another study found that young adults with Multiple Sclerosis had reduced processing speed and simple reaction time correlated with negative abnormalities in their superior occipito-frontal fasciculus, corpus callosum, and corticospinal tracts (Govindarajan et al. 2021). Thus, confirming that the superior occipital-frontal fasciculus relays important information between the visual, motor, and executive functioning brain regions (Govindarajan et al. 2021)(Table 2.2).

Uncinate fascicle

The uncinate fascicle is an important white matter tract that connects the temporal cortex with the prefrontal cortex (Figure 2.2). The structure originates in the temporal pole and travels posteriorly to the amygdala before the body of the uncinate fascicle curves superiorly through the external capsule medial to the insular cortex, and then has a unique hook shape to turn antero-medially towards the prefrontal cortex (Bhatia et al. 2017; Hau et al. 2017; Kier et al. 2004). The body of the uncinate fascicle then branches in three directions towards the lateral orbital gyri, frontopolar cortex, and subgenual cingulate cortex (Bhatia et al. 2017; Hau et al. 2017).

Based on the anatomical location of this structure and its close connection to the prefrontal cortex and amygdala, it has been shown that the uncinate fascicle is involved in mood regulation, emotional expression, and depression (Bhatia et al. 2017; Bhatia et al. 2018) and even problems interpreting facial expressions (Tottenham et al. 2011)(Table 2.2). The uncinate fascicle also passes close to the hippocampus and due to its presence in the temporal lobe has been associated with learning and memory (Binney et al. 2012; Thomas et al. 2015). Furthermore, it has also been linked to language due to its position within the parietal lobe (Binney et al. 2012; Papagno et al. 2011; Saur et al. 2008).

TABLE 2.2: A summary of 10 white matter brain regions and their associated functions and concussion-related symptoms.

Brain region	**Associated functions**	**Concussion-related symptoms**
Acoustic radiation	- Auditory and language comprehension - Auditory processing deficits - Language processing (left hemisphere)	- Headache - Noise sensitivity - Difficulty concentrating - Difficulty remembering
Callosal body	- Inter-hemisperic connection - Visual - Motor - Visuospatial perception - Information processing speed and ability - Moral reasoning - Tactile and somatosensory perception - Behaviour - Higher cognitive functions - Learning bimanual tasks	- Balance problems - Light sensitivity - Noise sensitivity - Irritability - Nervousness - More emotional - Numbness - Feeling "slow" or "foggy" - Difficulty concentrating - Difficulty remembering - Visual problems - Movement impairments
Cingulum	- Executive control - Attention - Episodic memory - Pain sensation - Psychiatric disorders (Depression, anxiety, psychosis)	- Trouble falling asleep - Excessive sleep - Loss of sleep - Drowsiness - Irritability - Sadness - Nervousness - More emotional - Feeling "slow" or "foggy" - Difficulty concentrating - Difficulty remembering
Corticospinal tract	- Voluntary motor control	- Balance problems - Fatigue - Trouble falling asleep - Irritability - Numbness - Feeling "slow" - Movement impairments
Fornix	- Episodic memory - Learning capabilities - Attention	- Drowsiness - Irritability - Nervousness - More emotional - Feeling "slow" or "foggy" - Difficulty concentrating - Difficulty remembering

Inferior occipito-frontal fascicle	- Social cognition - Episodic memory - Attention and multitasking - Behavioural-cognitive flexibility - Executive function - Decision-making - Language - Hearing - Visual conceptualization and recognition	- Headache - Light sensitivity - Noise sensitivity - Irritability - Sadness - Nervousness - More emotional - Feeling "slow" or "foggy" - Difficulty concentrating - Difficulty remembering - Visual problems
Optic radiation	- Visual field - Retinal function - Light perception	- Nausea - Vomiting - Dizziness - Drowsiness - Light sensitivity - Visual problems

Superior longitudinal fascicle	Dorsal -Visuospatial attention (right) - Motor (bilateral)) Ventral - Attention and social cognition (right) - Language, auditory comprehension and articulation processing (left) - Motor (bilateral)) Posterior - Auditory and visuospatial comprehension (right) - Auditory comprehension, reading and lexical access (left) Arcuate fasciculus - Social and visuospatial cognition (right) - Phonological language processing (left)	Dorsal - Nausea - Vomiting - Balance problems - Dizziness - Fatigue - Light sensitivity - Visual problems - Movement impairments Ventral - Nausea - Vomiting - Balance problems - Dizziness - Fatigue - Noise sensitivity - Irritability - Sadness - Nervousness - Feeling "slow" or "foggy" - Difficulty concentrating - Difficulty remembering - Movement impairments Posterior - Dizziness - Noise sensitivity - Sadness - Feeling "slow" or "foggy" - Difficulty concentrating - Difficulty remembering - Visual problems Arcuate fasciculus - Light sensitivity - Noise sensitivity - Sadness- Feeling "slow" or "foggy" - Difficulty concentrating - Visual problems
Superior occipito-frontal fascicle	- Speech - Motor - Language - Sensory - Visual field - Visuospatial cognition - Spatial working memory - Processing speed and simple reaction time	- Headache - Balance problems - Dizziness - Drowsiness - Light sensitivity - Noise sensitivity - Irritability - Feeling "slow" - Difficulty concentrating - Difficulty remembering - Visual problems - Movement impairments

Uncinate fascicle	- Mood regulation - Emotional expression - Interpreting facial expressions - Learning and memory - Language (left)	- Trouble falling asleep - Loss of sleep - Noise sensitivity - Irritability - Sadness - Nervousness - More emotional - Feeling "slow" or "foggy" - Difficulty concentrating - Difficulty remembering

2.4.3 Cerebellum

The cerebellum is a unique part of the brain that is located posteriorly within the skull, inferior to the occipital lobe. Despite the cerebellum being substantially smaller than the cerebrum, it has been shown to contain about four times as many cells as the entire cerebrum (Andersen et al. 1992). Similar to the cerebrum, the cerebellum is separated into two hemispheres by the cerebellar vermis and consists of three lobes; the anterior, posterior and flocculonodular lobes (Andersen et al. 1992; Ashida et al. 2018; Diedrichsen et al. 2009). Each lobe is also separated into lobules, which can be further separated into folia (Andersen et al. 1992). The cerebellum has 10 lobules known as I, II, III, IV, Crus I, Crus II, VIIb, VIIIa, VIIIb, IX, and X on each cerebellar hemisphere (Ashida et al. 2018; Diedrichsen et al. 2009)(Figure 2.3). These lobule regions are organized with distinctions between lobules from the superior to inferior external surface (Ashida et al. 2018; Diedrichsen et al. 2009).

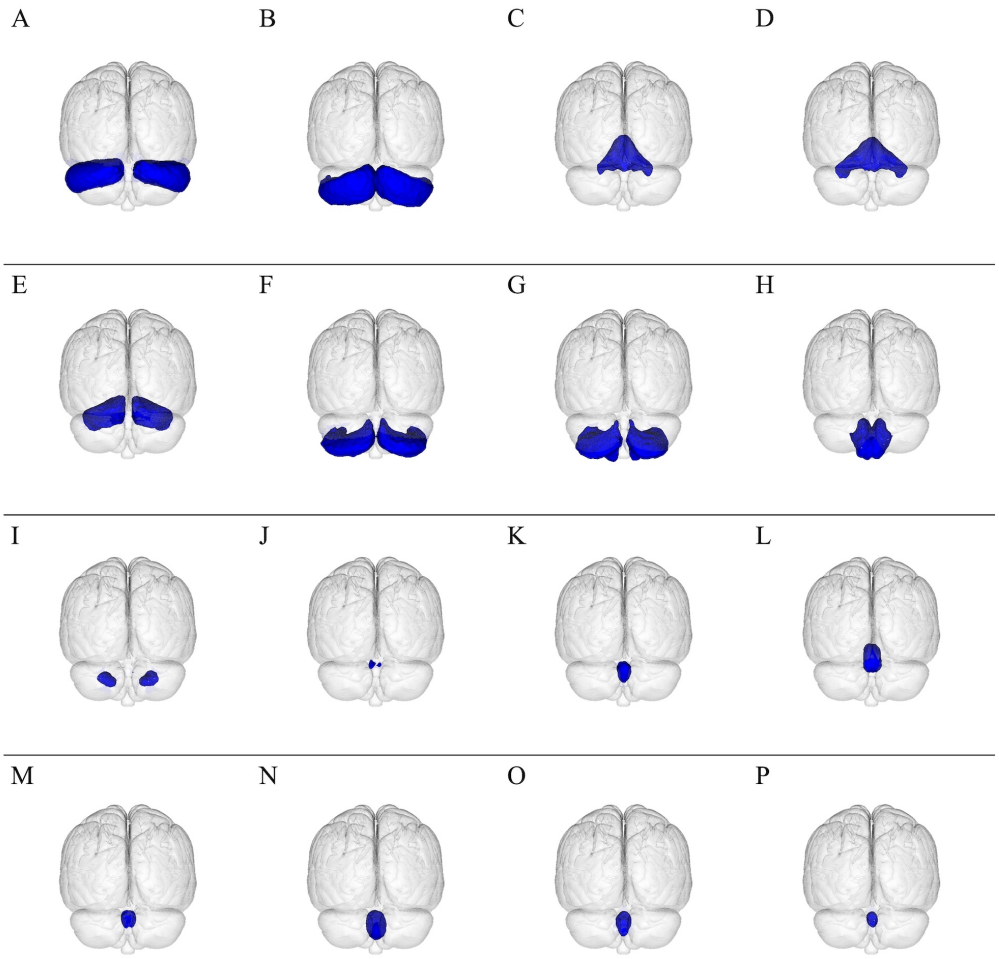

FIGURE 2.3: Visualization of the cerebellum subdivisions overlayed onto the MNI152 1mm standard space T1-weighted brain from the posterior, frontal plane perspective. There are 16 cerebellar regions in this figure, organized as follows: (A) crus I, (B) crus II, (C) I-IV, (D) V, (E) VI, (F) VII, (G) VIII, (H) IX, (I) X, (J) vermis crus I, (K) vermis crus II, (L) vermis VI, (M) vermis VII, (N) vermis VIII, (O) vermis IX, and (P) vermis X. These brain regions were from the Probabilistic (FNIRT) cerebellar atlas (Diedrichsen et al. 2009).

From a cognitive and functional perspective, our understanding of the cerebellum has undergone a revolution. For around 200 years, the cerebellum was believed to be strictly involved with motor control (Schmahmann et al. 2019). However, the advent of functional medical imaging techniques have allowed for the realization that the cerebellum is involved in motor control, language, attention, working memory, emotion, and social processing (Guell and Schmahmann 2020; Marek et al. 2018; Schmahmann et al. 2019). Functional MRI studies have

shown that the cerebellum and its lobules can be subdivided into 2 motor regions and 3 non-motor regions (Guell and Schmahmann 2020). Based on a summary article by Guell and Schmahmann (2020), lobules I-IV make up the first motor region, lobule VI and crus I make up the first non-motor region, crus II and lobule VIIb make up the second non-motor region, lobule VIII makes up the second motor region, and lobules XI and X make up the third non-motor region (Guell and Schmahmann 2020). Although the primary functions of the cerebellum, motor, attentional/executive and default mode network activation, are expressed quite generally across the lobules, the less involved functions of emotional, vestibular, language and social processing are exhibited in more specific cerebellar regions (Guell and Schmahmann 2020)(Table 2.3). Emotional processing has been found close to the cerebellar vermis and thus is more associated with the crus I and crus II vermal aspects (Guell et al. 2018; Guell and Schmahmann 2020). Vestibular activation has been found on the vermal aspects of lobules Crus I, Crus II and VII, and lobules IX and X (Manto and Mariën 2015), however this activation may overlap with visual, emotional, and other motor functions (Guell and Schmahmann 2020). Similar to the lateralization of the cerebrum, the language activation is lateralized contralaterally to the cerebrum and found in the right cerebellar hemisphere (Guell and Schmahmann 2020; Marien et al. 2001). Finally, social cognition overlaps greatly with the default mode network activation in the cerebellum, which can be generally seen in the crus I, crus II, XI and X lobules (Guell et al. 2018; Guell and Schmahmann 2020). Due to the vast number of functions associated with the cerebellum, further research is required to determine the risk of injury to the cerebellum during a concussive event and what post-concussion symptoms could be linked to regional functional abnormalities.

TABLE 2.3: Cerebellar regions and their associated functions and concussion-related symptoms, based primarily on the summary provided by Guell and Schmahmann (Guell and Schmahmann 2020).

Brain region	**Associated functions**	**Concussion-related symptoms**
I	- Motor	- Balance problems - Feeling "slow" - Movement impairments
II	- Motor	- Balance problems - Feeling "slow" - Movement impairments
III	- Motor	- Balance problems - Feeling "slow" - Movement impairments
IV	- Motor - Attention - Executive functions - Default mode processing	- Headache - Balance problems - Feeling "slow" or "foggy" - Difficulty concentrating - Movement impairments
Crus I	- Attention - Executive functions - Default mode processing - Emotion - Vestibular - Social cognition	- Headache - Balance problems - Dizziness - Irritability - Sadness - Nervousness - More emotional - Feeling "slow" or "foggy" - Difficulty concentrating
Crus II	- Attention - Executive functions - Default mode processing - Emotion - Vestibular - Social cognition	- Headache - Balance problems - Dizziness - Irritability - Sadness - Nervousness - More emotional - Feeling "slow" or "foggy" - Difficulty concentrating
VII	- Attention - Executive functions - Default mode processing - Vestibular	- Headache - Balance problems - Dizziness - Feeling "slow" or "foggy" - Difficulty concentrating
VIII	- Motor	- Balance problems - Feeling "slow" - Movement impairments

IX	- Attention - Executive functions - Default mode processing - Vestibular - Social cognition	- Headache - Balance problems - Dizziness - Feeling "slow" or "foggy" - Difficulty concentrating
X	- Attention - Executive functions - Default mode processing - Vestibular - Social cognition	- Headache - Balance problems - Dizziness - Feeling "slow" or "foggy" - Difficulty concentrating

2.5 Conclusions

This review aimed to highlight the intimate connection between post-concussion symptoms in the event of concussion-related damage to specific brain regions. A complete incorporation of all brain structures and post-concussion symptoms was not feasible, especially considering spatial resolution limitations of medical imaging techniques for very small brain regions, and thus this review is understandably not exhaustive at that scale.

The heterogeneity of concussions has challenged clinicians and patients alike. Although further research should be directed into determining why some individuals seem more susceptible to worse post-concussion symptoms and a lengthy recovery, symptom presentation and personalized, injury-specific treatment for concussions can be more readily understood by knowing the functional and anatomical characteristics of the brain. Unfortunately, identifying that a concussion patient is suffering from light sensitivity and has visual cortex and optic radiation abnormalities, for example, does not guarantee their complete recovery. However, the summed knowledge we present here can help patients rationalize their symptoms and allow clinicians to focus their efforts on injury and patient-specific treatment options.

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Chapter 3

Diffusion tensor imaging and fractal complexity of resting state functional MRI

3.1 Overview

3.1.1 Context of the study

The acute and chronic clinical diagnoses of concussion-related brain injuries are subjective, and routine clinical magnetic resonance imaging (MRI) scans fail to detect microstructural or functional damage. Fortunately, advanced MRI techniques such as diffusion tensor imaging (DTI) and functional MRI (fMRI) scans are able to quantify microstructural and functional brain changes, respectively.

By implementing a Z-scoring analysis using a large normative dataset, personalized regional abnormalities in retired, aging professional (American-style) football players could be identified and quantified for each subject. The exact effects of concussions and repetitive sub-concussive impacts in athletes later in life remains inconclusive, and an individualized assessment of concussion-related brain damage has rarely been implemented. The results of this study revealed very little microstructural damage present in the retired athletes; however, 8 of the 17 athlete subjects had numerous functional abnormalities.

3.1.2 Declaration statement

Ethan Danielli, as first author, was involved in the study conceptualization, data curation, methodology, data processing, formal statistical analysis, writing of the original draft, and revisions to the final manuscript. Nicholas Simard, as second author and another PhD candidate with Dr. Noseworthy, was involved in data curation, data processing, formal analysis, methodology, and revisions to the final manuscript. Dr. Bhanu Sharma, as third author on this project and a Post-Doctoral Fellow with Dr. Noseworthy, provided instrumental revisions to the manuscript. Mitchell Doughty, as fourth author and former MASc student in the research group, was involved in the recruitment of subjects, data acquisition, data curation, methodology, and revisions to the final manuscript. Finally, Dr. Michael D. Noseworthy, as the corresponding author and primary investigator of our research group, was involved in the study conceptualization, data curation, funding acquisition, investigation, methodology, statistical analysis, resources, supervision, and revisions to the final manuscript.

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3.2 Functional, but minimal microstructural brain changes present in aging Canadian football league players years after retirement

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3.2.1 Abstract

Introduction: This brain imaging study examined subjects with a history of repetitive concussive and sub-concussive impacts sustained over the course of their careers in the Canadian Football League (CFL). We hypothesized that microstructural and functional abnormalities, assessed using diffusion tensor imaging (DTI) and resting state functional magnetic resonance imaging (rsfMRI) respectively, would be present in these retired athletes, that are not present in matched controls.

Materials & methods: Seventeen aging, retired CFL players (aged 58.5±6.2y, ranged 45–66) completed three neuropsychological tests, and had anatomical, diffusion and functional MRI scans performed. Healthy age- and sex-matched control data (n= 2117) were used to develop a subject-specific and region-wise Z-scoring approach. Regional DTI fractional anisotropy (FA) and rsfMRI signal complexity (fractal dimension; FD) Z-score data was further analyzed as a subject-specific total, left, and right injury burden (IB) value for each MRI metric.

Results: Microstructural abnormality was detected in 6 of 17 subjects based on DTI FA. The rsfMRI data showed 4 subjects with higher total FD_{IB}, and several regions had Z-score outliers detected in multiple subjects. The right pre-motor cortex, right hippocampus dentate gyrus, and right visual cortex were the most abnormally functioning grey matter brain regions. Total FA_{IB} was negatively correlated with career length, social functioning, and significantly with emotional well-being, and positively correlated with physical health. Total FD_{IB} was negatively correlated with energy and fatigue and general health, and positively correlated with age, career length, and education.

Conclusion: This study provides evidence of brain changes years after professional athletes have retired.

Key words: Repetitive concussive impacts, DTI, fMRI, Concussion, Retired athletes

Abbreviations: BDI-II, Beck Depression Inventory-II; CEI, Cognitive Efficiency Index; dMRI, Diffusion Magnetic Resonance Imaging; DTI, Diffusion Tensor Imaging; EFAT, Energy and Fatigue; EH, Emotional Health; EWB, Emotional Well-Being; FA, Fractional Anisotropy; FD, Fractal Dimension; GH, General Health; IC, Impulse Control; ImPACT, Immediate Post-concussion Assessment and Cognitive Testing; MS, Motor Speed; NPC, Number of Previous Diagnosed Concussions; PHF, Physical Functioning; PHH, Physical Health; ROI, Region-of-Interest; rsfMRI, Resting State Functional Magnetic Resonance Imaging; RT, Reaction Time; SF-36, Short Form Survey Instrument; SOFU, Soial Functioning; VBM, Verbal Memory; VIM, Visual Memory; YSLC, Number of Years Since Last Concussion.

3.2.2 Introduction

Contact, collision, and combat sports expose athletes to an increased risk of sustaining a concussion (Gardner et al. 2019; Majdan et al. 2016; Zuckerman et al. 2015). About 90% of adults will recover from a concussion in the first 10–14 days, however, many people suffer from lasting post-concussion symptoms (Hon et al. 2019; McCrory et al. 2017). Despite some contradictory findings (Belanger et al. 2016; Dierijck et al. 2018), recent research has shown that repetitive sub-concussive head impacts can also lead to short- and long-term microstructural and functional brain changes (Di Virgilio et al. 2019; Fickling et al. 2021; Mainwaring et al. 2018; Poole et al. 2015; Slobounov et al. 2017; Tsushima et al. 2019). Although rule changes and equipment are regularly updated to protect athletes from sustaining head injuries, concussions still occur in practices and games in all levels of play (Levy et al. 2004; Mack et al. 2021; McKeithan et al. 2019; Nauman et al. 2020; Stemper et al. 2019; Zuckerman et al. 2015). Specifically, male American college football players had a sport-related concussion incidence rate of 6.71 per 10,000 athletic exposures (30.07/10,000 from competition; 4.20/10, 000 from practice), with about 57% of those concussions being sustained during practice (Zuckerman et al. 2015). Meanwhile, a recent study concluded that the average National Football League player would experience about 1000 head impacts in their professional career, but that number can vary greatly for certain positions (i.e., the offensive and defensive linemen) who experience a far higher than average number of head impacts (Karton et al. 2020). Although retired professional athletes are not in need of improved concussion diagnostic tools, it is important to better understand the effects of repetitive sub-concussive and concussive head impacts on aging brain health to determine if there are lasting complications.

Several magnetic resonance imaging (MRI) techniques have demonstrated utility in research settings with respect to characterizing acute and chronic concussion pathology (Chamard and Lichtenstein 2018; Danielli et al. 2020). Diffusion MRI (dMRI) can be used to assess microstructural brain health based on the degree of restriction of water diffusivity in the myelin surrounding central nervous system axons (Alexander et al. 2019). Using a dMRI technique, such as diffusion tensor imaging (DTI), allows for the quantitation of brain white matter health and

relative axonal integrity. This approach is sensitive to the degree of axonal shearing and tearing that has been demonstrated following concussive forces (Asken et al. 2018; Gonzalez et al. 2021; Stillo et al. 2021; You et al. 2019). As a compliment to dMRI, functional MRI (fMRI) allows for the assessment of grey matter health and cognition through the blood oxygen-level dependent (BOLD) signal (Ogawa et al. 1990; Smitha et al. 2017). Resting state fMRI (rsfMRI) allows for an assessment of overall, base-level brain function without the complication of subject-based task heterogeneity/performance (Mak et al. 2017; Smitha et al. 2017). One method to measure signal complexity is through use of temporal fractals. Assessment of rsfMRI using a temporal fractal approach, a way to estimate signal complexity, is ideally suited for studying brain function in a heterogenous clinical population such as seen with concussion (Dona et al. 2017; Herman et al. 2011). Both DTI and fMRI can allow for a connection between post-concussion symptom presentation and the underlying health and function of specific brain regions.

Although extensive research has been conducted on concussions using dMRI and fMRI techniques, most analyses have been group-wise and few studies have examined subject-specific symptoms and brain damage (Dona et al. 2017; Stillo et al. 2021). There is merit in determining brain regions that are especially vulnerable to injury, but each concussion is unique to the individual's physiological properties and the forces applied during the concussive event. Therefore, new research assessments should incorporate patient-specific clinical measurements. This concept lays the foundation for the current study, which aimed to assess the presence of microstructural and functional abnormalities using DTI and rsfMRI, respectively.

In this study we examined subjects who have a history of repetitive concussive and sub-concussive injuries sustained over the course of their professional athletic career in the Canadian Football League (CFL). The aim of the study was to conduct a microstructural and functional brain study using DTI and rsfMRI, respectively, to identify and quantify the possible lasting effects of concussive brain injuries in aging, professional athletes. It was hypothesized that aging, retired CFL (rCFL) players would express both microstructural and functional abnormalities, and that several regions would be more commonly abnormal, suggestive of a concussion-related injury, than others. Also, we hypothesized that cortical

brain regions, relative to deep brain structures, and longer white matter fibre tracts would be more commonly injured because they are more vulnerable to the effects of rotational forces produced during a concussive event such as stretching, shearing, and tearing.

3.2.3 Material & methods

Demographics

This study was approved by our local research ethics board and the work described was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Seventeen rCFL players (all male, aged 58.5 ± 6.2y, range 45–66) were recruited to participate in this study through local newspaper advertisements in Southern Ontario, Canada. Informed, written consent was obtained for all subjects prior to participation and the privacy rights of human subjects were observed. Subjects were excluded from the study if they had documented substance abuse, diagnosed neurological or psychiatric illness, had sustained any concussion in the past 5 years, or had any health condition that required daily treatment/therapy (e.g., diabetes, cancer). A neuroradiologist also reviewed the MRI scans to rule out possible co-morbidities (e.g., microstrokes, T2 hyperintensities, profound ventricular hypertrophy and brain atrophy (beyond that of normal aging), brain lesions visually causing structural damage), and no former player included in the study had brain abnormalities visible at the time of the study. Demographic information collected included age, sport position of play (position: i.e., certain positions have higher likelihood of repeated head impact) (Baugh et al. 2015; Karton et al. 2020), career length (career), years of education (education), number of previous diagnosed concussions (NPC), and the number of years since their last known concussion (YSLC) (Table 3.1). Education, NPC and YSLC were only available for 14 subjects.

Healthy control MRI data was downloaded from Neuroimaging Tools and Resources Collaboratory (NITRC) (*www.NITRC.org*) (Kennedy et al. 2016) and Imaging Data Archive (IDA)(*https* : *//ida.loni.usc.edu/*) (Crawford et al. 2016). The healthy control data was age and sex matched to the rCFL players resulting in

1208 3D anatomical and functional (male, aged 59.7 ± 7.8, ranged 43–68) brains and 2117 brains for DTI analysis (male, aged 61.0 ± 6.0, ranged 43–68). Healthy control subjects included in these online databases were screened as healthy with no previous brain conditions or concussions.

TABLE 3.1: Demographic and concussion history summary for each subject including age, the type of head impacts associated with their football position (position), career length, years of education, number of previous diagnosed concussions (NPC), and the number of years since their last concussion (YSLC).

Subject	**Age (years)**	**Position**	**Career (years)**	**Education (years)**	**NPC**	**YSLC (years)**
1	55	1	1	16	4	7
2	60	1	6	-	-	-
3	60	1	11	16	2	36
4	49	1	3	18	2	27
5	65	2	4	16	6	38
6	62	2	6	-	-	-
7	57	2	5	19	2	33
8	48	2	9	18	3	16
9	60	1	13	17	2	32
10	58	1	12	15	11	27
11	46	1	13	17	1	13
12	66	1	11	16	1	45
13	66	2	6	18	4	39
14	63	1	14	19	3	36
15	61	1	3	17	2	37
16	55	1	7	-	-	-
17	64	1	11	16	3	36
	58.5±6.2	1.3±0.5	7.9±4.1	17±1.2	3.3±2.6	30.1±11

Note: The type of head impacts associated with football positions was based on the frequency and magnitude of contact during practice and play. A positional value of 1 equates to low impact, high frequency head impacts, and a value of 2 equates to high impact, low frequency head impacts. Dashes (-) indicate that data for that particular metric was not available for that subject. The bottom row contains the mean and standard deviation for each column.

Neuropsychological assessment

Sixteen of the 17 subjects completed neuropsychological testing. First, the Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) was used to assess verbal memory (VBM), visual memory (VIM), motor speed (MS), reaction time (RT) and impulse control (IC) and provide a cognitive efficiency index

(CEI) score (Allen and Gfeller 2011). Second, the Beck Depression Inventory-II (BDI-II) was used to assess depressive symptoms (Smarr and Keefer 2011). Third, the Short Form Survey Instrument (SF-36) was used to assess physical functioning (PHF), physical health (PHH), emotional health (EH), energy and fatigue (EFAT), emotional well-being (EWB), social functioning (SOFU), pain, and general health (GH) (Ware 2000).

MRI acquisition protocol

The rCFL subjects were scanned using a 3T GE MR750 Discovery MRI system and 32-channel head and neck coil (GE Healthcare, Milwaukee, WI). Anatomical, microstructural, and functional scans were acquired for each subject. The anatomical scan was a high-resolution axial 3D T1-weighted inversion-recovery prepared fast spoiled gradient (IR-prepped fSPGR) sequence; (TR/TE/TI = 11.34 ms/4.25 ms/450 ms; flip = 12°; 256 × 256 matrix, slice thickness = 1 mm, FOV = 25.6 cm, number of slices = 140, 1 mm isotropic acquisition). Microstructural quantitation was done using a dual spin echo, echo-planar imaging (EPI) DTI sequence (60 non-coplanar directions, TR/TE = 8800 ms/87 ms, flip angle = 90°, b = 1000 s/mm^2, 6 non-diffusion weighted images (i.e., b= 0 s/mm^2), number of slices = 70, slice thickness = 2 mm, FOV = 24.4 cm, matrix = 122 × 122, ASSET = 2 i.e., 2 mm isotropic resolution). The functional (resting state functional MRI, rsfMRI) was done with eyes closed using a gradient echo EPI sequence (TR/TE/flip = 2000 ms/35 ms/90°, slice thickness = 4 mm, space between slices = 4 mm, FOV = 22 cm, matrix = 64 × 64, time points = 240). The healthy control data, downloaded from several repositories and studies, had similar scan parameters and was acquired with the same scanner type (vendor and field strength) (Crawford et al. 2016; Kennedy et al. 2016).

MRI data processing

Pre-processing of the raw MRI data included brain extraction, eddy current corrections and data warping to the MNI152 T1-weighted 1 mm standard brain space for further processing (Jenkinson et al. 2012; Saad et al. 2009). The FSL "flirt" command with 12 degrees of freedom and a linear affine registration was

used to register all healthy brains into one standardized space (Jenkinson and Smith 2001; Jenkinson et al. 2002; Greve and Fischl 2009).

The DTI data was processed using the FSL commands "bet", "eddy" (Smith 2002; Andersson and Sotiropoulos 2016) and "flirt" (Jenkinson and Smith 2001; Jenkinson et al. 2002; Greve and Fischl 2009) to perform preprocessing steps of brain extraction, eddy current correction and linear registration to the MNI152 T1-weighted 2 mm standard space. The FSL program "dtifit" was used to calculate the DTI metric fractional anisotropy (FA) (Behrens et al. 2003; Behrens et al. 2007). This was the only DTI metric considered because FA was the most sensitive measure of concussion damage shown in our previous work (Stillo et al. 2021). Voxel-wise maps were used to compare each rCFL subject's DTI data against the normative dataset's mean and standard deviation values to calculate regional Z-scores. Eighteen ROI masks from the Juelich Histological Atlas and the JHU DTI-based White Matter Atlas (Hua et al. 2008; Mori et al. 2005; Wakana et al. 2007) were used to segment voxel-wise white matter FA maps to determine region-wise Z-score values for each rCFL subject relative to the normative dataset. Therefore, a regional Z-score value calculated for FA allowed for personalized assessment of brain microstructural abnormality.

Using a series of proprietary algorithms (TBIfinder software (TBIFinder Inc. 2021)), the gray matter was segmented into 91 ROIs from the functional data using ROI masks based on the Juelich Histologic Atlas (Eickhoff et al. 2005; Eickhoff et al. 2006; Eickhoff et al. 2007). Data from these masks were further analyzed to calculate rsfMRI temporal complexity (Hurst exponent and fractal dimension, FD) (Dona et al. 2017). Similar to the DTI approach, region-wise Z-score maps were then calculated to compare each subject's temporal complexity against the normative dataset.

Statistical analysis

The approach described provided personalized analysis of each individual's brain. However, because the ROI based analysis was not directly comparable to neuropsychological testing, which often results in a summary score, a way to determine subject-specific abnormality severity was needed for each MRI metric.

Based on our previous work (Stillo et al. 2021), injury burden (IB) was classified as grade 1 ($-3.0<Z\leq-2.0$), grade 2 ($-4.0<Z\leq-3.0$), or grade 3 ($Z\leq-4.0$). We calculated a total IB score based on the numbers of both left and right abnormal ROI values. Using IB to describe the presence and quantity of brain injuries is a novel method. By distilling an individual's graded brain injury into a single value provides the opportunity to rationalize the state of a single person's brain health and compare MRI metrics, such as FA and FD, between subjects, and more easily against clinical post-concussion presentation (Stillo et al. 2021).

Based on the literature, we assumed that concussive brain injuries result in lower regional DTI FA for damaged white matter (Asken et al. 2018; Schneider et al. 2019). Therefore, IBs for FA were based only on outliers that were at least 2 standard deviations lower than the normative mean (i.e., from the healthy control data). For the rsfMRI data, it was expected that signal complexity would decrease relative to the healthy normative data (i.e., reduced functional complexity (Dona et al. 2017)). The IB values were then compared against the demographic and neuropsychological data through a series of multiple linear regressions and correlations with the level of significance set at $p = 0.05$. All statistical tests were conducted using R software (Rstudio version 1.3.1093).

3.2.4 Theory/calculation

Theory

Concussions have proven to be a challenge for both clinicians and patients due to the unpredictable nature of symptom onset and resolution (McCrory et al. 2017). Moreover, evidence of lasting brain damage in a portion of concussion patients has spurred research into understanding why some individuals are more susceptible to a prolonged recovery, and what the long-term consequences are of repetitive sub-concussive and concussive forces to the head and brain. Until now, there have been limited options for a clinically available quantitative objective concussion diagnosis tool (Chamard and Lichtenstein 2018; Danielli et al. 2020). The aim of our current work was to apply a novel subject-wise statistical approach to examine the functional and microstructural health of former professional athletes with a history of experiencing repetitive concussive and sub-concussive head blows. With

these athletes there is no way to understand how many blows to the head they may have received, or to provide a total measure of the damaging forces the brain may have been subjected to over their careers. The benefit of our methodology is that it can objectively identify and grade brain anomalies, which can then be used in streamlining diagnosis and treatment of those suffering from post-concussion syndrome (PCS) (Stillo et al. 2021). This could allow for future personalized diagnoses, the possibility to target treatment, and the ability to track recovery more precisely over time.

Calculation

The statistical methods implemented in this study relied on the use of large normative datasets. Gaussian behavior for FA and FD, in each normative ROI over all brains, was determined as valid. Calculations were performed to estimate control numbers required. Interim analysis was performed on 20 random healthy control subjects during our previous work (Stillo et al. 2021). A sample size (n) for a Z-distribution was calculated from the Cochran method: n = (Z-score)^2 • σ (1-σ) / E^2. For our proposed work, a false negative rate of 1% is ideal, where our worst-case error is 1.01% (Stillo et al. 2021). Thus, with power = 0.01 (i.e., Z = 2.58), standard deviation of 1.01% (worst case), and a 1% margin of type I error would require 2.582 × 0.0101(1–0.0101)/0.012 = 665.506, or 666 normal controls. However, in a worst-case scenario, a 5% false negative rate (i.e., 2.242 × 0.0101(1–0.0101)/0.05 = 51.6296, or n = 50 healthy controls was deemed acceptable. Although over 1700 normal, healthy controls were used in our study, former athletes were age matched where each had greater than 100 healthy brains as a comparison set. Thus, we assumed our false negative rate as being between 1% and 5%.

3.2.5 Results

Regions-of-interest

Within-group analyses were used to identify the location of, and quantify the grade of, brain abnormalities using a Z-scoring approach. Therefore, outlier Z-scores falling outside 2 standard deviations of the normative mean were assumed

indicative of previous concussion-related brain damage. Exploring DTI results, the mean FA Z-score was decreased in 14 of the 18 ROIs. The only ROIs with increased mean FA were the left and right superior occipito-frontal fascicle and uncinate fascicle (Table 3.2). Subject 2 had positive outliers for both the left and right cingulum. Thus, outliers greater than the normative mean from subject 2 were not included in the subsequent IB counts because only FA decreases were assumed associated with concussion-related brain abnormality. The specific ROI with the most FA outliers across all subjects was the left cingulum with two outliers, while the left acoustic radiation, right cingulum, right inferior occipito-frontal fascicle, left optic radiation, and left superior longitudinal fascicle had a single grade 1 (i.e. $-3.0<Z\leq-2.0$) FA outlier.

Regarding the rsfMRI results, at least one Z-score outlier was detected in 48 of the 91 ROIs that were examined across all subjects (Table 3.3). Only the ROIs are shown that had at least one outlier being classified as grade 1 or greater (i.e. 43 ROIs are not included as they appeared within normative values). All outliers were below the normative mean indicating reduced rsfMRI BOLD signal complexity in these regions. The ROIs with the most outliers were the right pre-motor cortex BA6 (n= 4), right hippocampus dentate gyrus (n= 3), right visual cortex V1 BA17 (n= 3), and right visual cortex V2 BA18 (n= 3).

Subject-wise Z-scores and injury burden

Microstructural and functional metrics were used to calculate Z-scores for each subject relative to a large normative dataset. Injury burden (IB) scores were calculated as a composite of Z-scores. From the DTI FA Z-scores outliers, we found that 6 of the 17 subjects had outliers. The FA_{IB}s were only based on decreased FA Z-scores, relative to the normal mean values (FA is expected to decrease following a concussive injury). Subject two had 2 FA outliers, however they were both above the normal FA mean value. Therefore, we did not include subject two's FA outliers and found that 5 of the 17 subjects had FA Z-score outliers to contribute to their FA_{IB} score (Table 3.2 & 3.4). Subject six had a total FA_{IB} of 3 (Fig. 3.1), while the other four subjects each had a total FA_{IB} of 1. All FA outliers were grade 1 (i.e., $(-3.0<Z\leq-2.0)$.

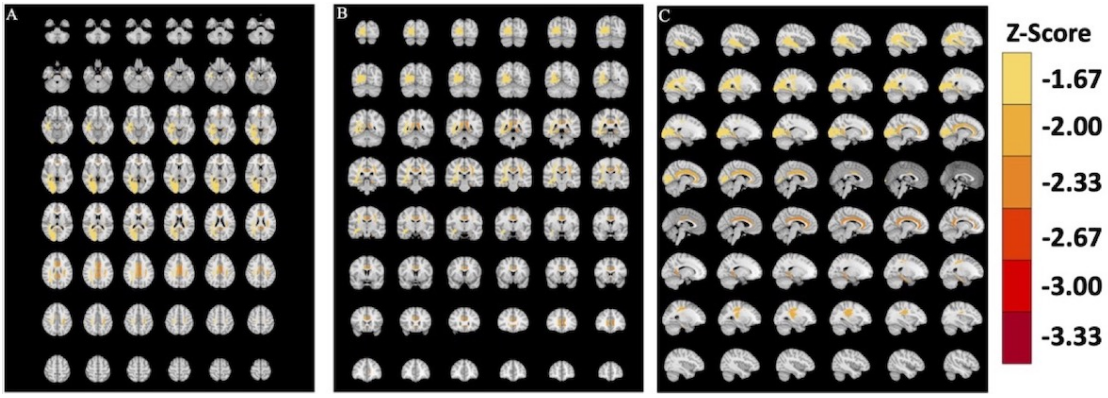

FIGURE 3.1: A colour coded visualization of the personalized DTI-based fractional anisotropy (FA) Z-scores from a subject who sustained a total FA injury burden (IB) of 3. The Z-score outliers, indicative of injury, were detected in the left superior longitudinal fascicle and the left and right cingulum. The figure legend colours are scaled from light orange to maroon to represent smaller Z-score outliers indicative of mild brain injury and larger Z-score outliers indicative of more severe brain injury, respectively. Outlier Z-scores greater than 2 were considered significant, and therefore indicative of an abnormality. Fig. 3.1 is separated into three to show the injured ROI from the axial (A), coronal (B) and sagittal (C) perspectives.

From the rsfMRI Z-scores, the FD_{IB}s were based on decreased Z- scores because all the outliers were calculated to be below the normative mean. FD Z-score outliers were detected in 8 of the 17 subjects. Four subjects had a low FD_{IB} (1, 1, 2, 6), however the other four subjects had higher FD_{IB} (9, 11, 15, 28)(Table 3.3 & 3.4). The left and right FD_{IB} was also calculated for each subject. Of the 8 subjects who had a FD_{IB} >0, three had bilateral IBs while the other five were unilateral. Subject 14 had the abnormalities calculated with a total FD_{IB} of 28, a left FD_{IB} of 11, and a right FD_{IB} of 17 (Fig. 3.2). Subject 14 had four grade 2 abnormalities (i.e., $-4.0<Z\leq-3.0$) and subject 17 had one grade 2 abnormality, however the other six subjects' FD outliers were all grade 1 (i.e., $-3.0<Z\leq-2.0$).

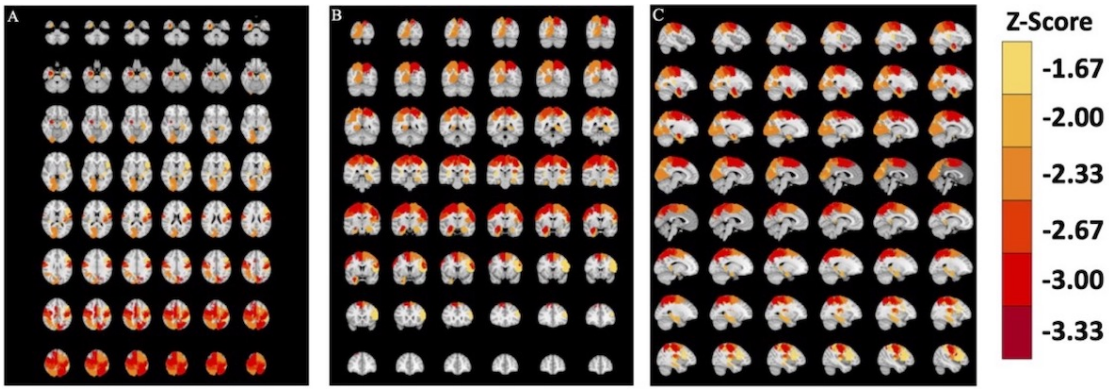

FIGURE 3.2: A colour coded visualization of the personalized rsfMRI-based fractal dimension (FD) Z-scores from a subject who sustained a total FD injury burden (IB) of 28, with a left IB of 11 and right IB of 17. The Z-score outliers were detected in the right amygdala laterobasal group, right anterior intra parietal sulcus hIP1, right anterior intra parietal sulcus hIP3, left hippocampus cornu ammonis, right hippocampus entorhinal cortex, left premotor cortex BA6, right pre-motor cortex BA6, left primary motor cortex BA4a, right primary motor cortex BA4a, right primary motor cortex BA4p, right primary somatosensory cortex BA1, right primary somato- sensory cortex BA2, right primary somatosensory cortex BA3a, left primary somatosensory cortex BA3b, right primary somatosensory cortex BA3b, left secondary somatosensory cortex OP2, left secondary somatosensory cortex OP3, left superior parietal lobule 5 L, left superior parietal lobule 7A, right superior parietal lobule 7A, left superior parietal lobule 7P, right superior parietal lobule 7P, right visual cortex V1 BA17, and right visual cortex V2 BA18. The figure legend colours are scaled from light orange to maroon to represent smaller Z-score outliers indicative of mild brain injury and larger Z-score outliers indicative of more severe brain injury, respectively. Outlier Z-scores greater than 2 were considered significant, and therefore indicative of an abnormality. Fig. 3.2 is separated into three to show the injured ROI from the axial (A), coronal (B) and sagittal (C) perspectives.

TABLE 3.2: A heatmap table of the fractional anisotropy (FA) Z-score values for each region-of-interest (ROI) for each subject. This heatmap table is color coordinated to indicate Z-score values that are positive outliers (yellow), within the normative range (orange), and negative outliers (red). The personalized Z-scores were calculated in relation to a large normative age and sex matched control sample. Regarding brain injuries, FA Z-scores 2 or more standard deviations below the normative mean were considered abnormal and damaged, and are indicated in the heatmap table as coloured red.

	Subject																
Region-of-interests	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Acoustic Radiation Left	-1.03	-0.40	-1.87	-0.63	-1.04	-1.26	-2.06	-0.89	-0.17	0.15	-1.13	-0.68	-1.12	-1.48	-0.84	-1.53	-1.67
Acoustic Radiation Right	-1.24	0.37	-1.06	-0.82	-0.51	-1.11	-1.72	-0.23	0.25	-0.25	-0.61	-0.73	-1.03	-0.59	0.29	-1.82	-1.67
Callosal Body	-0.91	-0.01	-0.04	-0.78	-0.16	0.15	-0.45	-0.37	-0.08	0.35	-0.37	-0.24	0.00	-0.33	0.06	-1.07	-0.32
Cingulum Left	-2.04	2.79	-0.28	-0.47	-0.57	-2.42	-0.99	-0.95	-0.18	-1.55	-1.53	-0.76	-0.02	-1.98	-1.72	-1.03	-0.61
Cingulum Right	-1.17	2.47	-0.15	-0.19	-0.57	-2.04	-1.15	-0.64	0.20	-1.26	-1.43	-0.37	-0.11	-1.19	-1.33	-1.09	-0.78
Corticospinal Tract Left	-0.66	0.08	-1.96	-0.75	-0.02	-1.64	-0.39	-0.33	0.15	-1.01	-0.70	-0.53	-0.40	-0.89	-0.64	-1.00	-0.15
Corticospinal Tract Right	-1.56	0.78	-1.68	-0.85	-0.38	-1.60	-1.52	-0.31	-0.14	-0.51	-0.56	-0.35	-0.62	-1.14	-0.48	-1.82	-0.27
Fornix	0.83	-1.10	-0.54	-1.10	0.02	1.22	-0.34	-0.91	-0.65	1.64	-0.18	-0.05	-0.36	-0.49	1.01	-1.45	-0.12
Inferior Occipito Frontal Fascicle Left	-1.63	0.53	-0.15	-0.58	0.58	-0.16	-0.11	-0.99	-0.07	0.27	-0.44	0.59	-0.12	-0.38	-0.19	0.15	-0.74
Inferior Occipito Frontal Fascicle Right	-1.74	-0.71	-0.45	-1.43	-1.11	-1.09	-0.53	-1.60	-2.04	-1.02	-0.94	0.41	-1.19	-1.49	-1.05	-1.13	-1.85
Optic Radiation Left	-1.73	0.55	-1.49	-0.70	-0.95	-1.37	-0.83	-0.59	-1.32	-1.11	-0.93	-0.84	-1.02	-0.76	-2.11	-0.93	-1.18
Optic Radiation Right	-1.93	-0.12	-1.56	-0.88	-1.32	-1.71	-1.31	-0.96	-1.21	-1.10	-0.76	-0.84	-1.39	-1.23	-1.80	-1.55	-1.38
Superior Longitudinal Fascicle Left	-1.48	-1.40	-1.61	-0.75	-1.04	-2.27	-0.78	-0.38	-1.49	-0.95	-0.56	-0.52	-1.11	-0.62	-0.77	0.15	-0.79
Superior Longitudinal Fascicle Right	-1.02	0.49	-1.00	-1.02	-0.67	-1.68	-0.98	-0.34	-0.96	-0.90	-0.49	-0.38	-1.91	-0.37	-1.13	-0.44	-1.02
Superior Occipito Frontal Fascicle Left	0.43	0.79	0.93	-0.39	0.64	0.72	-0.13	-0.04	1.16	1.31	-0.73	0.08	-0.01	0.67	0.71	-0.24	0.02
Superior Occipito Frontal Fascicle Right	-0.21	0.20	0.70	-0.38	0.80	0.29	0.01	0.57	1.10	1.34	-0.39	0.19	0.00	-0.20	0.83	-0.09	0.33
Uncinate Fascicle Left	1.34	1.68	-0.47	0.24	0.85	1.63	0.16	0.00	0.50	0.13	0.17	-0.25	0.15	0.61	0.68	-0.29	0.32
Uncinate Fascicle Right	-0.64	0.29	0.34	0.08	0.26	0.55	0.69	-0.56	0.14	-0.44	0.00	0.56	-0.28	-0.77	0.25	0.51	-0.69

Note: FA Z-scores 2 or more standard deviations below the normative mean were considered abnormal and may be so because of concussion-related damage. These negative outliers are indicated in red colour and by an asterisk (∗).

TABLE 3.3: A heatmap table of the personalized rsfMRI-based fractal dimension (FD) Z-scores for the 48 ROI that were calculated to have an outlier in at least one subject. This heatmap table is color coordinated to indicate Z-score values that are positive outliers (yellow), within the normative range (orange), and negative outliers (red). The Z-score outliers were identified if they were greater or less than 2 standard deviations from the normative mean value of each ROI. All detected outliers were negative (2 standard deviations below the normative mean).

	Subject																
Region-of-interests	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Amygdala Centromedial Group Right	0.00	-1.07	-0.07	-0.80	-0.10	0.53	-2.44	-0.34	-0.72	-0.16	-0.02	-1.26	-0.73	-1.38	-1.07	0.42	-1.39
Amygdala Laterobasal Group Right	-0.33	-1.04	0.03	-0.75	-0.07	0.33	-0.57	-0.28	-0.76	-0.11	0.15	-1.08	-0.08	-3.03	-1.04	0.36	0.32
Amygdala Superficial Group Right	-0.31	-1.02	0.01	-1.06	-0.05	0.56	-2.77	-0.12	-0.80	-0.11	0.05	-1.09	0.09	-1.33	-1.02	0.38	-0.01
Anterior Intra Parietal Sulcus hIP1 Right	-0.14	0.07	-0.88	0.34	0.10	0.06	-0.09	0.48	-0.85	0.03	0.27	-1.18	-2.10	-2.47	0.06	-0.55	-0.39
Anterior Intra Parietal Sulcus hIP2 Right	-0.62	0.04	-0.90	0.23	0.07	0.03	-0.12	-0.63	-1.04	0.00	0.51	-1.34	-2.12	-1.43	0.04	-0.76	-1.16
Anterior Intra Parietal Sulcus hIP3 Right	-0.23	0.02	-0.70	0.17	0.04	0.01	-0.15	-0.59	-0.78	-0.02	0.43	-0.99	0.35	-2.62	0.01	-0.56	-2.74
Broca Area bA44 Left	0.28	0.01	-0.70	0.23	0.04	-2.87	-0.11	-0.71	-0.78	-0.03	0.56	-1.17	0.03	-1.98	0.01	-0.74	0.00
Broca Area bA45 Left	0.35	-0.04	-0.64	0.25	-0.02	-2.41	-0.14	-0.77	-0.74	-0.08	0.51	-1.11	-0.03	0.09	-0.05	-0.88	-0.05
Hippocampus Cornu Ammonis Left	0.25	-1.20	-0.01	-1.23	-0.20	-0.69	-0.89	-0.40	-0.76	-0.21	-0.54	-0.82	-0.22	-2.27	-1.20	-0.84	-0.24
Hippocampus Cornu Ammonis Right	-0.01	-1.04	0.01	-0.53	-0.06	0.30	-2.09	-0.42	-0.84	-0.10	-0.20	-1.20	-1.95	-1.60	-1.04	-0.69	-2.17
Hippocampus Dentate gyrus Right	0.05	-1.05	0.03	-0.48	-0.07	0.24	-2.34	-0.46	-0.83	-0.11	-0.23	-1.22	-2.20	-1.04	-1.05	-0.82	-2.35
Hippocampus Entorhinal Cortex Left	-0.62	-1.36	-0.55	-1.20	-0.36	-2.25	-1.96	-0.42	-0.81	-0.35	-0.68	-0.60	-0.38	-0.61	-1.36	-0.68	-0.40
Hippocampus Entorhinal Cortex Right	0.19	-1.09	-0.10	-0.97	-0.11	0.21	-1.24	-0.61	-0.83	-0.15	-0.11	-0.74	-0.12	-2.31	-1.09	-0.54	-0.03
Hippocampus Subiculum Right	-0.02	-1.03	-0.03	-0.64	-0.06	0.34	-2.73	-0.42	-0.83	-0.10	-0.14	-1.05	-1.37	-1.34	-1.04	-0.66	-2.80
Inferior Parietal Lobule PF Right	-0.15	-0.93	-1.30	-0.94	0.02	0.02	-0.16	-0.41	-0.98	-0.04	-0.20	-1.09	-2.21	-0.01	-0.93	-0.92	-2.11
Inferior Parietal Lobule PFm Right	-0.43	-0.92	-0.66	-0.80	0.02	-0.02	-0.18	-0.48	-0.86	-0.04	-0.39	-1.17	-2.76	0.01	-0.92	-0.78	-1.10
Inferior Parietal Lobule PFt Right	-0.20	-0.96	-0.72	-1.53	0.01	0.00	-0.17	-0.50	-0.99	-0.05	-0.26	-1.22	-2.88	-0.02	-0.96	-0.77	-0.64
Insula id1 Left	-0.02	-1.11	-0.26	-0.67	-0.11	-2.79	-0.74	-0.28	-0.60	-0.15	-0.54	-0.98	-0.13	-0.78	-1.11	-0.58	-0.15
Insula id1 Right	0.19	-0.96	0.02	-0.78	-0.03	0.30	-0.23	-0.46	-0.79	-0.10	0.02	-1.50	-2.05	0.43	-0.96	-0.52	0.24
Insula ig1 Left	0.02	-1.07	-0.16	-1.16	-0.08	-2.52	-1.94	-0.54	-0.73	-0.14	-0.63	-0.97	-0.09	-1.92	-1.07	-0.71	-0.11
Insula ig2 Left	0.04	-1.04	-0.36	-1.10	-0.04	-2.23	-0.73	-0.57	-0.65	-0.10	-0.68	-0.89	-0.06	-1.95	-1.04	-0.80	-0.08
Lateral Geniculate Body Right	-0.39	-1.13	0.12	-0.54	-0.15	0.37	-2.61	-0.14	-1.14	-0.22	0.22	-1.16	-2.06	-0.84	-1.14	-1.03	-0.37
PreMotor Cortex BA6 Left	0.29	-0.71	-1.71	-1.65	0.06	-1.58	-0.17	-1.95	-0.72	0.07	-2.02	-0.94	-0.02	-2.44	-0.70	0.18	-0.04
PreMotor Cortex BA6 Right	0.22	-2.47	-1.65	-1.65	0.43	-1.80	-0.16	-2.06	-0.84	-0.70	-2.11	-0.79	-0.57	-3.28	-1.70	0.46	0.02
Primary Motor Cortex BA4a Left	0.26	-0.12	-1.11	-0.52	-0.02	-1.09	-0.19	-0.96	-0.78	-0.09	-1.08	-1.03	-0.04	-2.78	-0.13	-0.58	-0.05
Primary Motor Cortex BA4a Right	0.17	0.11	-1.15	-0.75	0.00	0.21	-0.18	-1.13	-0.83	-0.06	-1.28	-1.00	0.50	-2.38	0.11	-0.56	-0.02
Primary Motor Cortex BA4p Left	0.32	-0.56	-0.77	-0.13	0.02	-2.32	-0.15	-0.66	-0.82	-0.04	0.59	-1.07	0.01	-1.82	-0.56	-0.62	-0.01
Primary Motor Cortex BA4p Right	0.18	-0.39	-0.51	-0.12	0.06	0.45	-0.12	-0.67	-0.86	0.00	-0.98	-1.10	-1.35	-2.15	-0.40	-0.63	-0.66
Primary Somatosensory Cortex BA1 Right	-0.02	-0.22	0.42	0.06	-0.05	-0.08	-0.24	-0.82	-0.83	-0.11	0.89	-1.04	-0.86	-2.80	-0.22	-0.54	0.05
Primary Somatosensory Cortex BA2 Right	-0.13	-0.68	0.10	-0.75	0.01	-0.02	-0.18	0.37	-0.82	-0.05	0.39	-1.18	-0.71	-2.68	-0.68	-0.69	-1.19
Primary Somatosensory Cortex BA3a Left	0.31	-0.86	0.36	-0.92	0.04	-2.96	-0.13	0.14	-0.80	-0.02	-0.03	-1.03	0.03	-1.48	-0.86	-0.58	0.01
Primary Somatosensory Cortex BA3a Right	0.16	-0.78	-0.02	-1.28	0.07	-1.03	-0.10	0.10	-0.86	0.02	0.41	-1.16	-2.52	-2.40	-0.78	-0.72	-1.44
Primary Somatosensory Cortex BA3b Left	0.31	-0.63	-0.64	-0.14	0.01	-1.17	-0.16	-0.63	-0.83	-0.06	0.61	-1.02	-0.01	-3.09	-0.63	0.48	-0.03
Primary Somatosensory Cortex BA3b Right	0.18	-0.40	0.43	-0.21	0.04	0.30	-0.14	-0.73	-0.89	-0.02	-0.98	-1.14	-1.77	-2.88	-0.40	-0.60	-0.51
Secondary Somatosensory Cortex OP1 Right	0.35	0.01	0.11	-0.02	0.04	-2.89	-0.14	0.42	-1.00	-0.02	0.83	-1.29	0.25	0.08	0.01	-0.61	-2.38
Secondary Somatosensory Cortex OP2 Left	0.06	-0.06	-0.79	0.12	-0.02	-1.83	-1.05	0.40	-0.63	-0.08	0.48	-0.94	-0.04	-2.87	-0.06	-0.75	-0.06
Secondary Somatosensory Cortex OP3 Left	0.17	-0.03	-0.91	0.20	0.01	-2.03	0.35	-0.67	-0.84	-0.05	0.64	-0.90	-0.01	-2.48	-0.03	-0.77	-0.03
Secondary Somatosensory Cortex OP4 Right	-0.63	0.02	-0.27	-0.23	0.05	-2.88	-0.12	0.48	-0.96	-0.01	0.83	-1.32	0.44	0.02	0.02	-0.50	0.21
Superior Parietal Lobule 5Ci Left	0.06	-0.95	0.20	-0.92	-0.02	-2.21	-0.20	-0.23	-0.61	-0.08	-0.57	-0.95	-0.03	-0.62	-0.95	-0.80	-0.05
Superior Parietal Lobule 5L Left	0.17	-0.44	-0.75	0.16	-0.04	-0.03	-0.21	-0.50	-0.81	-0.10	0.69	-0.92	-0.06	-2.54	-0.45	-0.89	-0.07
Superior Parietal Lobule 7A Left	0.06	-0.92	0.13	-0.74	-0.05	-0.07	-0.23	-0.12	-0.79	-0.10	-0.36	-0.77	-0.07	-3.16	-0.92	-0.68	-0.05
Superior Parietal Lobule 7A Right	-0.01	-0.83	0.08	-0.80	-0.03	-0.05	-0.21	-0.10	-0.75	-0.07	-0.11	-0.89	-0.03	-2.54	-0.83	-0.57	0.28
Superior Parietal Lobule 7M Right	0.00	-0.99	0.05	-1.28	-0.02	-0.02	-0.22	-0.80	-0.82	-0.07	-0.84	-0.71	-0.04	-2.00	-0.99	0.48	-2.74
Superior Parietal Lobule 7P Left	0.06	-1.01	0.11	-1.00	-0.07	-0.09	-0.25	-0.32	-0.77	-0.10	-0.76	-0.85	-0.08	-2.76	-1.02	-0.60	-0.04
Superior Parietal Lobule 7P Right	-0.05	-0.97	-0.11	-1.49	-0.05	-0.07	-0.24	-0.69	-0.73	-0.08	-0.62	-0.88	-0.06	-2.06	-0.97	0.48	-0.06
Visual Cortex V1 BA17 Right	0.04	-1.08	-0.15	-1.25	-0.07	-2.04	-0.25	-0.53	-0.88	-0.12	-0.61	-1.01	0.39	-2.33	-1.08	-0.69	-3.26
Visual Cortex V2 BA18 Right	0.05	-1.08	-0.09	-1.24	-0.07	-2.17	-0.24	-0.48	-0.86	-0.12	-0.55	-0.99	-0.54	-2.54	-1.08	-0.67	-2.69
Visual Cortex V3V Right	0.05	-1.09	0.01	-0.91	-0.08	-2.20	-0.26	-0.41	-0.80	-0.13	-0.16	-1.01	-0.03	-1.34	-1.09	-0.63	-2.89

Note: FD Z-scores 2 or more standard deviations below the normative mean were considered abnormal and may be so because of concussion-related damage. These negative outliers are indicated in red colour and by an asterisk (*).

TABLE 3.4: Summary of the total, left and right injury burden (IB) scores for each subject for the DTI metric fractional anisotropy (FA) and the rsfMRI metric fractal dimension (FD).

Subject	Total FA_{IB}	Left FA_{IB}	Right FA_{IB}	Total FD_{IB}	Left FD_{IB}	Right FD_{IB}
1	1	1	0	0	0	0
2	0	0	0	1	0	1
3	0	0	0	0	0	0
4	0	0	0	0	0	0
5	0	0	0	0	0	0
6	3	2	1	15	10	5
7	1	1	0	6	0	6
8	0	0	0	1	0	1
9	1	0	1	0	0	0
10	0	0	0	0	0	0
11	0	0	0	2	1	1
12	0	0	0	0	0	0
13	0	0	0	9	0	9
14	0	0	0	28	11	17
15	1	1	0	0	0	0
16	0	0	0	0	0	0
17	0	0	0	11	0	0

Note: IB was calculated based only on FA and FD on the Z-score outliers that were 2, 3 or 4 standard deviations below the normative mean, as they would be expected to decrease due to concussion-related brain damage.

Models and correlations on demographic and neuropsychological metrics

A series of multiple linear regressions were performed to estimate the influence of covariates on MRI IB metrics. Both the total FA_{IB} and total FD_{IB} were separately compared against the demographic information, ImPACT scores, the BDI-II score, and SF-36 scores. A significant relationship was found for demographics in the total FD_{IB} model based on standardized beta (ß) estimates (residual standard error= 4.693 on 7df, adjusted R-squared= 0.6398, p= 0.02872), where age (ß= 1.0853, p= 0.0254) and education (ß= 6.4242, p= 0.0029) were significantly associated with total FD_{IB} (Table 5). Following this test, a refined multiple linear regression was performed with total FD_{IB} and only age and education as covariates. This resulted in another significant model (Residual standard error= 6.179

on 11 df, adjusted R-squared= 0.3757, p= 0.0299) where education remained significantly associated with total FD_{IB} (ß= 3.9458, p= 0.0176), but age was not significantly associated (ß= 0.5181, p= 0.0725). No significant relationships were found based on linear regressions between total FA_{IB} and the demographic metrics, or total FA_{IB} and total FD_{IB} with the neuropsychological metrics. Correlation calculations were also performed on the demographic and neuropsychological data with total FA_{IB} and total FD_{IB} (Figs. 3.3 & 3.4). For total FA_{IB}, a significant negative correlation with emotional well-being (r= −0.532, p= 0.034) was noted. However, non-significant correlations were found between FA_{IB} and career length (r= −0.411, p= 0.144), social functioning (r= −0.403, p= 0.122), and physical health (r= 0.321, p= 0.226). In terms of total FD_{IB}, non-significant correlations were found with energy and fatigue (r= −0.340, p= 0.197), general health (r= −0.350, p= 0.184), age (r= 0.313, p= 0.277), career length (r= 0.353, p= 0.215), and education (r= 0.531, p= 0.0505).

3.2.6 Discussion

The results from this study partially aligned with the hypothesis in that abnormal Z-scores were detected in many ROIs and quantified as IB in several subjects. There was no microstructural anomaly detected from the DTI data in 12 of the former players (i.e., total FA_{IB} of 0). However, 5 retired players had a total FA_{IB} $\geq$1, meaning at least one area of their brain had lower microstructural integrity compared to normative data. Functional anomaly, detected using rsfMRI data, was absent in 9 of the former players. However, 8 had at least one region of the brain that had reduced functional complexity (total FD_{IB} 1–6: n= 4, total FD_{IB} $\geq$6: n= 4). Moreover, there were few significant relationships found between the MRI data and the demographic and neuropsychological metrics. This study provided evidence of brain changes present in some subjects that may have been caused by their history of concussions sustained decades earlier during their professional football career. Furthermore, this study found interesting information on brain regions particularly vulnerable to multiple sub-concussive and concussive injuries at a single-subject level.

Imaging techniques

By first considering the results from the different imaging techniques the regional and subject-wise explorations become more explainable. The DTI FA metric suggested microstructural anomaly was present in only a small number of former players (n= 6). The general trend of decreased FA associated with normal aging (Chad et al. 2018) and concussions was expected (Asken et al. 2018; Bazarian et al. 2014; Schneider et al. 2019). Our previously published study of paediatric concussions showed FA was a highly effective metric for quantifying post-concussive white matter damage, more so than other tensor-derived scaler metrics (Stillo et al. 2021). Another recent study on subjects of similar age to our current study, who had persistent cognitive impairment post-concussion, showed that FA and mean diffusivity (MD) were correlated with poor cognitive test scores (Gonzalez et al. 2021).

Our rsfMRI results followed a similar trend of decreased BOLD signal activity with normal aging (Farokhian et al. 2017) and concussions (Dona et al. 2017). In our study, the FD values, and resultant Z-scores, of all subjects in all ROIs were decreased relative to the healthy control values, indicating that a history of concussions decreased brain functional complexity, which is suggestive as correlating with reduction in brain health. Although the method of analyzing the rsfMRI data was different in the current study, cognitive and motor control decline has been found in otherwise healthy retired athletes (Gallo et al. 2020; De Beaumont et al. 2009).

Subject-specific injury burden

Examining the subject-specific IBs, only one subject had a FA_{IB} of 3 while the others that did have any outliers had an FA_{IB} of 1. This could be due to minimal lasting microstructural damage that is repaired over time, or that the DTI metrics implemented for this study were not sensitive enough to detect white matter abnormalities in such a cohort of retired athletes. Minimal abnormalities have also been found from DTI data in other studies on aging retired athletes (Multani et al. 2016; Terry et al. 2019). However, it was expected that lasting microstructural damage would be present (Asken et al. 2018; Tremblay et al. 2014;

Wilde et al. 2016). From the functional analysis, there were 8 of the 17 subjects (i.e., 47%) with a total FD_{IB} greater than zero. Three of those 8 had a low FD_{IB} (i.e., 1 or 2), but the other subjects were calculated to have noteworthy IBs; four of which had a high FD_{IB} of 9, 11, 15 and 28 (Table 3.4). More details related to these four former players, and how their rsfMRI findings provide evidence of functional deficits, is discussed below.

Regions-of-interest and related symptoms

From an ROI perspective there were limited white matter microstructural abnormalities, but several grey matter ROIs exhibited decreased cognitive complexity in multiple subjects. The white matter abnormalities were present in longer fibre tracts as was expected from our hypothesis. It was expected that some abnormalities would be detected in the corpus callosum (Tremblay et al. 2014; Wright et al. 2021), but there were outliers detected in both the left and right cingulum which travels parallel to the corpus callosum through the center of the brain. Moreover, the inferior occipito-frontal fascicle and left superior longitudinal fascicle are especially long white matter fibre tracts that are often abnormal following a concussion (Tremblay et al. 2014; Wright et al. 2021). However, there were few FA outliers detected possibly indicating that any previous structural damage has long since repaired.

TABLE 3.5: A summary of the multiple linear regression model calculated for total fractal dimension (FD) injury burden (IB) relative to the demographic subject infor- mation of age, type of head impacts based on playing position, career length, years of education, number of previous diagnosed concussions, and years since last concussion.

Variables	**Estimate**	**Std. Error**	**t-value**	**p-value**
(Intercept)	-157.3693	32.594	-4.828	0.0019**
Age	1.0853	0.3835	2.83	0.0254*
Positional	-5.5042	3.5095	-1.568	0.1608
Career	0.6164	0.3217	1.916	0.0969.
Education	6.4242	1.4372	4.47	0.0029**
NPC	0.7762	0.6266	1.239	0.2553
YSLC	-0.3903	0.2317	-1.685	0.1359

Note: The model characteristics were as follows: Residual standard error: 4.693 on 7 degrees of freedom, Multiple R-squared: 0.806, Adjusted R-squared: 0.6398, F-statistic: 4.849 on 6 and 7 DF, and p-value: 0.02872. The coefficient estimates (ß) are standardized values. The significance codes are: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 with p<0.05 being considered significant.

From the rsfMRI data, the right pre-motor cortex BA6 (Z-score outliers= 4), right hippocampus dentate gyrus (Z-score outliers= 3), right visual cortex V1 BA17 (Z-score outliers= 3), and right visual cortex V2 BA18 (Z-score outliers= 3) were the ROIs with the highest number of outliers across all subjects. All four of the commonly abnormal grey matter regions were from the right hemisphere. This suggests that those ROIs may be more susceptible to concussion-related injury, but further evidence from a larger sample is required to conclude if the right hemisphere is more likely to be damaged. The fact that the injured ROIs were only found in the right hemisphere conflicts with literature as bilateral or at least less polarized results have been found in the previously discussed concussion studies. The four commonly abnormal ROIs were from varying parts of the brain and are responsible for very different functions. The pre-motor and visual regions are cortical, which agreed with our hypothesis, but the many other grey matter ROIs that had FD Z-score outliers were a mix of cortical and deep brain structures. The

pre-motor cortex is a key region for executing healthy motor function, responsible for motor preparation and reaction time (Dogonowski et al. 2013; Hinder et al. 2012; Verstraelen et al. 2021). The hippocampus on the other hand is generally responsible for memory and learning, and the hippocampal dentate gyrus has been specifically associated with episodic and spatial memory formation (Amaral et al. 2007; Saab et al. 2009). Finally, the two injured visual cortex regions are involved in aspects of visual information processing. The primary visual cortex (V1, BA17) is the first location for visual input (Hinds et al. 2009), and the secondary visual cortex (V2, BA18) directly receives information from the primary visual cortex and performs processing discrimination of visuospatial properties (Waberski et al. 2008), light intensity, patterns, finger gestures and attention (Larsson et al. 2006; Tuleasca et al. 2018). In relation to concussion-related symptoms: the pre-motor cortex is associated with headaches, nausea, vomiting, balance problems, fatigue, trouble falling asleep, excessive sleep, drowsiness, irritability, numbness and feeling "slow"; the hippocampus is associated with headaches, balance problems and vision problems; and the visual cortex is associated with headaches, nausea, vomiting, balance problems, dizziness, fatigue, trouble falling asleep, drowsiness, light sensitivity, feeling "foggy", difficulty concentrating, and visual problems (Churchill et al. 2017; TBIFinder Inc. 2021). These injured regions and their associated functions and associations align with those found in other concussion studies on long-term prognosis and aging retired athletes. In studies on retired athletes, hippocampal volume decreases (June et al. 2020; Shenton et al. 2012) and memory problems have been found often (Strain et al. 2015; Tarazi et al. 2018). Moreover, general cognitive impairment has also been found in several studies (Tarazi et al. 2018; Zhang et al. 2019). Although these symptom and cognition factors were not found in our study, further research should be conducted on aging athletes to draw conclusions as our sample size may have limited our results.

Demographics and neuropsychological tests

Finally, the demographic metrics and neuropsychological tests provided some interesting relationship information related to total FA_{IB} and total FD_{IB}. This was expected as multiple concussions (Ford et al. 2013; Terry et al. 2019), cognitive impairment (Hampshire et al. 2013), memory issues (Ford et al. 2013), and depression

(Hart et al. 2013; Strain et al. 2013) have all been correlated with dMRI or rsfMRI determined brain damage. From the demographic and career information, higher age and years of education were both associated and correlated with greater FD_{IB}, and career length was correlated with FA_{IB} and FD_{IB}. The influence of education on total FD_{IB} was unexpected. A study by Banks et al. (2014) found a potential neuroprotective effect of education for the cognition of professional fighters (Banks et al. 2014). However, our study calculated a positive association (Table 3.5) and correlation between education and FD_{IB} would suggest that a higher IB was associated more years of education. Moreover, the correlations with career length were conflicting between the quantitative measures where higher FA_{IB} was correlated with a shorter career ($r = -0.411$), but a higher FD_{IB} was correlated with a longer career ($r = 0.353$). Although conflicting, this may suggest that longer careers can lead to lasting cognitive brain alterations, but microstructural changes may heal with time. Exploring the neuropsychological data, the results from our study indicated that a history of repetitive head trauma could be linked to decreased physical health, social functioning, emotional well-being, general health, and energy levels. The connection between a career in high collisions sports, repetitive concussive and sub-concussive head impacts, and neurodegenerative diseases such as dementia and Alzheimer's Disease is impactful (Abner et al. 2014; Amen et al. 2016; Gallo et al. 2020; Gardner and Yaffe 2015; June et al. 2020), and our study added to this hypothesis by exploring demographic, professional athletic career, and neuropsychological health data in combination with quantitative MRI techniques. Further research with a larger subject sample or alternative MRI techniques should be conducted to expand on the relationships between long-term neuropsychological function, neurodegeneration, and concussions.

To compare the neuropsychological results on a subject-wise manner, the four subjects with high total FD_{IB} values can be examined (Table 3.6). Subject 6, who had a total FD_{IB} of 15, reported to be worse off than the other CFL subjects in 9 of the 15 test factors (motor speed, impulse control, cognitive efficiency index, depression, energy and fatigue, emotional well-being, social functioning, and general health). Subject 13, who had a total FD_{IB} of 9, scored worse off in 9 of the 15 test factors (verbal memory, motor speed, reaction time, impulse control, depression,

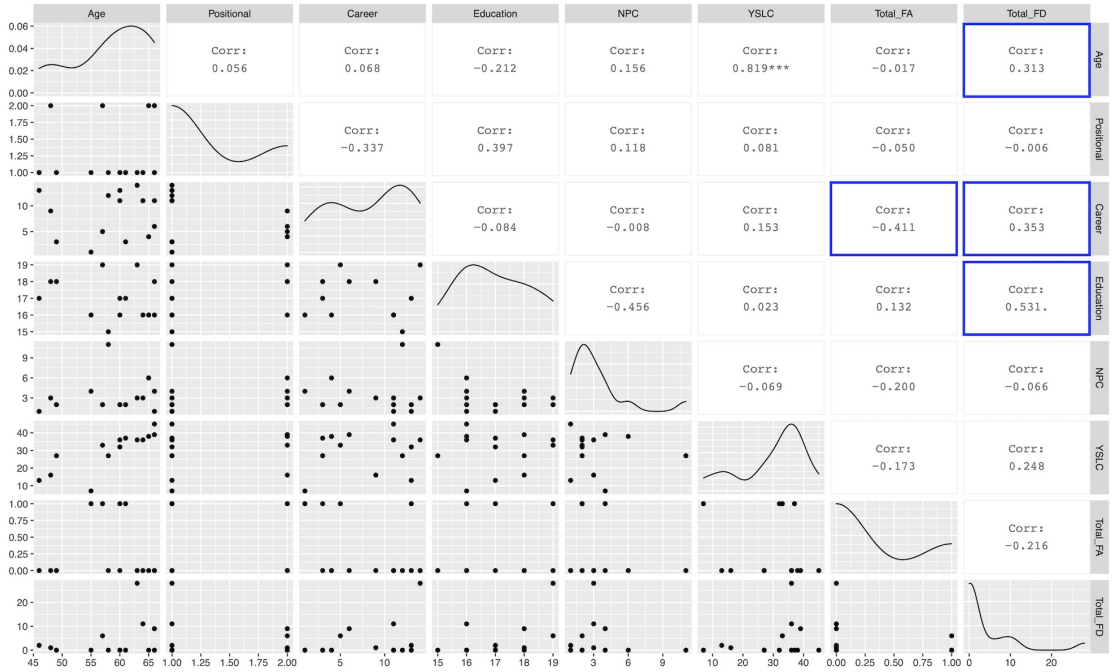

FIGURE 3.3: A correlation matrix of the relationships between the demographic data compared to the total FA_{IB} and total FD_{IB}. The stronger correlations with total FA_{IB} and total FD_{IB} are outlined with a blue square. Total FA_{IB} was moderately correlated with career length (r= −0.411). Total FD_{IB} was moderately correlated with age (r= 0.313), career length (r= 0.353), and education (r= 0.531). Of the variables considered for this correlation matrix, the abbreviations can be interpreted as "positional" was in regard to the frequency and intensity of head impacts relative to the subject's football position, "career" was the years of professional football, "education" was the number of years of formal education, "NPC" was the number of previous concussions, and "YSLC" was the number of years since the subject's last concussion.

physical functioning, physical health, social functioning, and general health). Subject 14, who had a total FD_{IB} of 28, scored worse off in 7 of 15 test factors (verbal memory, motor speed, reaction time, energy and fatigue, social functioning, pain, and general health). Lastly, subject 17, who had a total FD_{IB} of 11, scored worse off in 10 of 15 test factors (visual memory, motor speed, reaction time, impulse control, depression, physical functioning, physical health, energy and fatigue, emotional well-being, social functioning, and general health). Interestingly, all four of

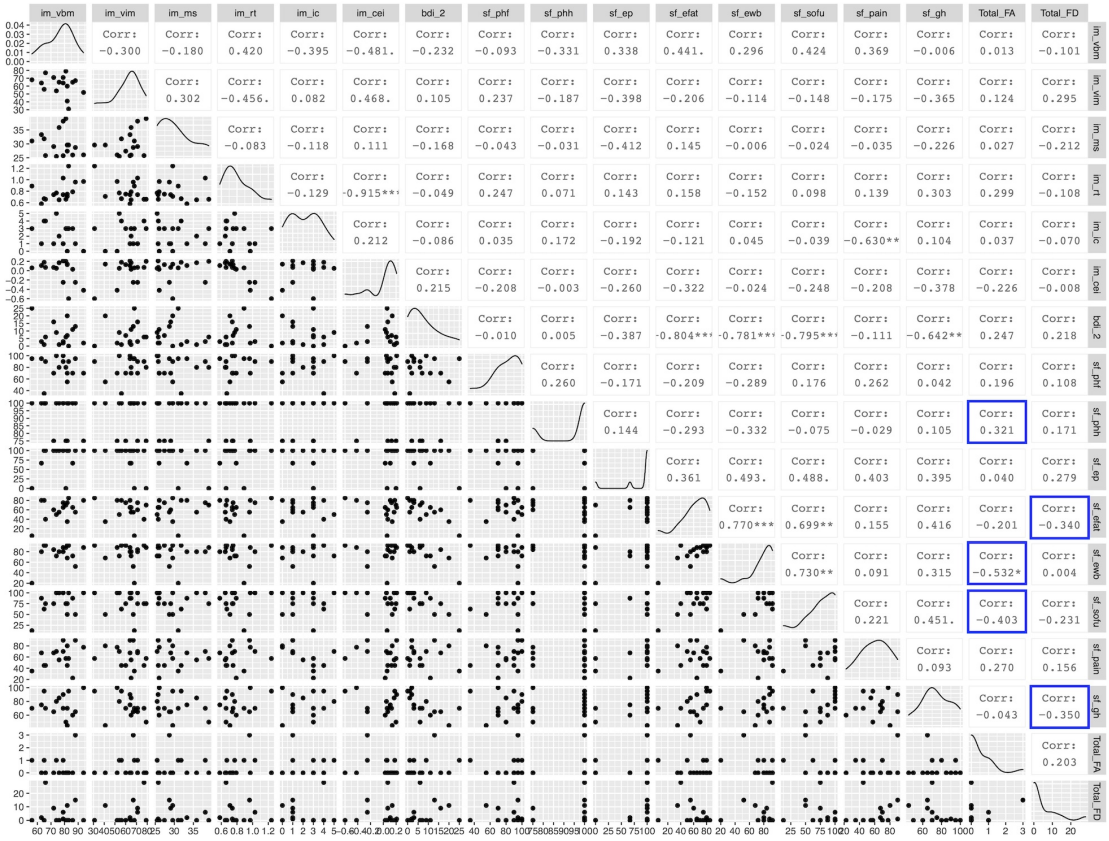

FIGURE 3.4: A correlation matrix of the relationships between the neuropsycholgical data compared to the total FA_{IB} and total FD_{IB}. The stronger correlations with total FA_{IB} and total FD_{IB} are outlined with a blue square. Total FA_{IB} was moderately correlated with physical health (r= 0.321), social functioning (r= −0.403), and significantly with emotional well-being (r= −0.532). Total FD_{IB} was moderately correlated with energy and fatigue (r= −0.340) and general health (r= −0.350). Of the variables considered for this correlation matrix, the abbreviations can be interpreted based on the ImPACT (im), BDI-II (bdi_2) and SF-36 (sf) neuropsychological tests and their sub-categories as follows: verbal memory (im_vbm), visual memory (im_vim), motor speed (im_ms), reaction time (im_rt), impulse control (im_ic), cognitive efficiency index (im_cei), Beck Depression Inventory-II (bdi_2), physical functioning (sf_phf), physical health (sf_phh), emotional health (sf_eh), energy and fatigue (sf_efat), emotional well-being (sf_ewb), social functioning (sf_sofu), pain (sf_pain), and general health (sf_gh).

these subjects reported to be worse off than the other subjects in motor speed, social functioning, and general health. These findings could be useful in monitoring aging athletes, but again this is best interpreted on a per-person basis. While the statistical power achieved with groupwise comparisons is beneficial for comparing effects and/or differences, these sub-analyses show that single-subject analyses can reveal insights into concussions that are overshadowed at the group-level. This was an example of the need to consider single-subject data in the context of larger group effects.

TABLE 3.6: The neuropsychological test data for the 4 subjects who had high total fractal dimension (FD) injury burden (IB) scores. The test data for the 4 subjects can be compared against the rCFL subjects' group mean.

Test Factor	**Subject 6 (Total FD_{IB} = 15)**	**Subject 13 (Total FD_{IB} = 9)**	**Subject 14 (Total FD_{IB} = 28)**	**Subject 17 (Total FD_{IB} = 11)**	**Subject Group Mean**
im_vbm	88	72*	66*	82	76.63
im_vim	67	71	77	41*	61.56
im_ms	28.7*	29.05*	25.8*	29.58*	30.16
im_rt	0.96	0.74*	0.66*	0.71*	0.80
im_ic	1*	1*	4	0*	2.19
im_cei	-0.25	0.07	0.07	0.14	-0.01
bdi_2	13*	16*	6	20*	7.81
sf_phf	95	70*	90	55*	80.31
sf_phh	100	75*	100	100	93.75
sf_ep	100	100	100	100	83.33
sf_efat	55*	60	40*	35*	60.94
sf_ewb	52*	84	92	68*	77.50
sf_sofu	50*	75*	75*	50*	78.13
sf_pain	90	67.5	45*	80	60.94
sf_gh	65*	65*	70*	45*	74.06

Note: Values that have an asterisk (*) indicate that the test factor score was worse for that subject than the group mean score of the other CFL subjects. The neuropsychological test factors used in this table are short-forms representative of the test and the sub-category of symptoms or feelings being assessed. In the table above the abbreviations can be interpreted based on the ImPACT (im), BDI-II (bdi_2) and SF-36 (sf) neuropsychological tests and their sub-categories as follows: verbal memory (im_vbm), visual memory (im_vim), motor speed (im_ms), reaction time (im_rt), impulse control (im_ic), cognitive efficiency index (im_cei), Beck Depression Inventory-II (bdi_2), physical functioning (sf_phf), physical health (sf_phh), emotional health (sf_eh), energy and fatigue (sf_efat), emotional well-being (sf_ewb), social functioning (sf_sofu), pain (sf_pain), and general health (sf_gh).

Limitations

The results of this study should be interpreted with the understanding of some limitations. The study utilized a very large normative dataset to calculate the Z-scores, but having only 17 retired athletes may have hindered the ability for correlations and a true representation of this population. Of note, many subjects in this study did not exhibit any FD outliers. This may simply be because there was no lasting cognitive impairment from the subjects' long history of concussive and repetitive sub-concussive impacts, but there were several subjects who exhibited very high FD_{IB} scores. There is also a lot of life lived after a professional sport career. Some athletes who go into media, start businesses, begin coaching, etc. may receive the cognitive stimulation, or environmental enrichment, necessary for adaptive neurophysiological changes. Further research with more subjects and from various concussion sources (i.e., different sports, accidents, falls, etc.) is required to draw more reliable conclusions. Another note is that data was only collected at a single time point for these subjects. Despite the interesting results found in the current study, a longitudinal study would provide greater insights into the effect of concussions on a brain aging. Further research is required to accurately determine whether there is a concussive 'threshold' (numbers, amplitudes, etc.) that would ensure long-term damage, why some individuals are more susceptible to acute and lasting brain damage, and how concussion severity is linked to neurodegenerative onset and progression. Finally, our novel method of injury quantification allows for the option to examine the Z-scoring results independently to identify injuries grades for each subject for each ROI, and binned together, calculated as IB. By reporting IB, as in Table 3.4, some information and injury specificity was lost, however, the exact details of each subject's injuries can be found in Tables 3.2 and 3.3 if the IBs need to be broken down.

Conclusions

In conclusion, several ROIs were injured more often than others based on the FD_{IB} scores calculated from the rsfMRI data. However, there was minimal white matter damage detected as only 7 outliers were detected in the DTI metric of FA. This study provides evidence of functional brain activity deficits,

and neuropsychological and demographic-related impairments, but minimal microstructural damage, in some retired professional football athletes with a history of repetitive concussive and sub-concussive head impacts.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Michael D. Noseworthy is the co-founder and CEO of TBIfinder, Inc. Mr. Nicholas Simard is the COO of TBIfinder, Inc.

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Chapter 4

Regional quantification of arterial spin labelling

4.1 Overview

4.1.1 Context of the study

Consistent cerebral blood flow (CBF), and tissue perfusion, is essential to maintaining brain health. However, a history of concussions has been shown to cause a global decrease in CBF and varying regional hypo- and hyperperfusion in athletes years after their last concussion and retirement from professional sport. This variability in regional perfusion highlights the presence of concussion induced CBF alterations and the need for further research to determine the clinical implications of these alterations.

This work aimed to apply a non-invasive magnetic resonance imaging (MRI) technique called arterial spin labeling (ASL) to quantify CBF on a regional basis and utilize a novel ASL metric, ASL spatial coefficient of variance (sCoV). The ASL sCoV metric has only been applied on a whole brain and hemispheric level, thus an additional purpose of this study was to see if regional abnormalities were calculated to be consistent across both CBF and ASL sCoV. This would contribute to the validation of ASL sCoV as a supplement to traditional CBF measurements and could provide information on arterial transit time and be more robust metric for patients of microvascular injuries.

4.1.2 Declaration statement

Ethan Danielli, as first author, was involved in the study conceptualization, data curation, methodology, data processing, formal statistical analysis, writing of the original draft, and revisions to the final manuscript. Beatriz Padrela, a PhD candidate with Dr. Mutsaerts, was involved in the methodology, data processing, and revisions to the final manuscript. Mathijs BJ Dijsselhof, another PhD candidate of Dr. Mutsaerts, was involved in data curation, data processing, and manuscript revisions. Mitchell Doughty, as fourth author and former MASc student in the research group, was involved in the recruitment of subjects, data acquisition, data curation, methodology, and revisions to the final manuscript. Dr. Lawrence C Mbuagbaw, an expert biostatistician, was involved in the formal statistical analysis of the data and manuscript editing. Dr. Jan Petr, a senior scientist for this project, was involved in the data curation, methodology, data processing, and revisions to the final manuscript. Dr. Henk-Jan Mutsearts, another senior scientist on this project, was involved in data curation, methodology, data processing, and revisions to the final manuscript. Finally, Dr. Michael D. Noseworthy, the corresponding author and primary investigator for this research group, was involved in the study conceptualization, data curation, funding acquisition, investigation, methodology, statistical analysis, resources, supervision, and revisions to the final manuscript.

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4.2 Assessment of regional cerebral blood flow and arterial spin labelling spatial coefficient of variance in retired Canadian Football League players: an exploratory study

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4.2.1 Abstract

Introduction: Concussions can alter cerebral blood flow (CBF), however there are often regional CBF discrepancies. We aimed to determine if CBF and spatial coefficient of variance (sCoV) were abnormal in retired athletes relative to healthy controls. It was hypothesized that former athletes would exhibit bilateral abnormalities in brain regions-of-interest (ROIs).

Materials & Methods: Seventeen retired Canadian Football League (rCFL)

players (male, aged 58±6.32 years) and 50 healthy controls (male, aged 59±8.01 years) had pseudocontinuous ASL (PCASL) data acquired. One hundred and two bilateral ROIs (51 left, 51 right) using CBF and ASL sCoV data were included in a Mann-Whitney U statistical analysis. Pearson's r correlations were performed with abnormal ROIs from rCFL subjects and their demographic and clinical test data.

Results: Ninety-one abnormal ROIs were detected from the 102 ROIs examined in each of the 17 rCFL subjects. Four ROI were bilaterally abnormal with CBF and ASL sCoV methods. Three of the four ROI had elevated CBF relative to the healthy controls, but all four had reduced ASL sCoV.

Conclusion: The superior parietal gyrus had the highest number of important correlations, and elevated CBF and ASL sCoV seemed to be correlated with an aggravated concussion history and worsened clinical test scores. Thus, microvascular dysregulation was present and may have been related to repetitive head impacts sustained decades earlier.

Key words: cerebral blood flow (CBF), concussion, pseudo-continuous arterial spin labelling (PCASL), repetitive head trauma, microvascular dysregulation

Abbreviations: (BDI-II) Beck Depression Inventory-II; (CBF) cerebral blood flow; (CEI) cognitive efficiency index; (CFL) Canadian Football League player; (CN) caudate nucleus; (EFAT) energy and fatigue; (EH) emotional health; (EWB) emotional well-being; (fSPGR) fast spoiled gradient; (GH) general health; (GM) grey matter; (IC) impulse control; (ImPACT) Immediate Post-concussion Assessment and Cognitive Testing; (IR) inversion-recovery; (MRI) Magnetic Resonance Imaging; (MS) motor speed; (NPC) number of previously diagnosed concussions; (PCASL) 3D pseudo-continuous ASL; (PHF) physical functioning; (PHH) physical health; (ROI) region-of-interest; (RT) reaction time; (sCoV) spatial coefficient of variance; (SF-36) Short Form 36 Survey Instrument; (SPG) superior parietal gyrus; (SI) symmetry index; (SOFU) social functioning; (TOFC) temporal occipital fusiform cortex; (VBM) verbal memory; (VIM) visual memory; (YSLC) number of years since last concussion

4.2.2 Introduction

Concussions are a leading cause for hospitalization (Hon et al. 2019; Langlois et al. 2006; Taylor et al. 2017), and are the result of forces applied to the head, neck, or body that transmit forces to the head, and does not necessarily include a loss of consciousness (Cassidy et al. 2004; McCrory et al. 2017). High collision sports, such as (American) football, ice hockey, and lacrosse, and sports involving head contact, such as soccer and boxing, demonstrate the highest incidence rates for sport-related concussions (SRC) in both youth and adults (Halstead et al. 2018; Zuckerman et al. 2015). Although concussions have recently been receiving greater acknowledgement, many concussions remain unreported – this is especially true with athletes (Kaut et al. 2003; Kroshus et al. 2017; Meehan et al. 2013).

Most adults completely recover from concussions in 10-14 days, but many athletes return to play prior to a full recovery (Carson et al. 2014; DeMatteo et al. 2021; McCrory et al. 2017), which makes them more vulnerable to a worsened second concussion in acute succession (Lazaridis et al. 2019; Prins et al. 2013). Moreover, repetitive sub-concussive blows have been shown to cause similar microstructural and cognitive effects over the course of a practice, season or career to diagnosable concussions, thus the incidence of both concussive and sub-concussive impacts can lead to neurodegenerative diseases later in life (Baugh et al. 2012; Brett et al. 2020; Poole et al. 2015; Povolo et al. 2020). Therefore, athletes who have never sustained a diagnosed concussion could still be cognitively impaired later in life due to the accumulation of sub-concussive injuries (Bailes et al. 2013; Mainwaring et al. 2018).

Consistent, homeostatic cerebral blood flow (CBF) is essential for healthy brain function and cognition (Cipolla 2009). Remodelling of microvasculature and decreased CBF is associated with aging and neurodegeneration (Brown and Thore 2011). One non-invasive, non-ionizing and repeatable method to measure in-vivo CBF is through a magnetic resonance imaging (MRI) technique called arterial spin labelling (ASL). By magnetically labelling water molecules, ASL provides an efficient and robust option to quantify CBF (Hernandez-Garcia et al. 2019). There is evidence from ASL studies that alterations, seen most frequently as a decrease in global (whole-brain) CBF, are present following a concussion (Wang et al. 2020).

However, there is also evidence of regional brain hypo- and hyperperfusion in acute (Churchill et al. 2017) and chronic SRC patients (Hart et al. 2013). In retired National Football League (NFL) players, regional CBF increases and decreases aligned with symptoms and depression (Hart et al. 2013). Further research is required to identify and characterize the inconsistent CBF changes associated with a history of concussions more accurately.

Standardization within ASL and concussion research could lead to more accurate diagnoses and effective treatments for SRC (Alsop et al. 2015). In addition to measuring CBF, a novel metric called the ASL spatial coefficient of variance (sCoV) has been shown to be an alternative tool to quantify blood flow in the brain (Mutsaerts et al. 2017). The ASL sCoV values are based on grey matter CBF values and are defined as the CBF standard deviation divided by the CBF mean, per region-of-interest (ROI) (Mutsaerts et al. 2017). As a possible supplement to CBF, ASL sCoV may enhance recovery and treatment options by detecting heterogeneity of grey matter CBF that may be related to pathology. ASL sCoV has only been analyzed for whole-brain grey matter, and it has yet to be applied on an ROI-basis (Mutsaerts et al. 2017). In this exploratory study, we examined both CBF and ASL sCoV to perform a preliminary comparison of the two ASL quantification methods, and to determine if ASL sCoV could be used on smaller, focal brain regions. The ASL sCoV has been strongly associated with age and sex, and associations remain significant with motion and partial volume corrections (Mutsaerts et al. 2017). The incorporation of ASL sCoV into future research may provide more accurate and standardized information that may be a more reliable metric than CBF in patients with impaired or damaged cerebrovasculature and reduce inter-subject physiological and whole-brain differences (Mutsaerts et al. 2017).

The current study aimed to determine if CBF or ASL sCoV abnormalities were present in aging, retired Canadian Football League (rCFL) players, relative to healthy controls, that may have been caused by the repetitive concussive and sub-concussive injuries decades earlier during their professional football career. Furthermore, the CBF and ASL sCoV abnormalities were correlated with post-concussion effects and approximate rCFL subject concussion history. It was

hypothesized that the rCFL players would exhibit abnormalities in ROIs relative to healthy controls. It was expected that ROIs would be bilaterally abnormal and both CBF and ASL sCoV would be sensitive enough to identify abnormalities. It was also expected that abnormal ROIs would be correlated with common post-concussion effects based on the primary function of each ROI.

4.2.3 Materials & methods

Subject demographics

This study was approved by the Hamilton Integrated Research Ethics Board (HiREB) in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Seventeen rCFL players (100% male, aged 58±6.32 years, range 45-66 years) who completed at least one year of CFL play participated. Subjects were recruited through local newspaper advertisements in the Toronto, Hamilton and Niagara regions of Ontario, Canada, and written informed consent was obtained prior to participation. Demographic information was collected for each subject including age, head impact based on their on-field game position, career length (measured in years), education (measured in years), number of previously diagnosed concussions (NPC), and the number of years since their last concussion (YSCL) (Table 4.1). The demographic and neuropsychological information on these subjects was also reported in another article focused on resting state functional MRI and diffusion tensor imaging data (Danielli et al. 2022b). Study exclusion criteria entailed documented substance abuse, diagnosed neurological or psychiatric illness, whether they had sustained a sport-related concussion in the past 5 years, or had any health condition that required daily treatment/therapy (e.g. diabetes, cancer). A neuroradiologist also reviewed the MRI scans to rule out any undiagnosed neuropathology (e.g. microbleeds, T2 hyperintensities, profound ventricular hypertrophy and brain atrophy (beyond that of normal aging), brain lesions visually causing structural damage). No former player included in the study had brain abnormalities visible at the time of the study.

A healthy control dataset was drawn from Rokicki et al. (Rokicki et al. 2021). The healthy control dataset (n= 341) was narrowed to include only sex

and age-matched subjects (n= 52). Two subjects were excluded, based on CBF map and motion artefacts yielding a final healthy control dataset (n= 50, 100% male, aged 59±8.01 years, range 44-68 years). The healthy controls were included if they reported no history of concussions and were not clinically diagnosed with cognitive impairment or a neurodegenerative disease (Rokicki et al. 2021).

TABLE 4.1: Demographic information of subjects that includes their age, education, career information and concussion history. Subjects 1, 2, 6, and 16 were not included in the correlation analysis performed on the abnormal CBF and ASL sCoV ROIs.

Subject	Age (years)	Positional Rating	Career (years)	Education (years)	NPC	YSLC (years)
1	55	1	1	16	4	7
2	60	1	6	-	-	-
3	60	1	11	16	2	36
4	49	1	3	18	2	27
5	64	2	4	16	6	38
6	62	2	6	-	-	-
7	57	2	5	19	2	33
8	47	2	9	18	3	16
9	60	1	13	17	2	32
10	58	1	12	15	11	27
11	45	1	13	17	1	13
12	66	1	11	16	1	45
13	66	2	6	18	4	39
14	63	1	14	19	3	36
15	61	1	3	17	2	37
16	55	1	7	-	-	-
17	63	1	10	15	11	31
	58.29±6.32	1.29±0.47	7.88±4.04	16.93±1.33	3.88±3.30	29.79±10.87

Note: The column positional refers to the type of head impacts that that subject was most likely to have experienced while playing their position (1= high frequency, low impact; 2= low frequency, high impact). The column NPC (number of previous concussions) is based on the subjects self-reporting the number of diagnosed concussions they have sustained. The column YSLC (number of years since last concussion) is based on the subjects self-reporting the number of years since their last diagnosed concussion. Education, NPC and YSLC was only available for 14 of 17 volunteers. Education was measured in years including grade school (1-12) and post-secondary education. The bottom row of this table is the mean and standard deviation for each column.

Clinical tests

The rCFL participants completed a series of self-reporting clinical tests to assess their cognition, memory, post-concussion symptoms, and general health. The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) was used to assess cognition and memory (Lovell 2006). Beck Depression Inventory-II (BDI-II) was used to assess depressive symptoms (Smarr and Keefer 2011). Finally,

the Short Form Survey Instrument (SF-36) was used to evaluate the general health of the subjects (Ware 2000). The ImPACT tool consists of a cognitive efficiency index (CEI) and 5 sub-tests for the evaluation of verbal memory (VBM), visual memory (VIM), motor speed (MS), reaction time (RT), and impulse control (IC). The BDI-II test quantifies a subject's level of depression over the past two weeks based on a response of 0-3 on 21 questions, thus having a scoring range of 0-63. Higher scores indicate more severe depression, with ranges of depression for minimal (0-13), mild (14-19), moderate (20-28), and severe (29-63). The SF-36 test assessed general health criteria such as physical functioning (PHF), physical health (PHH), emotional health (EH), energy and fatigue (EFAT), emotional well-being (EWB), social functioning (SOFU), pain, and general health (GH).

MRI acquisition protocol

The rCFL subjects were scanned using a 3T Discovery MR750 MRI and a 32-channel head coil (GE Healthcare, Milwaukee, WI) to acquire structural and arterial spin labelling (ASL) data. Structural imaging included: a whole brain high-resolution 3D T1-weighted inversion-recovery prepared fast spoiled gradient (IR-prepared fSPGR: repetition time (TR)/echo time (TE)/inversion time (TI)= 11.34/4.25/450ms; flip angle (FA)= 12°; 256 X 256 matrix; 1mm isotropic resolution). To assess cerebral blood flow (CBF): a 3D pseudo-continuous ASL sequence was employed (PCASL: TR/TE= 4886/10.528ms; FA= 111°; post-labelling delay (PLD)/labelling duration (LD)= 2025/1450ms; number of signal averages (NSA)=3 and background suppression; acquired in 8 spiral arms, each with 512 points; images were reconstructed to a 128 X 128 matrix and 1.875 X 1.875mm in-plane resolution; 4mm slice thickness). A separate M0 image was acquired for use in CBF calculation.

The healthy control (HC) dataset MRI data was collected at a different location than the rCFL sample, but with the same scanner model and pulse sequences, with very similar acquisition parameters (Rokicki et al. 2021). The healthy control data was collected using a 3T Discovery MR750 scanner and a 32-channel head coil (GE Healthcare, Milwaukee, WI) in Oslo, Norway. Whole

brain T1-weighted data was collected using an inversion recovery fast spoiled gradient echo sequence: TR/TE/TI= 8.16/3.18/450ms; FA= 12°; 256 X 256 matrix; 1mm isotropic resolution. The ASL data was collected with a PCASL sequence: TR/TE= 5025/11.072ms; PLD/LD= 2025/1450ms; NSA= 3; acquired 8 spiral arms, each with 512 points; reconstructed to a 2 X 2 X 3mm resolution (Rokicki et al. 2021).

Data analysis

The PCASL and T1-weighted scans were processed using ExploreASL (version 1.6.0), an ASL image processing software (Mutsaerts et al. 2020). In brief, T1-weighted images were segmented to grey matter (GM) and white matter (WM) and spatially normalized to the MNI152 1.5mm isotropic standard brain space. PCASL images were motion corrected, co-registered with M0 and T1w images, partial volume corrected, and CBF was quantified according to the consensus paper (Alsop et al. 2015; Mutsaerts et al. 2020). Additionally, ASL sCoV values were calculated (Mutsaerts et al. 2017). The PCASL data was re-examined at multiple processing stages to ensure that the CBF and ASL sCoV values were not going to be augmented by artefacts or unsymmetric hemispheric signal. The ASL sCoV of CBF was also used because ASL sCoV was expected to be more robust than CBF in subjects with compromised cerebrovasculature, to minimize macro-vascular artifacts, and to be less sensitive to physiological and whole brain differences between subjects (Mutsaerts et al. 2017). The CBF and ASL sCoV values were analyzed separately but with the same methodology from this point forward.

Using the Harvard-Oxford (Desikan et al. 2006) and Hammers (Hammers et al. 2003) brain atlases, CBF and ASL sCoV values were calculated for 102 ROIs (51 left and 51 right). As some ROIs were present in both atlases, the Harvard-Oxford atlas was used in full, and ROIs present in the Hammers atlas not present in the Harvard-Oxford atlas were also included. A considerable challenge posed in this study was the variability of ASL data between MRI vendors, scanners, locations, and intra-subject reproducibility (Gevers et al. 2011; Mutsaerts et al. 2015; Mutsaerts et al. 2018). Thus, the left and right ROI data was normalized

to each subject's own left and right total grey matter, respectively, in the aim of substantially reducing this bias. This was done by, for example, dividing a left ROI CBF value by the left total grey matter value for that subject. This was then repeated across all ROIs for that subject, and for all subjects. In addition to the 102 independent ROIs, a total hemisphere comparison (i.e., total left hemisphere CBF= mean left CBF), and a symmetry calculation based on the total left and right hemisphere values (i.e., CBF symmetry= (R-L)/(R+L)).

The current study utilized non-parametric Mann-Whitney U statistical tests to compare the 102 ROIs between rCFL and HC groups based on ROI hemisphere (i.e., left and right) and method of ASL quantification (i.e., CBF and ASL sCoV). Thus, group-wise statistics could be calculated to individually compare all the left hemisphere ROIs for the normalized CBF values, the right hemisphere ROIs for the normalized CBF values, left hemisphere ROIs for the normalized ASL sCoV values, and the right hemisphere ROIs for the normalized ASL sCoV values. Due to the exploratory nature of this study a Bonferroni correction was not applied and no inferences are made about p-values (Li et al. 2016). Confidence intervals (95%) were used to identify group differences, where if the confidence interval did not straddle zero the groups were considered different. The ROIs that were different between the rCFL and HC groups had post-hoc Pearson's r correlation tests to determine if the abnormal ROI rCFL data correlated with the demographic and neuropsychological metrics. This correlation analysis was only performed on 13 of the 17 rCFL subjects who had all their data available, and correlations were deemed important if -0.55$\geq$ r $\geq$0.55.

4.2.4 Results

Group-wise differences

The Mann-Whitney U tests revealed group differences between the normalized CBF and ASL sCoV values for rCFL subjects relative to the HC subjects. Of the 51 ROIs included for each comparison (e.g. left, right, CBF, ASL sCoV), numerous were different (Figure 4.1, Tables 4.2 & 4.3).

Left ROIs with normalized CBF data

Twenty-two left CBF ROIs were deemed to be different between the rCFL and HC groups (Figure 4.2, Table 4.2). The rCFL group expressed higher normalized CBF than the HC group (24%, 12 of 51 ROIs) in the frontal pole, lateral occipital cortex superior division, precuneus cortex, parahippocampal gyrus posterior division, lingual gyrus, temporal fusiform cortex posterior division, temporal occipital fusiform cortex (TOFC), occipital fusiform gyrus, cerebellum, lateral remainder occipital lobe, inferior frontal gyrus, and superior parietal gyrus (SPG). In contrast, the rCFL group expressed lower normalized CBF than the HC group (20%, 10 of 51 ROIs) in the superior frontal gyrus, juxtapositional lobule cortex (formerly supplementary motor cortex), subcallosal cortex, parahippocampal gyrus anterior division, hippocampus, amygdala, caudate nucleus (CN), anterior temporal lobe medial part, straight gyrus, and medial orbital gyrus.

Right ROIs with normalized CBF data

Twenty-six right CBF ROIs were deemed to be different between the rCFL and HC groups (Figure 4.2, Table 4.2). The rCFL group expressed higher normalized CBF than the HC group (28%, 14 of 51 ROIs) in the middle temporal gyrus posterior division, middle temporal gyrus temporooccipital part, supramarginal gyrus posterior division, angular gyrus, lateral occipital cortex superior division, precuneus cortex, temporal fusiform cortex posterior division, TOFC, occipital fusiform gyrus, cerebellum, lateral remainder occipital lobe, SPG, supramarginal gyrus, and insula anterior inferior cortex. In contrast, the rCFL group expressed lower normalized CBF than the HC group (24%, 12 of 51 ROIs) in the superior frontal gyrus, frontal medial cortex, juxtapositional lobule cortex (formerly supplementary motor cortex), subcallosal cortex, paracingulate gyrus, hippocampus, amygdala, CN, putamen, anterior temporal lobe medial part, straight gyrus, and medial orbital gyrus.

TABLE 4.2: Mann-Whitney U results for group-wise comparisons using the normalized CBF values which were calculated if specific brain regions-of-interest (ROIs) were elevated or reduced in the rCFL subjects relative to the health controls. There were 22 left ROIs and 26 right ROIs deemed abnormal if the 95% confidence interval did not straddle zero.

Abnormal left CBF ROIs	**W statistic**	**95% Confidence intervals**	**Group difference**
Frontal pole	581	0.012 to 0.14	0.079
Superior frontal gyrus	260	-0.19 to -0.017	-0.1
Lateral occipital cortex superior division	572	0.0079 to 0.18	0.097
Juxtapositional lobule cortex (formerly Supplementary motor cortex)	153	-0.23 to -0.088	-0.16
Subcallosal cortex	78	-0.27 to -0.13	-0.2
Precuneus cortex	640	0.035 to 0.13	0.078
Parahippocampal gyrus anterior division	217	-0.095 to -0.021	-0.057
Parahippocampal gyrus posterior division	609	0.023 to 0.12	0.07
Lingual gyrus	742	0.095 to 0.19	0.14
Temporal fusiform cortex posterior division	612	0.022 to 0.115	0.07
Temporal occipital fusiform cortex	648	0.037 to 0.14	0.083
Occipital fusiform gyrus	729	0.11 to 0.28	0.19
Hippocampus	262	-0.11 to -0.011	-0.063
Amygdala	223	-0.10 to -0.020	-0.061
Caudate nucleus	105	-0.19 to -0.081	-0.14
Anterior temporal lobe medial part	250	-0.094 to -0.0096	-0.047
Cerebellum	697	0.050 to 0.13	0.093
Lateral remainder occipital lobe	591	0.016 to 0.18	0.09
Straight gyrus	75	-0.26 to -0.12	-0.18
Inferior frontal gyrus	563	0.00089 to 0.16	0.076
Superior parietal gyrus	609	0.021 to 0.13	0.069
Medial orbital gyrus	152	-0.22 to -0.072	-0.15
Abnormal right CBF ROIs	**W statistic**	**95% Confidence intervals**	**Group difference**
Superior frontal gyrus	95	-0.25 to -0.11	-0.18
Middle temporal gyrus posterior division	610	0.034 to 0.18	0.11
Middle temporal gyrus temporooccipital part	615	0.035 to 0.23	0.13
Supramarginal gyrus posterior division	641	0.055 to 0.21	0.14
Angular gyrus	580	0.011 to 0.15	0.079
Lateral occipital cortex superior division	661	0.059 to 0.21	0.13
Frontal medial cortex	211	-0.19 to -0.046	-0.11
Juxtapositional lobule cortex (formerly Supplementary motor cortex)	72	-0.24 to -0.12	-0.18
Subcallosal cortex	21	-0.27 to -0.15	-0.21
Paracingulate gyrus	186	-0.18 to -0.056	-0.12
Precuneus cortex	592	0.016 to 0.13	0.074
Temporal fusiform cortex posterior division	579	0.0091 to 0.10	0.05
Temporal occipital fusiform cortex	595	0.012 to 0.12	0.063
Occipital fusiform gyrus	601	0.027 to 0.17	0.1

Hippocampus	182	-0.16 to -0.053	-0.1
Amygdala	191	-0.11 to 0.030	-0.065
Caudate nucleus	199	-0.15 to 0.044	-0.1
Putamen	276	-0.11 to -0.0055	-0.057
Anterior temporal lobe medial part	237	-0.10 to -0.015	-0.057
Cerebellum	562	0.00055 to 0.096	0.044
Lateral remainder occipital lobe	600	0.025 to 0.19	0.11
Straight gyrus	63	-0.23 to -0.12	-0.18
Superior parietal gyrus	598	0.014 to 0.13	0.071
Medial orbital gyrus	155	-0.20 to -0.071	-0.14
Supramarginal gyrus	719	0.11 to 0.22	0.17
Insula anterior inferior cortex	551	0.0084 to 0.16	0.08

Left ROIs with normalized ASL sCoV data

Eighteen left ASL sCoV ROIs were deemed to be different between the rCFL and HC groups (Figure 4.3, Table 4.3). The rCFL group expressed higher normalized CBF than the HC group (12%, 6 of 51 ROIs) in the frontal orbital cortex, superior temporal gyrus middle part, insula posterior long gyrus, lateral remainder occipital lobe, posterior temporal lobe, and posterior orbital gyrus. In contrast, the rCFL group expressed lower normalized ASL sCoV than the HC group (24%, 12 of 51 ROIs) in the lateral occipital cortex superior division, cingulate gyrus anterior division, cingulate gyrus posterior division, parahippocampal gyrus anterior division, TOFC, CN, putamen, thalamus, cerebellum, SPG, cuneus, and insula anterior short gyrus.

Right ROIs with normalized ASL sCoV data

Twenty-five right ASL sCoV ROIs were deemed to be different between the rCFL and HC groups (Figure 4.3, Table 4.3). The rCFL group expressed higher normalized ASL sCoV than the HC group (4%, 2 of 51 ROIs) in the middle temporal gyrus posterior division and frontal orbital cortex. In contrast, the rCFL group expressed lower normalized ASL sCoV than the HC group (45%, 23 of 51 ROIs) in the insular cortex, lateral occipital cortex inferior division, frontal medial cortex, juxtapositional lobule cortex (formerly supplementary motor cortex), paracingulate gyrus, cingulate gyrus anterior division, cingulate gyrus posterior division, precuneus cortex, parahippocampal gyrus anterior division, parahippocampal gyrus posterior division, temporal fusiform cortex posterior division, TOFC, amygdala, CN, putamen, thalamus, anterior temporal lobe medial part, fusiform gyrus, cerebellum, SPG, cuneus, insula anterior short gyrus, and mean right hemisphere.

TABLE 4.3: Mann-Whitney U results for group-wise comparisons using the normalized ASL sCoV values which were calculated if specific brain regions-of-interest (ROIs) were elevated or reduced in the rCFL subjects relative to the health controls. There were 18 left ROIs and 25 right ROIs deemed abnormal if the 95% confidence interval did not straddle zero.

Abnormal left ASL sCoV ROIs	**W statistic**	**95% Confidence intervals**	**Group difference**
Lateral occipital cortex superior division	268	-0.36 to -0.037	-0.2
Cingulate gyrus anterior division	205	-0.24 to -0.061	-0.15
Cingulate gyrus posterior division	192	-0.24 to -0.077	-0.16
Frontal orbital cortex	707	0.18 to 0.43	0.29
Parahippocampal gyrus anterior division	231	-0.22 to -0.037	-0.13
Temporal occipital fusiform cortex	120	-0.32 to -0.13	-0.22
Caudate nucleus	36	-0.56 to -0.32	-0.45
Putamen	1	-0.73 to -0.54	-0.63
Thalamus	0	-0.60 to -0.46	-0.54
Superior temporal gyrus middle part	703	0.13 to 0.33	0.23
Cerebellum	157	-0.25 to -0.085	-0.16
Insula posterior long gyrus	591	0.037 to 0.29	0.15
Lateral remainder occipital lobe	799	0.30 to 0.52	0.4
Posterior temporal lobe	812	0.25 to 0.44	0.34
Superior parietal gyrus	272	-0.31 to -0.014	-0.16
Cuneus	278	-0.32 to -0.010	-0.17
Posterior orbital gyrus	577	0.019 to 0.38	0.21
Insula anterior short gyrus	227	-0.35 to -0.076	-0.21
Abnormal right ASL sCoV ROIs	**W statistic**	**95% Confidence intervals**	**Group difference**
Insular cortex	202	-0.28 to -0.063	-0.18
Middle temporal gyrus posterior division	577	0.024 to 0.26	0.13
Lateral occipital cortex inferior division	247	-0.32 to -0.045	-0.19
Frontal medial cortex	281	-0.28 to -0.014	-0.15
Juxtapositional lobule cortex (formerly Supplementary motor cortex)	262	-0.25 to -0.018	-0.13
Paracingulate gyrus	238	-0.19 to -0.034	-0.12
Cingulate gyrus anterior division	279	-0.24 to -0.0097	-0.13
Cingulate gyrus posterior division	93	-0.37 to -0.20	-0.28
Precuneus cortex	221	-0.25 to -0.053	-0.15
Frontal orbital cortex	622	0.056 to 0.30	0.17
Parahippocampal gyrus anterior division	155	-0.30 to -0.11	-0.21
Parahippocampal gyrus posterior division	278	-0.21 to 0.010	-0.11
Temporal fusiform cortex posterior division	248	-0.23 to -0.030	-0.14
Temporal occipital fusiform cortex	131	-0.23 to -0.11	-0.17
Amygdala	250	-0.20 to -0.029	-0.12
Caudate nucleus	256	-0.16 to -0.019	-0.093
Putamen	85	-0.33 to -0.19	-0.26
Thalamus	274	-0.15 to -0.0085	-0.08
Anterior temporal lobe medial part	133	-0.32 to -0.15	-0.23

Fusiform gyrus	186	-0.30 to -0.10	-0.21
Cerebellum	191	-0.22 to -0.065	-0.15
Superior parietal gyrus	194	-0.32 to -0.10	-0.22
Cuneus	253	-0.29 to -0.027	-0.16
Insula anterior short gyrus	165	-0.49 to -0.16	-0.32
Mean right hemisphere	284	-0.12 to -0.0035	-0.055

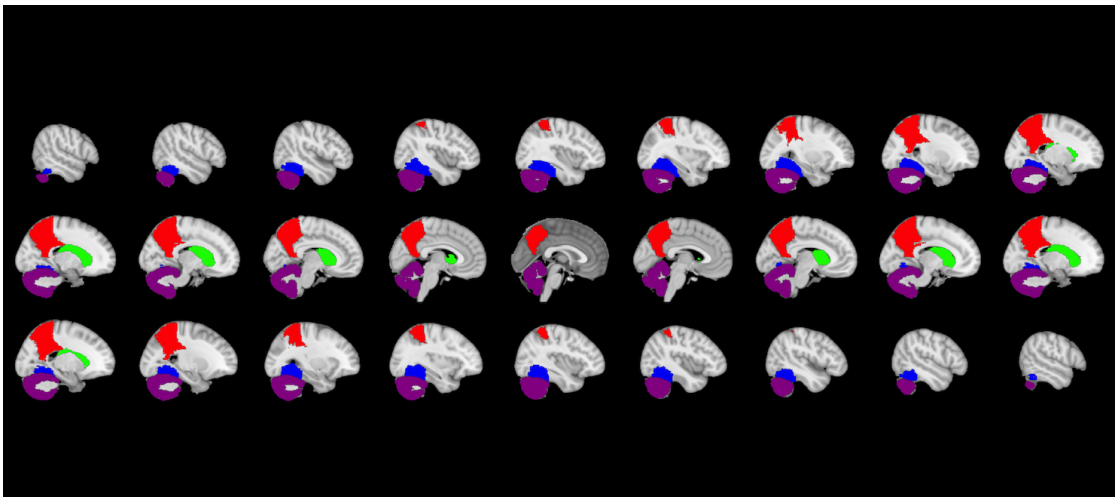

FIGURE 4.1: Visualization of the four bilaterally abnormal regions-of-interest (ROIs) detected based on both cerebral blood flow (CBF) and arterial spin labelling (ASL) spatial coefficient of variance (sCoV). The superior parietal lobule (above, red), temporal occipital fusiform cortex (above, blue), caudate nucleus (above, green), and cerebellum (above, purple) were significantly abnormal in the retired, aging Canadian Football League (rCFL) players relative to the age and sex-matched healthy control (HC) sample. The figure is portrayed with slices in the sagittal perspective.

Abnormal ROI correlations

The rCFL data from the ninety-one abnormal ROIs, as determined through the Mann-Whitney U tests, were selected for correlation analyses. Numerous important correlations (i.e., important if $-0.55 \geq r \geq 0.55$) between ROIs and demographic and clinical metrics were also found (Tables 4.4-4.7). In total, there were 50 important correlations with CBF ROIs (left= 26, right= 24), and 40 important correlations with ASL sCoV ROIs (left= 22, right= 13). From the CBF correlations, physical functioning (total= 7, left= 5, right= 2) and pain (total= 7, left= 4, right= 3) had the highest frequency of

important correlations. From the ASL sCoV correlations, pain (total= 7, left= 4, right= 3) had the highest frequency of important correlations.

Abnormal left CBF ROI correlations

From the abnormal left CBF ROIs, 13 of the 22 ROIs (59%) had at least one important correlation with a demographic or clinical test metric (Table 4.4). The SPG was found to have the highest number of important correlations with five, and was correlated with age (r=0.7, p=0.008), number of years since their last concussion (YSLC; r= 0.58, p= 0.0378), physical functioning (r= -0.67, p= 0.0117), social functioning (r= -0.59, p= 0.0333), and pain (r= -0.61, p= 0.0283).

Abnormal right CBF ROI correlations

From the abnormal right CBF ROIs, 14 of the 26 ROIs (54%) had at least one important correlation with a demographic or clinical test metric (Table 4.5). The precuneus and SPG both had the highest number of important correlations with four each. The precuneus was correlated with age (r= 0.71, p= 0.0064), number of years since their last concussion (YSLC; r= 0.59, p= 0.0335), physical functioning (r= -0.69, p= 0.0096), and pain (r= -0.65, p= 0.0156). The SPG was also correlated with age (r= 0.72, p= 0.0051), number of years since their last concussion (YSLC; r= 0.6, p= 0.0305), physical functioning (r= -0.72, p= 0.0058), and pain (r= -0.63, p= 0.0197).

TABLE 4.4: Summary table of the important correlations calculated between the 22 abnormal left CBF ROIs with demographic and clinical test metrics. Thirteen of the 23 ROI had at least one important correlation.

Region-of-interest	**Significant metric**	**Spearman's correlation (r)**
Frontal pole	Impulse control	-0.65
Lateral occipital cortex superior division	Physical functioning	-0.59
Juxtapositional lobule cortex (formerly Supplementary motor cortex)	Energy and fatigue	0.61
Precuneus cortex	Position	0.78
	YSLC	0.66
	Physical functioning	-0.57
	Pain	-0.64
Parahippocampal gyrus anterior division	Visual memory	0.68
	Reaction time	-0.64
	Cognitive efficiency index	0.61
	Social functioning	-0.56
Parahippocampal gyrus posterior division	Impulse control	0.59
	Beck's Depression Inventory II	0.61
Lingual gyrus	Beck's Depression Inventory II	0.62
	Pain	-0.58
Temporal fusiform cortex posterior division	Pain	-0.63
Temporal occipital fusiform cortex	Physical functioning	-0.77
Hippocampus	Physical health	0.58
Caudate nucleus	Physical health	-0.60
Inferior frontal gyrus	Physical functioning	-0.8
Superior frontal gyrus	Age	0.7
	YSLC	0.58
	Physical functioning	-0.67
	Social functioning	-0.59
	Pain	-0.61

TABLE 4.5: Summary table of the important correlations calculated between the 26 abnormal right CBF ROIs with demographic and clinical test metrics. Fifteen of those 26 ROI had a least one important correlation.

Region-of-interest	**Significant metric**	**Spearman's correlation (r)**
Middle temporal gyrus posterior division	Position	0.56
	Beck's Depression Inventory II	0.73
Middle temporal gyrus temporooccipital part	Beck's Depression Inventory II	0.64
Supramarginal gyrus posterior part	Age	0.59
Lateral occipital cortex superior division	Physical health	-0.56
Frontal medial cortex	NPC	-0.62
	Social functioning	0.59
Precuneus cortex	Age	0.71
	YSLC	0.59
	Physical functioning	-0.69
	Pain	-0.65
Temporal fusiform cortex posterior division	Pain	-0.86
Temporal occipital fusiform cortex	Education	-0.67
	NPC	0.88
Hippocampus	Impulse control	0.69
Amygdala	Cognitive efficiency index	0.61
Caudate nucleus	Energy and fatigue	-0.68
Putamen	Energy and fatigue	-0.57
Lateral remainder occipital lobe	Impulse control	-0.63
Superior parietal gyrus	Age	0.72
	YSLC	0.6
	Physical functioning	-0.72
	Pain	-0.63
Insula anterior inferior cortex	Emotional well-being	-0.7

Abnormal left ASL sCoV ROI correlations

From the abnormal left ASL sCoV ROIs, 15 of the 18 ROIs (83%) had at least one important correlation with a demographic or clinical test metric (Table 4.6). The lateral occipital cortex superior division had the highest number of important correlations with

three and was correlated with career length (r= -0.67, p= 0.0115), motor speed (r= 0.55, p= 0.0492), and emotional health (r= -0.62, p= 0.0243).

Abnormal right ASL sCoV ROI correlations

From the abnormal right ASL sCoV ROIs, 10 of the 25 ROIs (40%) had at least one important correlation with a demographic or clinical test metric (Table 4.7). The lateral occipital cortex inferior division, temporal fusiform cortex posterior division, and SPG had the highest number of important correlations with two. The lateral occipital cortex inferior division was correlated with number of previous concussions (NPC; r= -0.63, p= 0.0212) and physical health (r= 0.8, p= 0.001). The temporal fusiform cortex posterior division was correlated with the number of years since their last concussion (YSLC; r= 0.56, p= 0.047) and pain (r= -0.56, p= 0.0484). Finally, the SPG was correlated with the number of years since their last concussion (YSLC; r= 0.56, p= 0.0464) and pain (r= -0.58, p= 0.0383).

TABLE 4.6: Summary table of the important correlations calculated between the 18 abnormal left ASL sCoV ROIs with demographic and clinical test metrics. Fifteen of the 18 ROI had at least one important correlation.

Region-of-interest	**Significant metric**	**Spearman's correlation (r)**
Lateral occipital cortex superior division	Career	-0.67
	Motor speed	0.55
	Emotional health	-0.62
Cingulate gyrus anterior division	Physical functioning	0.62
Frontal orbital cortex	Energy and fatigue	-0.69
Parahippocampal gyrus anterior division	Verbal memory	0.66
Temporal occipital fusiform cortex	Visual memory	-0.68
	Impulse control	0.59
Putamen	Physical health	0.61
Thalamus	Physical health	0.7
Superior temporal gyrus middle part	Impulse control	0.56
	Pain	-0.56
Cerebellum	Pain	-0.58
Insula posterior long gyrus	NPC	-0.75
	Beck's Depression Inventory II	-0.58
Lateral remainder occipital lobe	Physical functioning	-0.56
	Pain	-0.76
Posterior temporal lobe	Physical functioning	-0.67
	Pain	-0.56
Superior parietal gyrus	YSLC	0.66
Cuneus	Impulse control	0.64
Posterior orbital gyrus	Verbal memory	-0.6

TABLE 4.7: Summary table of the important correlations calculated between the 25 abnormal right ASL sCoV ROIs with demographic and clinical test metrics. Ten of the 25 ROI had at least one important correlation.

Region-of-interest	Significant metric	Spearman's correlation (r)
Lateral occipital cortex inferior division	NPC	-0.63
	Physical health	0.8
Cingulate gyrus posterior division	NPC	-0.7
Temporal fusiform cortex posterior division	YSLC	0.56
	Pain	-0.56
Amygdala	Physical health	0.56
Caudate nucleus	Cognitive efficiency index	-0.65
Putamen	Motor speed	0.6
Anterior temporal lobe medial part	Emotional well-being	0.57
Cerebellum	Pain	-0.81
Superior parietal gyrus	YSLC	0.56
	Pain	-0.58
Cuneus	Emotional health	-0.6

4.2.5 Discussion

By applying a non-parametric statistical analysis on normalized CBF and ASL sCoV data, this study found differences between healthy aging individuals and former professional football players that should be explored with further research. Due to the demographic and medical history screening of rCFL and HC subjects prior to study inclusion, the group differences calculated in this study may be due to the concussive and sub-concussive events sustained decades earlier during the professional careers of the rCFL subjects. It was also found that CBF and ASL sCoV abnormalities could be linked to age, professional football career demographics, and overall health. Although ASL sCoV has been previously used for whole brain or hemispheric brain analyses (Mutsaerts et al. 2017), this method supplemented CBF for measurements on the smaller, regional basis with several overlapping abnormalities and correlations identified. The results and the methodological precautions performed to reduce biases showed that both CBF and ASL sCoV could quantify microvascular dysregulations on a regional manner.

Group-wise differences of normalized CBF and ASL sCoV data

There were numerous group-wise differences calculated with the CBF data (left: 23 of 51 ROIs, right: 26 of 51 ROIs). Of all the left and right ROIs that were found to be different, there were 18 that were bilaterally abnormal. Furthermore, all 18 of those ROIs (35%, 18 of 51 ROIs) were bilaterally increased or decreased relative to the HC group. This suggests a potential trend of symmetric microvascular dysfunction that may be related to concussive events that occurred decades earlier.

Exploring the ASL sCoV results, there were 12 ROIs that were bilaterally abnormal from the 18 different left ROIs and 25 different right ROIs (24%, 12 of 51 ROIs). Similar to the findings from the CBF results, the 12 bilaterally abnormal ROIs were uniformly increased or decreased in both hemispheres relative to the HC group. These findings complimented the CBF findings and further suggest that microvascular dysfunctions were present in this sample of retired CFL subjects.

Since ASL sCoV has been primarily calculated on hemispheric or entire brain basis in previous studies(Mutsaerts et al. 2017), the abnormal ASL sCoV ROIs were examined against the abnormal CBF ROIs to determine if ASL sCoV could be a valid supplementary ASL metric for concussion-related brain assessment. From the abnormal left CBF and ASL sCoV ROIs, eight ROIs were identified to be bilaterally abnormal in both techniques. Relative to the HC sample, CBF was increased and ASL sCoV was decreased in the lateral occipital cortex superior division, TOFC, cerebellum, lateral remainder occipital lobe, and SPG. Whereas the parahippocampal gyrus anterior division, CN, and putamen were decreased relative to the HC sample for both CBF and ASL sCoV techniques. Similarly, there were 13 right ROIs that were identified as abnormal using both measurement techniques. Only the middle temporal gyrus posterior division was found to be increased relative to the HC sample in both the CBF and ASL sCoV techniques, and the precuneus cortex, temporal fusiform cortex posterior division, TOFC, cerebellum and SPG were calculated to be increased with CBF but decreased with ASL sCoV. Finally, the frontal medial cortex, juxtapositional lobule cortex (formerly the supplementary motor cortex), paracingulate gyrus, amygdala, CN, putamen, and anterior temporal lobe medial part were decreased relative to the HC sample with both techniques.

Of particular note, the TOFC, CN, cerebellum, and SPG were found to be bilaterally abnormal using both the CBF and ASL sCoV quantification techniques, and

thus may be most vulnerable to microvascular dysfunction that is present decades after someone's most recent concussion (Figures 4.1-4.3). Examining just the CBF data, the TOFC, SPG, and cerebellum were bilaterally elevated, while the CN was bilaterally decreased. Based on just the ASL sCoV data, all four ROI were bilaterally decreased.

The fusiform cortex, including the temporal occipital and posterior division considered in this current study, spans the inferior aspect of the temporal and occipital lobes and is involved in the visual recognition of faces, words, and objects (Caspers et al. 2014; Palejwala et al. 2020; Zhang et al. 2016). The SPG, contained within the superior parietal lobule (associated with numerical processing and calculations) (Arsalidou and Taylor 2011), has been associated with recognition of and processing of non-numerical stimuli (Castaldi et al. 2020). The CN is part of the basal ganglia, where the CN has been shown to be involved in selecting appropriate sub-actions to achieve a goal-directed action (Grahn et al. 2008). Finally, the cerebellum is a complicated part of the human central nervous system that is involved in most aspects of human function such as motor control, stimulus-driven processes, and default mode processing (Guell and Schmahmann 2020). Due to the wide range of functions and processes associated with these four brain ROIs, and the other abnormal ROIs, correlation tests were performed to provide further information on the clinical presentation of these abnormalities.

Important correlations between abnormal ROI and demographic and clinical test metrics

The correlation tests were conducted to determine if the abnormalities detected in the rCFL sample may have had any connection to demographic metrics or led to clinical test deficits. The precuneus cortex, temporal fusiform cortex posterior division, and SPG were bilaterally correlated with pain using the normalized CBF values. Furthermore, the right temporal fusiform cortex posterior division and right SPG were also correlated with pain using the normalized ASL sCoV values. These findings suggest that the temporal fusiform cortex posterior division and the SPG may be the brain ROIs that were more likely to affect the well-being of individuals with a history of repetitive concussive brain injuries. It is especially important to consider that these alterations to CBF and ASL sCoV are altered relative to that of healthy aging. Referring to the four ROIs that were bilaterally abnormal across both techniques, although the SPG has been highlighted above as an ROI particularly involved in clinical presentation of pain, the other important

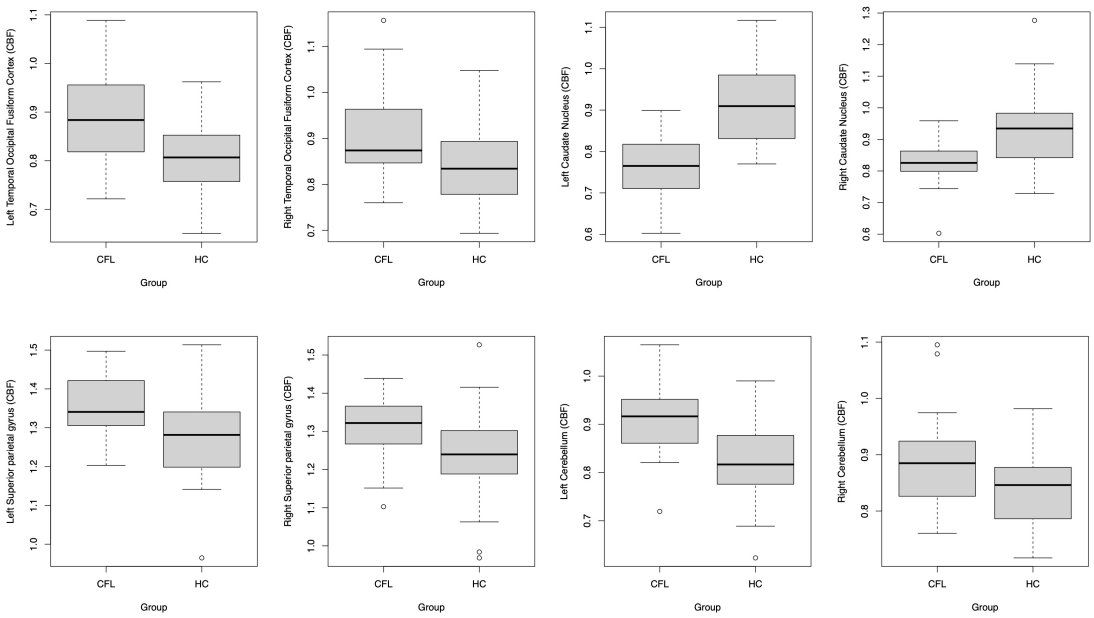

FIGURE 4.2: Boxplots showing values of cerebral blood flow (CBF) from both left and right temporal occipital fusiform cortex, caudate nucleus, cerebellum and superior parietal gyrus. These four brain regions showed significant difference, based on a Mann-Whitney U test, between retired Canadian Football League (rCFL) subjects and the healthy age/sex matched controls (HC). The rCFL subjects exhibited bilaterally elevated CBF in these regions relative to the HC subjects.

correlations (i.e., important if -0.55≥r≥0.55) with the four abnormal ROIs should be discussed.

Superior parietal gyrus

The SPG had nine important correlations (left= 5: age, YSLC, physical functioning, social functioning, and pain; right= 4: age, YSLC, physical functioning, and pain) with the CBF data (Tables 4.4 & 4.5). This suggests that the elevated CBF in rCFL subjects was correlated with older age at the time of this study, a higher number of years since their last concussion, lower physical functioning, lower social function, and lower bodily pain magnitude or interference. The SPG also had three important correlations from the ASL sCoV data (left= 1: YSLC; right= 2: YSLC and pain) (Tables 4.6 & 4.7). This suggests that the relatively decreased ASL sCoV in the rCFL subjects was

correlated with fewer year since their last concussion and higher pain scores.

Although the SPG is known to process non-numerical stimuli, that function was not overly apparent in the correlations. The direct function of this ROI was closest to the metric of social functioning, which could be affected by a reduced capacity to efficiently processes stimuli. Notably, YSLC was positively correlated with the SPG bilaterally and in both CBF and ASL sCoV techniques, suggesting that there may be a connection between increasing CBF and tissue perfusion over time. Similarly, the SPG was negatively correlated with the pain score on the SF-36 test bilaterally from the CBF data and with the right ASL sCoV data. This suggests that rCFL subjects who had lower CBF or ASL sCoV values in their SPG may have experienced higher magnitudes of pain and a greater interference in their daily life. Finally, the trend of elevated CBF in the rCFL subjects suggested that those elevations, which were identified to also be elevated relative to the HC sample, could be clinically present as worsened outcomes such as impairments to physical function in daily life and social functioning.

Temporal occipital fusiform cortex

The TOFC had three important correlations (left= 1: physical function; right= 2: education and NPC) from the CBF data. This suggests that increasingly elevated CBF found in the rCFL subjects relative to the HC was linked with lower physical functioning scores. Furthermore, elevated CBF in rCFL subjects also was correlated with less years of education and a higher number of previous concussions. From the ASL sCoV data, two important correlations (left= 2: visual memory and impulse control; right= 0) were calculated. This suggests that the decreased ASL sCoV in rCFL subjects was correlated with higher visual memory scores and fewer incorrect test answers (i.e., higher impulse control).

Similar to the SPG, the TOFC was not consistently correlated with test categories that directly relate to its function. As noted earlier, this region is involved in visual recognition of faces and objects, thus the important correlations between visual memory and impulse control scores and left ASL sCoV values would most closely align. Those two correlations suggested that rCFL subjects with lower ASL sCoV values had higher visual memory ability and fewer selection mistakes (i.e., fewer mistakes indicated better impulse control)(Lovell 2006). For example, the elevated CBF in the rCFL players was correlated with a lower capacity for physical functions such as walk, lifting or climbing steps, and a higher number of diagnosed concussions during their lifetime (Lovell 2006). Furthermore,

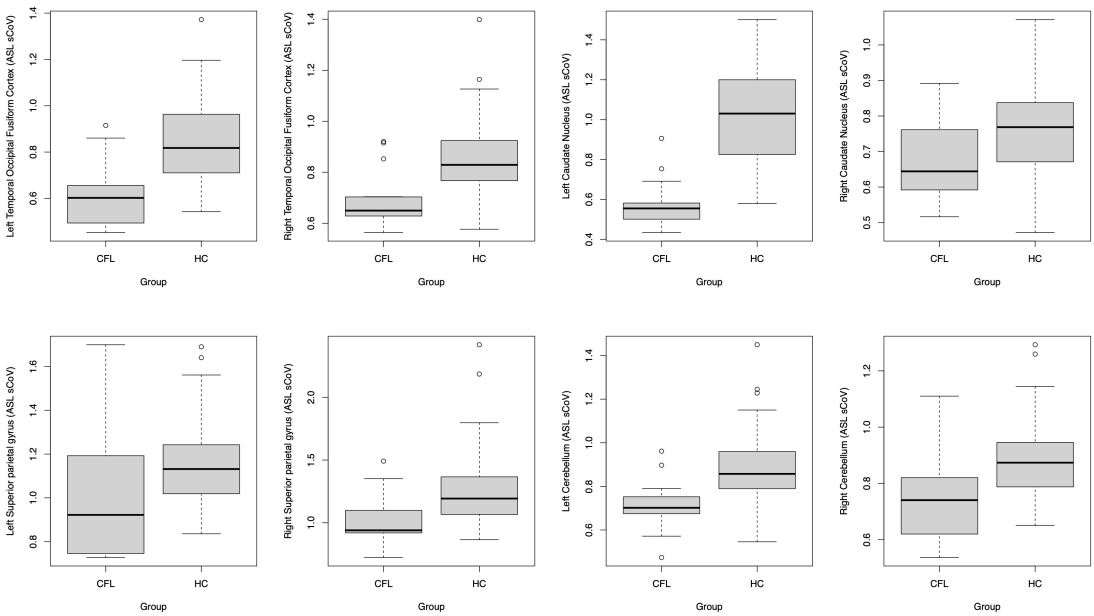

FIGURE 4.3: Boxplots showing arterial spin labelling (ASL) spatial coefficient of variance (sCoV) from both left and right temporal occipital fusiform cortex, caudate nucleus, cerebellum and superior parietal gyrus. These four brain regions showed significant difference, based on a Mann-Whitney U test, between retired Canadian Football League (rCFL) subjects and the healthy age/sex matched controls (HC). The rCFL subjects exhibited bilaterally reduced sCoV in these regions relative to the HC subjects.

elevated ASL sCoV values were correlated with lower visual memory scores and more incorrect ImPACT test answers (Lovell 2006). These correlations were interesting as they suggested that the elevation of both CBF and ASL sCoV values, which in the case of CBF was higher in the rCFL players relative to healthy controls, was associated with worse demographic or neuropsychological scores.

Caudate nucleus

The CN had two important correlations (left= 1: physical health; right= 1: energy and fatigue) from the CBF data. Since the CN was decreased relative to the HC sample, decreasing CBF values in the CN were correlated with better physical health and higher energy levels. One important correlation was calculated from the ASL sCoV data (left= 0; right= 1: cognitive efficiency index). This suggests that decreased ASL sCoV values

in the rCFL subjects was correlated with higher cognitive efficiency.

All three of the important correlations align closely with the normal function of the CN (Grahn et al. 2008). The negative correlation found with the ASL sCoV quantification suggests that higher ASL sCoV values in the CN could cause cognitive inefficiencies. This aligns with the normal function of the CN of sensorimotor coordination of requiring abnormal cognitive efforts to achieve a physical task. This finding was closely related to the negative correlations with the CBF data which found that elevated normalized CBF in the rCFL subjects could lead to greater difficulty in completing physical tasks and feeling worn out (Ware 2000). Although these correlations are logical, it was surprising that both CBF and ASL sCoV metrics were decreased in the rCFL sample relative to the healthy controls. This suggests that there was a general abnormality present in the rCFL subjects, but a higher degree of CBF or ASL sCoV in the CN of some subjects may have been affecting their physical health.

Cerebellum

Finally, the cerebellum had no important correlations with the CBF data but was calculated to have two from the ASL sCoV data (left= 1: pain; right= 1: pain). This suggests that the relatively reduced ASL sCoV found in the rCFL subjects was correlated with bilaterally higher pain scores. This was a correlation that contradicted the results of the other 3 bilaterally abnormal ROI by suggesting that an elevation in ASL sCoV was correlated with lower pain magnitude and interference in the rCFL subjects. Pain has been researched in the cerebellum recently and studies have shown the cerebellum is active and responds differently to somatic versus visceral (Claassen et al. 2020), expected pain (Michelle Welman et al. 2018), and pain-related motor alterations (Coombes and Misra 2016). The cerebellum is a unique part of the human brain that is involved in most aspects of cognition but may be affected differently than the cerebrum in terms of blood flow. As an additional consideration, the cerebellum receives blood primarily from the vertebral, basilar, and posterior cerebral arteries prior to reaching the Circle of Willis (Purves et al. 2001). Thus, trends associated with elevations or reductions of CBF in the cerebrum may not remain consistent in the cerebellum.

Limitations

The work presented was thoughtfully analyzed but should be interpreted with the understanding of some limitations. The most prominent limitations of this study were

the small sample of rCFL subjects and the comparison of ASL data acquired on different MRI scanners. A larger sample of rCFL players or subjects with a history of multiple concussions would have strengthened this work, and thus further research is encouraged to advance the understanding of concussion-related alterations to microvasculature. With respect to the group comparison of ASL datasets, this was performed with the understanding of this limitation (Mutsaerts et al. 2015). The bias of our multisite data acquisition was largely reduced through the use of ASL data acquired with the same MRI vendor and pulse sequence, and identical preprocessing. Furthermore, partial volume correction was performed and normalization of left and right CBF and ASL sCoV data to each subject's respective left and right grey matter volume allowed for the comparison of proportionate ratios rather than the raw CBF or ASL sCoV values.

It should be noted that some of our previous work with this data involved a statistical analysis using subject-specific Z-scoring to assess focally atypical ROIs, identified as outliers greater than two standard deviations from the group ROI mean, and symmetry of the total number of atypical ROIs (Danielli et al. 2021; Danielli et al. 2022a). However, this method was limited to intra-group analyses and substantial data exclusion due to the normal distribution requirement for robust Z-scoring. Therefore, a non-parametric statistical analysis was performed to improve the reliability of the analyses and reduce biases.

The ROIs selected and the statistical analysis used, the SPG and the superior parietal lobule were both included in this study. The SPG was an ROI from the Hammers Brain Atlas (Hammers et al. 2003) and the superior parietal lobule from the Harvard-Oxford Brain Atlas (Desikan et al. 2006). The naming convention of these two regions may not accurately describe their anatomical brain coverage as the SPG, which was the most significant ROI in this study based on outliers and correlations, would be assumed to be a superficial and smaller brain region, however, it actually covers a substantial portion of the parietal lobe (Hammers et al. 2003). Alternatively, the superior parietal lobule is much smaller than the SPG. Thus, the SPG parietally or fully captures several Harvard-Oxford ROIs including the superior parietal lobule, lateral occipital cortex superior division, precuneus, and postcentral gyrus (Desikan et al. 2006). With that note, this area of the brain was still detected to be especially vulnerable to concussive injury. In addition to this, based on the biostatistical work by Li et al. a Bonferroni correction was not applied in this study as it is exploratory in nature by using ASL sCoV on a regional basis, and thus multiplicity corrections were not necessary (Li et al. 2016).

Therefore, ROI were considered different based on if their 95% confidence interval did not include zero, and if correlations exceeded a magnitude of $\geq$0.55.

Finally, the true number of sub-concussive and concussive impacts an athlete sustains over their career is essentially impossible to determine without constant monitoring using newly available helmet accelerometers and force sensors (Fickling et al. 2021). Using concussion history is not always an accurate or reliable metric, especially for retired athletes who played in an era that largely did not understand or acknowledge head injuries. For example, helmets were made mandatory in the NFL in 1940 (after 20 years of competition), and rising head and spine injuries inspired the first helmet rules and regulations being implemented in 1973 (Levy et al. 2004a; Levy et al. 2004b). Moreover, the NFL only created their Committee on Traumatic Brain Injury in 1994 to make rules, equipment, and assessment improvements to reduce the rate of concussions (Casson et al. 2010). Although it is now known that reported concussion incidence has remained high in professional American football players (in 1979, 1:10,000 concussions per athletic exposures rising to 1.47:10,000 by 2019)(Clarke and Powell 1979; Mack et al. 2021), the number of serious head injuries and fatalities has drastically decreased (Levy et al. 2004a). That further strengthens the argument that head injuries were not being reported or diagnosed well, especially since athletes in certain positions are more likely to sustain a concussion (Mack et al. 2021; Nathanson et al. 2016). Therefore, the NPC and YSLC metrics are interesting to provide some general context but are not accurate quantitative measures because of their unreliability and inconsistent reporting.

Conclusions

This study on retired CFL players showed preliminary findings that regional abnormalities may have been present relative to HCs, that abnormalities could be present bilaterally, detected using both CBF and ASL sCoV values for quantification, and that regional CBF and ASL sCoV abnormalities were correlated with concussion history and the self-reported presentation of clinical test metrics. This study found four brain ROIs (SPG, TOFC, CN, and cerebellum) that may be more vulnerable to repetitive concussion-related microvascular injuries that are indicative of areas for future research. As this was the first study to analyse ASL data using ASL sCoV on a regional basis, the consistency between the CBF and ASL sCoV analyses results suggest that ASL sCoV may be a useful compliment to CBF data; however, further research is required to confirm this. Furthermore, the SPG had twelve important correlations with demographic

and clinical test metrics. Finally, there was a trend in three of the four bilaterally abnormal ROI that suggested that elevated levels of CBF and ASL sCoV was expressed as a more aggravated concussion history and worse neuropsychological test scores. Although further research is required, this study provides exploratory evidence of microvascular differences present in aging, retired professional football players that may have been related to their history of repetitive concussive and sub-concussive impacts decades earlier.

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Conflict of interest disclosure

Dr. Petr and Dr. Mutsaerts are co-creators of the ASL processing software, ExploreASL. Dr. Noseworthy is the CEO and co-founder of TBIfinder Inc., which is not relevant to this current work. All other authors declare that they have no conflict of interest.

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Chapter 5

Abnormal standard and fractional amplitude of low frequency fluctuations

5.1 Overview

5.1.1 Context of the study

Despite the many benefits of playing sports, concussions can cause lasting disturbances at all levels of competition including former collegiate and professional athletes. Much of the functional brain research on concussions has been performed using resting state functional brain activity (rsfMRI), which has shown concussion-related alterations to brain networks, some of which are essential to healthy cognition. However, other methods need to be implemented to identify functional brain damage with more regional accuracy. In future, higher spatial accuracy could lead to improvement in clinical concussion rehabilitation.

An alternative approach to a functional connectivity analysis is the examination of low frequency oscillations (0.01-0.08Hz) present in rsfMRI acquisition data. These are shown to be closely linked to neural activity based on spontaneous blood-oxygen level dependent (BOLD) signal composition. Analyses techniques measuring the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) can be used to determine the voxel-wise spontaneous neural

activity and frequency composition of the BOLD signal.

The purpose of this study was to apply the less commonly implemented ALFF and fALFF measurements to identify if regionally abnormal rsfMRI signal spontaneity was present in a sample of retired Canadian Football League (rCFL) players with a history of repetitive concussive head impacts and years after their last reported concussion. Based on our individual comparison of each rCFL subject against a large healthy dataset through a Z-scoring approach, it was expected that rCFL subjects would exhibit regionally unique BOLD signal spontaneity abnormalities but share similar differences across the whole rCFL group. It was also expected that BOLD signal spontaneity, measured by ALFF and fALFF, would be regionally reduced in areas of the brain with lower functional activity as a result of concussion-related damage.

5.1.2 Declaration statement

Ethan Danielli, as first author, was involved in the study conceptualization, data curation, methodology, data processing, formal statistical analysis, writing of the original draft, and revisions to the final manuscript. Dr. Bhanu Sharma, as second author, a Post-Doctoral Fellow in Dr. Noseworthy's group, was involved in data processing, formal statistical analysis, and revisions to the final manuscript. Cameron Nowikow, as third author and PhD candidate in Dr. Noseworthy's group, was involved in methodology, data processing, formal statistical analysis, and revisions to the final manuscript. Mitchell Doughty, as fourth author and former MASc student in the research group, was involved in the recruitment of subjects, data acquisition, and data curation. Finally, Dr. Michael D. Noseworthy, the corresponding author and primary investigator for this research group, was involved in the study conceptualization, data curation, formal statistical analysis, funding acquisition, investigation, resources, supervision, and revisions to the final manuscript.

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5.2 Spontaneous brain fluctuation abnormalities in retired football players

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5.2.1 Abstract

Introduction: Collision sports such as American-style football have been shown to cause acute and lasting functional brain alterations. One indicator of functional brain abnormality is the spontaneity of signal amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF), both of which are derived from resting state functional MRI (rsfMRI). These metrics provide a spatial map of areas in which spontaneity of signal departs from normal or control values. It was hypothesized that, using a personalized analysis approach, former professional American-style football players from the Canadian Football League (CFL) would show decreased ALFF and fALFF in some brain regions.

Materials & methods: Eighteen retired CFL (rCFL) players (male, aged 58.78 ±6.10) were scanned using a 3T MRI, and completed neuropsychological testing. Healthy age and sex-matched control data (n= 62, male, aged 58.81±5.69) was downloaded from the OASIS-3 study. Preprocessing was performed using CONN; ALFF metrics were computed in this package, and subsequently, voxel-wise and regional Z-scoring analysis was completed in MATLAB. 142 brain regions-of-interest (ROIs) were examined from the cortical, sub-cortical (Harvard-Oxford) and cerebellar (Probabilistic FNIRT) brain atlases. Through correlation analyses and regression tests, associations between participant demographics, clinical data, and the total number of their abnormal (-3≤Z-score≥+3) ALFF and fALFF brain ROIs was computed.

Results: The ALFF and fALFF analysis found two large clusters of decreased signal spontaneity and one large cluster of increased signal spontaneity in retired athletes compared to controls. The Z-scoring analysis calculated 30 ROIs to be significantly abnormal in more 50% of the rCFL subjects using ALFF, and 13 ROIs in more than 25% of subjects abnormal based on fALFF. These abnormal ROIs included the right amygdala, right thalamus, bilateral occipital pole, and bilateral cerebellum crus II. The total number of positive fALFF Z-score outliers correlated with a longer career length.

Conclusion: Spontaneous brain activity, a measure of brain health, was compromised in retired athletes in comparison to matched controls. Our analyses showed that cerebellar and central sub-cortical brain regions were most frequently and seriously abnormal. Adding to neuroimaging studies demonstrating post-retirement

neurological impairment using connectivity metrics, our study shows that spontaneous brain activity is also perturbed years after competitive sport.

Key words: concussions, repetitive sub-concussive head trauma, retired athletes, functional magnetic resonance imaging (fMRI), amplitude of low-frequency fluctuations (ALFF), fractional ALFF (fALFF)

5.2.2 Introduction

Sport-related concussions are a concern and known risk for those playing collision sports (Cassidy et al. 2004; Halstead et al. 2018; Zuckerman et al. 2015). Despite the benefits of sport participation (which include positive physical, cognitive, and neuropsychological adaptations)(Neufer et al. 2015; Penedo and Dahn 2005; Reiner et al. 2013; Zhang et al. 2022), concussions can cause acute disturbances (Yrondi et al. 2017) in former collegiate (Kerr et al. 2018; Montenigro et al. 2017) and professional athletes (Hart et al. 2013; Hutchison et al. 2018; Terpstra et al. 2019).

Much of the functional brain research on concussion has been performed per resting state functional brain activity (rsfMRI)(Greicius et al. 2003; Johnson et al. 2020; Zhu et al. 2015), which has shown concussion-related alterations to brain networks that are essential to healthy cognition (Power et al. 2011). Acutely post-concussion, damage has been shown in the inferior frontal lobe, cingulum, insula, and hippocampi (Churchill et al. 2017b). However, in former elite athletes, much of the research has utilized network connectivity analyses, demonstrating alterations to the default mode, visual, and dorsolateral frontal networks (Cassoudesalle et al. 2021; Hampshire et al. 2013; Plourde et al. 2019). Thus, other methods need to be implemented to identify functional brain damage with higher spatial accuracy with a goal of improved concussion rehabilitation.

An alternative approach to functional connectivity analysis is examination of low frequency oscillations (0.01-0.08Hz), present in rsfMRI acquisitions (Lowe et al. 2000) and shown to be closely linked to neural activity based on spontaneous blood-oxygen level dependent (BOLD) signal composition (Biswal et al. 1995; Kiviniemi et al. 2000). Analysis measuring the amplitude of low-frequency fluctuations (ALFF) can be used to determine the spontaneous neural activity and frequency composition of the BOLD signal in each voxel (Zang et al. 2007). Both techniques have been shown to be robust (Zuo et al. 2010), but fractional ALFF (fALFF) effectively removes contaminating some additional physiological noise present at frequencies while ALFF has better test-retest reliability (Zou et al. 2008).

Extending to clinical application, in the acute phase of concussion (<72 hours) ALFF was decreased in the default mode and frontoparietal networks (Ly et al. 2022). In the sub-acute phase post-concussion (i.e., 3-4 months), fALFF was found to be elevated in the left striatum (Stephenson et al. 2020), middle occipital cortex, right middle temporal cortex, and right angular gyrus (Vedaei et al. 2021). After about 4 years after a severe and diffuse traumatic brain injury and still experiencing chronic symptoms, one study found increased ALFF in the frontal pole, superior frontal gyrus, middle frontal gyrus, paracingulate gyrus, and superior parietal lobe (Palacios et al. 2013). However, the ALFF and fALFF methods have not yet been applied to a retired athlete population to assess the effects of a history of concussions (i.e., less severe head traumas).

The purpose of this study was to examine if retired aging collision sport athletes with a complex history of concussions and repetitive sub-concussive head impacts have any functional abnormalities present years after retirement from professional sport and their last (known) concussion. The sample of athletes were retired Canadian Football League (rCFL) players due to their extensive years of playing a collision sport. Functional abnormalities would be identified and quantified based on the BOLD signal composition using the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) to indicate whether brain regions exhibited abnormally decreased spontaneous BOLD signal activity relative to healthy controls. This study also aimed to identify brain regions that most commonly show disturbances in spontaneous brain activity years after competitive play. It was hypothesized that, using a personalized analysis approach, former professional American-style football players from the Canadian Football League (CFL) would show decreased ALFF and fALFF in some brain regions. These decreases in ALFF and fALFF would be expected based on the history of concussions sustained by the subjects.

5.2.3 Materials & methods

Subjects

This study was approved by our local research ethics board (Hamilton Integrated Research Ethics Board, HiREB) and the work described was conducted in

accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

We studied 18 rCFL athletes with a complex history of repetitive concussive and sub-concussive impacts (100% male, aged 58.78±6.10, range 46-66 years old). We say 'complex history' because it is not possible to know how many sub-concussive hits these players may have sustained over their careers, and not all concussive injuries were diagnosed formally. However, we do know the sport they played has a high likelihood of brain injury. The subjects were recruited through local newspaper advertisements and written informed consent was acquired (in person) for each subject prior to participation in our study. Subjects were included if they were rCFL players, had played in at least one CFL season, had no contraindications for MRI (e.g., pacemaker, claustrophobia, etc.), and had no documented substance abuse or psychological illnesses. Subjects were excluded if they did not meet the above criteria, as well as if they had sustained a concussion in the past 5 years, or had any health condition that required daily treatment/therapy (e.g., diabetes, cancer). Following scanning, a neuroradiologist reviewed the gross structural MR images (e.g., T1, T2, T2-FLAIR, SWI, etc.) to rule out possible co-morbidities. No rCFL players had brain abnormalities visible in their standard clinical scans at the time of the image acquisitions.

A healthy control dataset of 106 age and sex-matched subjects was downloaded from the OASIS-3 Longitudinal Neuroimaging, Clinical, and Cognitive Dataset for Normal Aging and Alzheimer's Disease (LaMontagne et al. 2019). All subjects were initially included in our control cohort, though following preprocessing and quality assurance checks to determine data quality, 44 subjects were excluded (because, for example, they had >30 invalid resting state fMRI (rsfMRI) data time points or poor signal-to-noise ratio). Therefore, a total of 62 subjects were included in the concussed cohort (100% male, aged 58.81±5.69, ranged 46-66 years old). None of the rCFL players were excluded based on denoising. Further details of denoising are provided below.

Demographic and clinical data acquisition

Demographic metrics of age, years of education, professional football career information (career length in years and position), and approximated concussion history (number of previous concussions (NPC) and years since their last sport-related concussion (YSLC)) were recorded from the rCFL players. Based on recent literature, the position of the players was used to approximate the type of head impacts that the players would have most likely experienced during their career, categorized as either low magnitude but high frequency or high magnitude but low frequency (Baugh et al. 2015; Karton et al. 2020). The rCFL subjects also completed a battery of clinical tests to measure cognitive, emotional, and physical health. These tests were explained in our previous study on the same subjects (Danielli et al. 2022) and included the Immediate Post-Concussion Assessment Tool (ImPACT)(Lovell 2006), Beck's Depression Inventory II (BDI-II)(Smarr and Keefer 2011), and the Short-Form 36 (Ware 2000).

MRI data acquisition

The 18 rCFL subjects obtained MRI brain scans in Hamilton, Canada using a 3T GE Discovery MR750 MRI scanner and 32-channel head coil (GE Healthcare, Waukesha WI). Each subject's scans included a high-resolution 3D T1-weighted scan and resting state functional MRI (rsfMRI). The 3D T1-weighted scan had the following parameters: axial 3D T1-weighted inversion-recovery prepared fast spoiled gradient (IR-prepared fSPGR); (TR/TE/TI= 11.34ms/4.25ms/450ms; flip angle= 12°; 256 X 256 matrix, slice thickness= 1mm, FOV= 25.6cm, number of slices= 140, 1mm isotropic acquisition). The rsfMRI scans had the following parameters: eyes closed, gradient echo EPI sequence (TR/TE/flip= 2000ms/35ms/ 90°, slice thickness= 4mm, no slice gap, FOV= 22cm, matrix= 64 X 64, in-plane resolution= 3.44mm, number of temporal points= 240). Each subject's scan also included T2, T2-FLAIR and SWI scans for assessment of any sub-clinical pathology by a neuroradiologist. The healthy control data was acquired with similar parameters, however, using a 3T Siemens MRI system (LaMontagne et al. 2019).

Data processing

The open-source MATLAB (v.R2020b 9.9.0.1467703)/SPM (v.12 7771)-based software, CONN (v.21.a), was used for the preprocessing, denoising, and first and second level analysis of the ALFF and fALFF data (Whitfield-Gabrieli and Nieto-Castanon 2012). The default CONN preprocessing pipeline was implemented with the addition of indirect segmentation and normalization to allow for co-registration of functional and anatomical data (Whitfield-Gabrieli and Nieto-Castanon 2012). This included motion correction, realignment, outlier detection, simultaneous grey matter, white matter and cerebrospinal fluid segmentation, Montreal Neurological Institute (MNI) standard brain space normalization using a 4th order spline interpolation (structural: 1mm isotropic, functional 2mm isotropic), smoothing, and the indirect co-registration of functional and anatomical data (Whitfield-Gabrieli and Nieto-Castanon 2012). An 8mm Gaussian kernel smoothing spatial convolution kernel was applied to the functional data (Whitfield-Gabrieli and Nieto-Castanon 2012). Finally, a conservative outlier detection of 95% was used based on CONN documentation recommendations (Whitfield-Gabrieli and Nieto-Castanon 2012).

Along with a default bandpass filter (0.008 to 0.09 Hz) to remove very low frequencies causing frequency drift and higher frequencies of physiological noise, denoising in CONN is done using an ordinary least squares regression to identify and remove potential confounding effects (Whitfield-Gabrieli and Nieto-Castanon 2012). It is recommended that the mean global signal, mean motion, and number of valid scan values should be greater than 95% relative to the null hypothesis distribution (i.e., normal distribution) for adequate denoising (Whitfield-Gabrieli and Nieto-Castanon 2012). The default dimensions (P) of confounding effects were adjusted to reach an optimal combination: white matter (15P), CSF (10P), realignment (infinite), effect of rest (infinite), scrubbing (infinite), and grey matter (1P) (mean global signal= 99.5%; mean motion= 99.3%; valid scans= 96.2%) (Power et al. 2011; Whitfield-Gabrieli and Nieto-Castanon 2012).

Following denoising, amplitude of low-frequency fluctuations (ALFF)(Zang et al. 2007) and fractional ALFF (fALFF)(Zou et al. 2008) analyses were performed. Both the voxel-wise ALFF and fALFF were calculated using the default CONN

settings with the addition of signal normalization (Whitfield-Gabrieli and Nieto-Castanon 2012). The ALFF (Equation 5.1) is defined as:

$$ALFF = \sum_{(k-1):f_k\in[0.01,0.1]}^{N-1} \sqrt{\frac{{a_k}^2(f_k) + {b_k}^2(f_k)}{N}} \tag{5.1}$$

Where f_k is the frequency and a_k and b_k are coefficients determined from the Fourier series in Equation 5.2:

$$x(t) = \sum_{k=0}^{N-1} [a_k \cdot \cos(2\pi f_k t) + b_k \cdot \sin(2\pi f_k t)] \tag{5.2}$$

Where x(t) is the BOLD signal, in any given voxel, at each time point. The fractional ALFF (fALFF) (Equation 5.3) is then calculated as:

$$fALFF = \frac{\sum_{(k-1):f_k\in[0.01,0.1]}^{N-1} \sqrt{\frac{{a_k}^2(f_k)+{b_k}^2(f_k)}{N}}}{\sum_{(k-1)}^{N-1} \sqrt{\frac{{a_k}^2(f_k)+{b_k}^2(f_k)}{N}}} \tag{5.3}$$

Finally, group-wise differences were calculated for ALFF and fALFF based on general linear modelling and threshold free cluster enhancement (TFCE) involving 10,000 permutations to identify significantly different voxel clusters (Whitfield-Gabrieli and Nieto-Castanon 2012). Significant difference of the clusters was based on family-wise error corrected p-values. The output for the TFCE analyses also provided the number of voxels in the significant clusters, the number of peaks, and the TFCE value.

Group and individual statistical Z-scoring analyses

A statistical Z-scoring approach was applied on a voxel-wise level in the same manner to both ALFF and fALFF data. The healthy control data were tested for a group normal distribution for each voxel using the Anderson-Darling normality test (Anderson and Darling 1952). The Anderson-Darling test was chosen because it has been found to have adequate statistical power on moderate sample sizes (n=

60) and the power of the test increases with more outliers present (Saculinggan and Balase 2013). Z-scoring requires a normal distribution, thus all voxels that failed (i.e., that were not normally distributed across the entire healthy control group) were excluded from further analyses. For the ALFF data 28,199 of the 242,545 (12%) of the voxels in the brain were excluded, and for the fALFF data 19,393 of the 242,545 (8%) brain voxels were excluded. Z-scoring of the rCFL subjects was applied on a subject-by-subject basis so that outliers in a single former football player could be delineated relative to the normative data. The mean and standard deviation for each voxel of the healthy control dataset was then used to calculate the Z-score of each voxel within brains of each of the 18 rCFL subjects. Z-scores that were at least three standard deviations away from the healthy control group mean were considered to be indicative of brain abnormality (here assumed to be related to previous brain injuries). For more clinical applicability, 142 brain ROIs were derived from the cortical and sub-cortical Harvard-Oxford brain atlases (Desikan et al. 2006; Frazier et al. 2005; Goldstein et al. 2007; Makris et al. 2006) and the FNIRT cerebellar brain atlas (Diedrichsen et al. 2009), where ROIs were segmented into left and right ROIs when appropriate (i.e., when bilateral and not a midline structure). A Z-score was then calculated for all 142 ROIs for each CFL subject using the mean Z-score of the abnormal voxels contained within each ROI. A mean Z-score was then calculated for each ROI across all 18 CFL subjects to determine the average degree of assumed concussion-related injury, and to identify the most commonly injured brain regions.

Finally, the distribution of Z-scores within the significantly different clusters produced by TFCE analysis were also calculated on a voxel-wise basis. This was done to visualize the consistency of decreased or increased spontaneous BOLD signal activity in the clusters, and how those clusters compared to the sign and magnitude of the ROI Z-scores.

Demographic and clinical test correlations

For each rCFL subject, the count of overall total, total positive, and total negative abnormal ROIs for both ALFF and fALFF were compared with demographic information, concussion history and clinical test results using Pearson's r

correlation (RStudio, v.1.3.1093). Furthermore, a series of linear regression and Pearson's r correlation tests were performed between the Z-scores of the six commonly vulnerable ROIs and the demographic and clinical test scores. This was done to determine if damage to the most consistently abnormal ROIs (per ALFF and fALFF analyses) were related to CFL subject concussion history, post-concussion symptoms, or cognitive changes. Bonferroni correction was applied to correct for family-wise errors (Armstrong 2014; Li et al. 2016). Therefore, for demographic and concussion history correlations (i.e., 6 measures in total), the p-value threshold of significance was $p<0.008$ (i.e., $0.05/6= 0.008$), and the p-value threshold of significance was $p<0.003$ (i.e., $0.05/15= 0.003$) for the neuropsychological correlations (i.e., 15 neuropsychological metrics considered).

5.2.4 Results

Threshold free cluster ehancement (TFCE) analyses

Using ALFF and fALFF analyses we noted clusters of voxels that were significantly different in rCFL athletes relative to healthy age/sex matched controls. The significantly different clusters were in similar locations based on both ALFF and fALFF approaches, revealing regions of decreased BOLD signal spontaneity (i.e., significantly decreased ALFF and fALFF) in areas of the rCFL subjects' deep brain, anterior cerebellum, and superior occipital lobe (Table 5.1), and increased spontaneous BOLD signal activity (i.e., significantly increased ALFF and fALFF) in rCFL subjects around exterior aspects of the entire brain and posterior cerebellum (Figure 5.1).

TABLE 5.1: Results of the ALFF and fALFF threshold free cluster enhancement (TFCE) analyses showing the largest three clusters calculated from each analysis. This table contains the central coordinates of each cluster, the number of voxels within each cluster, the number of peaks, the TFCE value, and the degree of significant difference between CFL subjects and the healthy controls with family-wise error correction applied to the p-values.

ALFF TFCE clusters				
Cluster (x,y,z)	**Size (voxels)**	**Peaks**	**TFCE**	**Peak p-FWE**
+04 -22 +6	66652	387	45857.79	0.00
-30 -78 +8	76449	473	15033.54	0.00
+10 -98 +26	2149	42	5686.71	0.00
fALFF TFCE clusters				
Cluster (x,y,z)	**Size (voxels)**	**Peaks**	**TFCE**	**Peak p-FWE**
+12 -80 -42	30805	575	2856.94	0.00
+24 -12 -16	20701	494	1741.84	0.00
+14 -92 +34	5111	106	3334.25	0.00

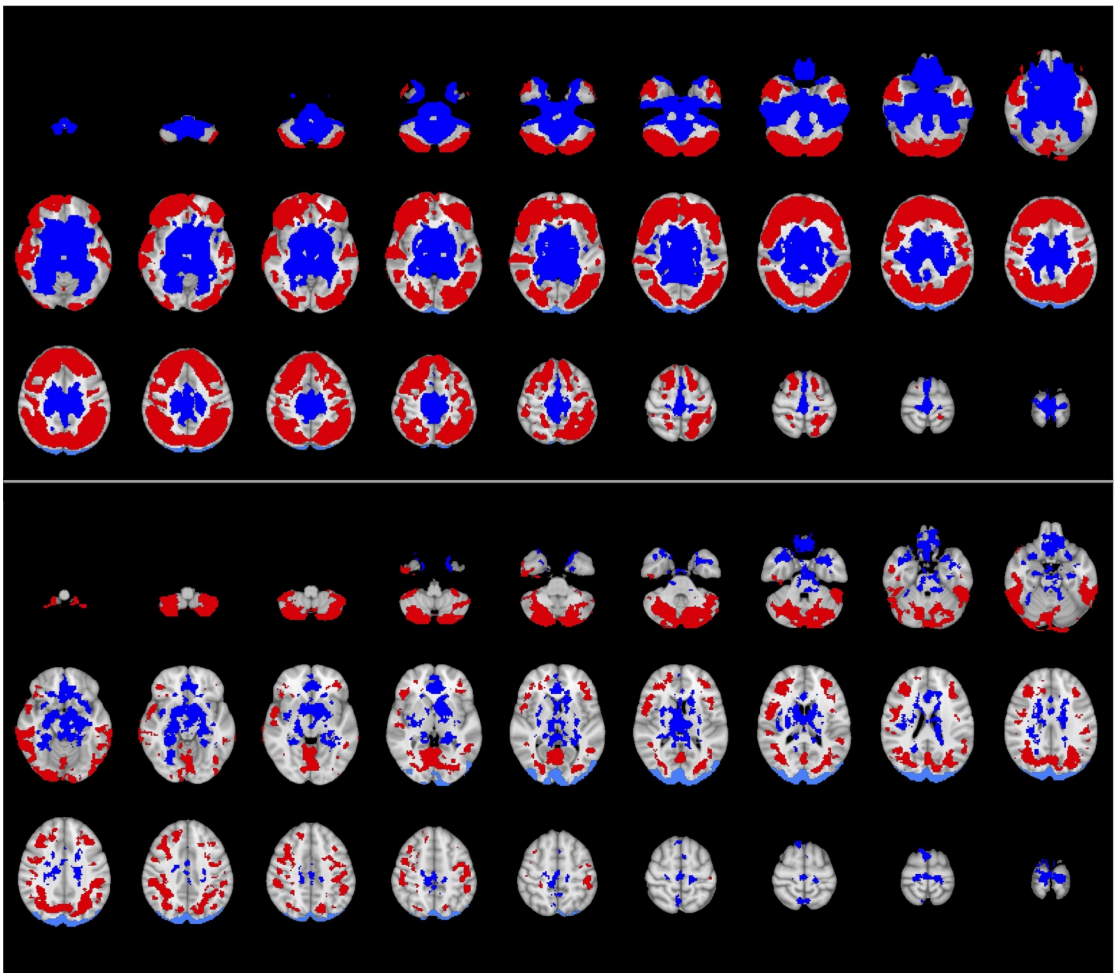

FIGURE 5.1: The significantly abnormal amplitude of low frequency fluctuations (ALFF) and fractional ALFF (fALFF) clusters as calculated with the threshold free cluster enhancement (TFCE) non-parametric statistical tests after 10,000 simulations. The clusters were of similar location for both ALFF (top) and fALFF (bottom), which found a large cluster of reduced signal spontaneity in the central aspect of the cerebrum and anterior cerebellum (cluster 1, blue), a large cluster of increased signal spontaneity in the lateral cerebral cortex and posterior cerebellum (cluster 2, red), and a smaller cluster of reduced signal spontaneity in the occipital lobe (cluster 3, light blue). These brain slices allow for visualization from the axial perspective.

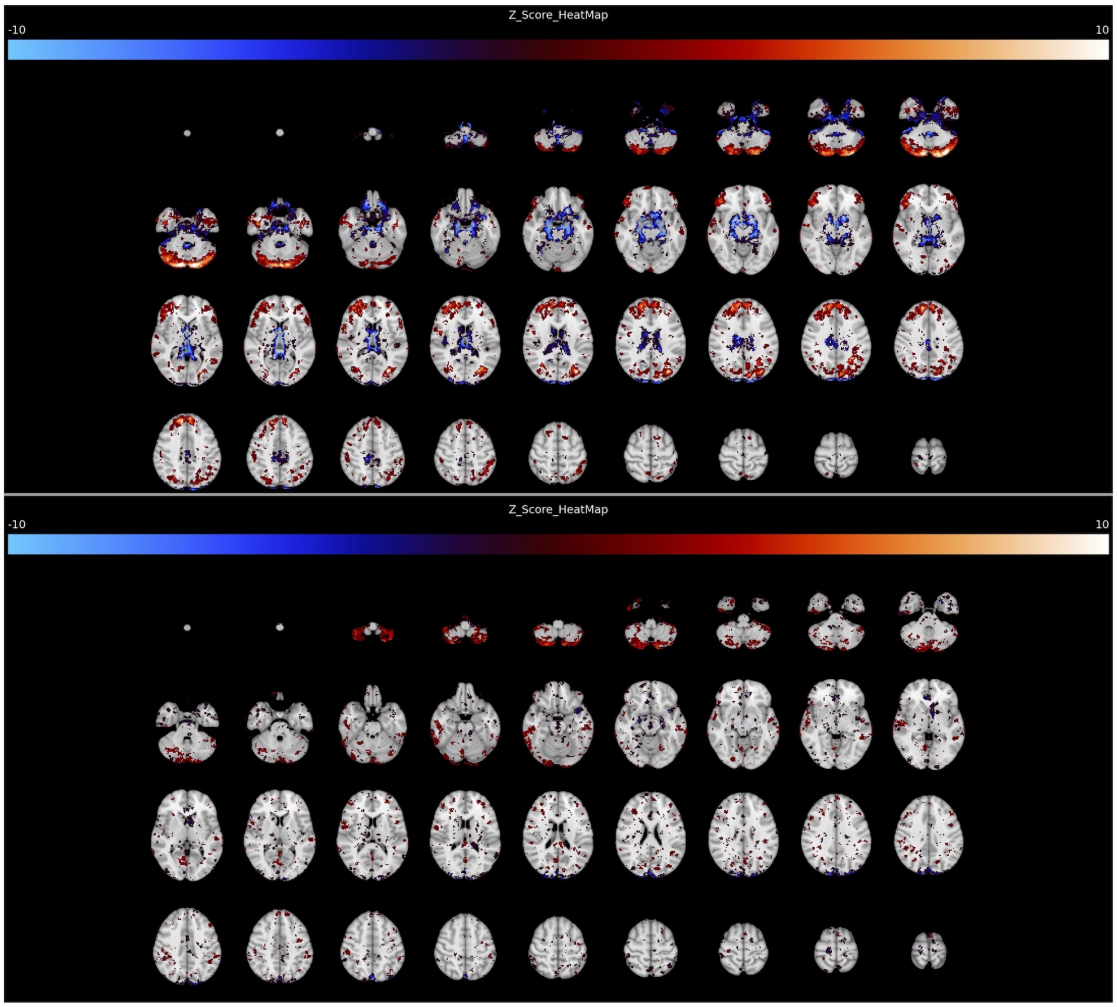

FIGURE 5.2: A heatmap of the significantly abnormal voxels using the ALFF (top) and fALFF (bottom) data that were greater than +3 standard deviations from the healthy control mean or less than -3 standard deviations from the healthy control mean. This heatmap is representing the number of CFL subjects that were found to have a significant Z-score in the same voxel. Therefore, voxels in white represent that at least 10 CFL subjects had a significantly positive Z-score in that voxel, whereas light blue voxels represent at least 10 CFL subjects had a significantly negative Z-score in that voxel. These brain slices allow for visualization from the axial perspective.

Voxel and ROI Z-scores

Voxel-wise group analysis is represented by ALFF and fALFF colourmaps indicating the number of shared voxels across all CFL subjects that contained abnormal Z-score values (Figure 5.2), where positive abnormal Z-score values are represented by red (i.e., voxels with increased spontaneous activity) and negative abnormal Z-scores by blue (i.e., voxels with decreased spontaneous activity).

Group-wise ROI Z-scores

Using the ALFF method, 30 ROIs were identified as being significantly abnormal ($-3 \leq Z \leq +3$) in a majority of the CFL subjects (i.e., at least 10 CFL subjects) (Figure 5.3 & Table 5.2). With the fALFF approach, 13 ROIs were found to be significantly abnormal in more than a quarter of the former players (Figure 5.3 & Table 5.3). ROIs were considered abnormal if the Z-score for that individual was ≥ 3 standard deviations away from the mean indicating elevated or reduced BOLD signal spontaneity within that ROI in different subjects. This was found in the left cerebellum crus I, left frontal orbital cortex, left lateral occipital cortex superior division, left occipital pole, right caudate, and right parahippocampal gyrus anterior division (Tables 5.2 & 5.3).

From a group perspective, there were many ROIs found as significantly abnormal based on ALFF or fALFF data. However, only six brain ROIs were noted to have abnormal ALFF in more than half of the former CFL players and with more than a quarter of the players being abnormal with regards to fALFF. Those ALFF and fALFF shared ROIs were the left and right cerebellum crus II, left and right occipital pole, right amygdala, and right thalamus (Figure 5.3). It was also determined that most ROIs that were consistently abnormal in the CFL subjects were found to have reduced BOLD signal spontaneity, represented by Z-scores lower than -3 standard deviations from the healthy control mean.

Of the 30 ROIs that had abnormal ALFF data, 22 ROIs (73%) had a mean Z-score below -3 standard deviations. Another 6 ROIs (20%) had conflicting ALFF data, represented as an ROI mean Z-score between +3 and -3, suggesting that either an increase or decrease in spontaneity was observed. Of the 13 ROIs that

TABLE 5.2: The number of CFL subjects that had each ROI deemed abnormal with ALFF values at >3 or <-3 standard deviations from the healthy control mean, as well as the mean Z-scores for each ROI. Of the 142 ROIs included in this study, the 30 ROIs in this table were abnormal in more than half (n= 10) of the CFL subjects.

ROI	Number of CFL subjects	Mean (mean±std)
Left Accumbens	11	-3.37 ± 0.22
Right Accumbens	10	-3.39 ± 0.24
Left Amygdala	17	-3.63 ± 0.80
Right Amygdala	17	-3.68 ± 0.37
Left Brainstem	14	-3.41 ± 0.65
Right Brainstem	14	-3.35 ± 1.07
Right Caudate	12	-2.73 ± 1.81
Left Cerebellum Crus I	11	2.99 ± 2.19
Left Cerebellum Crus II	13	3.25 ± 1.50
Right Cerebellum Crus II	13	3.17 ± 1.85
Left Cerebellum I-IV	12	-3.19 ± 0.88
Right Cerebellum I-IV	10	-3.33 ± 0.26
Right Cerebellum VIIIb	10	-3.29 ± 0.27
Cerebellum Vermis X	13	-3.62 ± 0.38
Right Cingulate Gyrus posterior division	10	-3.50 ± 0.33
Left Frontal Orbital Cortex	12	-2.87 ± 1.78
Left Hippocampus	15	-3.62 ± 0.36
Right Hippocampus	15	-3.58 ± 0.36
Left Lateral Occipital Cortex superior division	11	2.52 ± 2.26
Left Occipital Pole	13	-2.35 ± 2.34
Right Occipital Pole	12	-3.06 ± 1.40
Left Pallidum	10	-3.37 ± 0.28
Right Parahippocampal Gyrus anterior division	11	-2.82 ± 1.74
Left Parahippocampal Gyrus posterior division	10	-3.49 ± 0.32
Left Putamen	16	-3.48 ± 0.29
Right Putamen	14	-3.31 ± 0.23
Left Subcallosal Cortex	15	-3.04 ± 1.35
Right Subcallosal Cortex	11	-3.16 ± 0.85
Left Thalamus	18	-3.56 ± 0.42
Right Thalamus	18	-3.55 ± 0.44

had abnormal fALFF data, 5 ROIs (38%) had a mean Z-score below -3 standard deviations, but another 4 ROIs (31%) had conflicting fALFF activity.

Individual (personalized) ROI Z-scores

The ROI-based Z-score analysis was also applied to individual rCFL athletes to identify abnormalities unique to each person rather than searching for group-wise trends (Tables 5.4 & 5.5). From this it was clear that on an individual basis rCFL subjects had many abnormalities. The CFL subjects had on average 73±10 abnormal ALFF ROIs and 63±10 abnormal fALFF ROIs. There was also more than twice as many ROIs exhibiting significantly elevated BOLD signal spontaneity

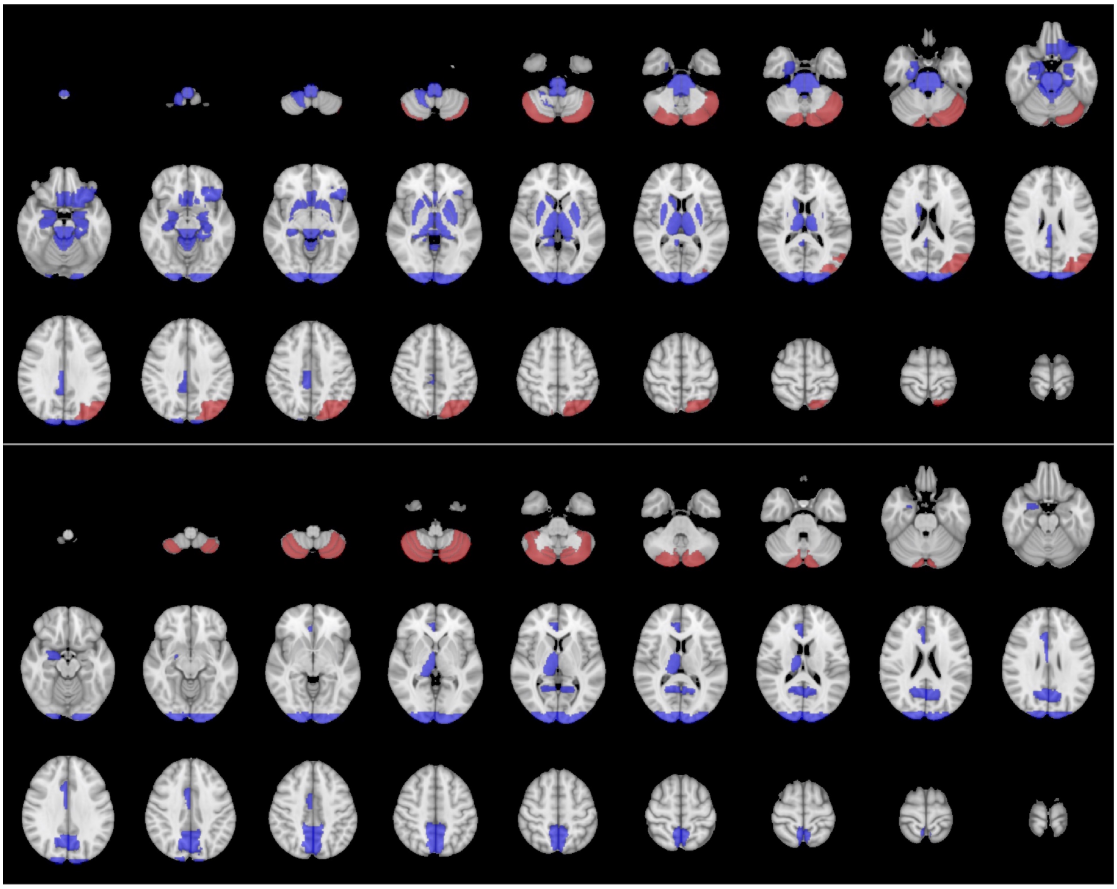

FIGURE 5.3: Based on the voxel-wise Z-scoring of the ALFF (top) and fALFF (bottom) CFL subject data relative to the healthy control data, ROIs were identified as significantly abnormal. There were 30 ROI found to have abnormal ALFF values in at least half of the CFL subjects (n≥ 10), and 13 ROI found to have abnormal fALFF values in at least one quarter of the CFL subjects (n≥ 5). The left and right cerebellum crus II, left and right occipital pole, right amygdala and the right thalamus were significantly abnormal using both ALFF and fALFF methods. ROIs coloured blue were found to have significantly lower Z-scores, indicating reduced signal spontaneity, and ROI coloured red were found to have significantly higher Z-scores, indicating increased signal spontaneity. These brain slices allow for visualization from the axial perspective.

(51±8) than ROIs exhibiting reduced BOLD signal spontaneity (22±5) calculated with the ALFF data. There was also almost twice as many significantly elevated

TABLE 5.3: The number of CFL subjects that had each ROI deemed abnormal with fALFF values at >3 or <-3 standard deviations from the healthy control mean, as well as the mean Z-scores for each ROI. Of the 142 ROIs included in this study, the 13 ROIs in this table were abnormal in more than a quarter (n=5) of the CFL subjects.

ROI	**Number of CFL subjects**	**Mean (mean±std)**
Right Amygdala	5	-3.31 ± 0.21
Left Cerebellum Crus II	5	2.88 ± 2.01
Right Cerebellum Crus II	5	2.79 ± 2.0
Left Cerebellum VIIIa	5	3.28 ± 0.95
Right Cerebellum VIIIa	5	3.22 ± 1.19
Left Cerebellum VIIb	5	3.55 ± 0.81
Right Cerebellum VIIb	6	3.45 ± 0.84
Right Cingulate Gyrus anterior division	5	-3.42 ± 0.96
Left Occipital Pole	7	-3.30 ± 1.04
Right Occipital Pole	9	-3.05 ± 1.74
Left Precuneus Cortex	6	-0.003 ± 3.39
Right Precuneus Cortex	6	-0.99 ± 3.25
Right Thalamus	5	-3.43 ± 0.3

BOLD signal spontaneity fALFF ROIs (40±8) than reduced BOLD signal spontaneity fALFF ROIs (23±7). For both ALFF and fALFF analyses, most of the abnormal ROIs were less than 4 standard deviations away from the healthy control mean, with none more than 5 standard deviations away.

Referring back to the original significantly different clusters (Figure 5.1), the heatmap of abnormal voxels (Figures 5.2) and the consistently abnormal ROIs for ALFF and fALFF (Figure 5.3) aligned spatially very closely with the TFCE identified clusters. Of particular note from the ALFF analysis, 18 CFL subjects (100%) were found to have a significantly decreased bilateral thalamic BOLD signal spontaneous activity, 17 CFL subjects (94%) had decreased bilateral amygdala spontaneous activity, the left putamen had decreased spontaneous activity in 16 CFL subjects (89%), the right putamen had decreased spontaneous activity in 14 CFL subjects (78%), the hippocampus had bilaterally decreased spontaneous activity in 15 CFL subjects (83%), and the left subcallosal cortex also had decreased spontaneous activity in 15 of the 18 CFL subjects (83%) (Table 5.2). Furthermore, 7 of the 30 (23%) of the most consistently abnormal ALFF ROIs were from the cerebellum. Bilaterally, the cerebellum crus II showed increased spontaneous

TABLE 5.4: The number of ROIs that have a mean significantly abnormal ALFF Z-scores separated in this table into the total number of ROIs with positive or negative abnormal Z-scores as well as ROIs falling within the listed abnormal Z-score ranges.

Subject	**Total positive**	**[3, 4)**	**[4, 5)**	**[>5]**	**Total negative**	**(-4, -3]**	**(-5, -4]**	**[<-5]**
1	40	40	0	0	35	34	1	0
2	19	19	0	0	31	31	0	0
3	24	24	0	0	48	48	0	0
4	19	19	0	0	47	47	0	0
5	24	24	0	0	44	44	0	0
6	22	22	0	0	48	48	0	0
7	30	30	0	0	43	43	0	0
8	29	29	0	0	36	36	0	0
9	24	24	0	0	44	44	0	0
10	15	15	0	0	34	34	0	0
11	16	16	0	0	36	35	1	0
12	17	17	0	0	44	44	0	0
13	23	23	0	0	34	34	0	0
14	21	21	0	0	26	26	0	0
15	12	12	0	0	59	59	0	0
16	33	33	0	0	38	38	0	0
17	14	14	0	0	35	35	0	0
18	26	26	0	0	37	35	2	0

Note: With regard to the column titles, a square bracket indicates boundary value inclusion, and a rounded bracket indicates exclusion of the boundary.

activity (but also had significantly decreased voxels), the cerebellum crus I had significantly increased spontaneous activity in some CFL subjects and significantly decreased in others (Z-score=2.99±2.19)(Figure 5.4), and the left cerebellum I-IV, right cerebellum I-IV, right cerebellum VIIIb, and cerebellum vermis X had significantly increased BOLD signal spontaneous activity.

From the fALFF data, 9 of the 18 CFL subjects (50%) were found to have significantly decreased spontaneous activity in their right occipital pole, and 7 of the 18 CFL subjects (39%) had significantly decreased spontaneous activity in their left occipital pole.

TABLE 5.5: The number of ROIs that have a mean significantly abnormal fALFF Z-scores separated in this table into the total number of ROIs with positive or negative abnormal Z-scores as well as ROIs falling within the listed abnormal Z-score ranges.

Subject	**Total positive**	**[3, 4)**	**[4, 5)**	**[>5]**	**Total negative**	**(-4, -3]**	**(-5, -4]**	**[<-5]**
1	40	40	0	0	35	34	1	0
2	19	19	0	0	31	31	0	0
3	24	24	0	0	48	48	0	0
4	19	19	0	0	47	47	0	0
5	24	24	0	0	44	44	0	0
6	22	22	0	0	48	48	0	0
7	30	30	0	0	43	43	0	0
8	29	29	0	0	36	36	0	0
9	24	24	0	0	44	44	0	0
10	15	15	0	0	34	34	0	0
11	16	16	0	0	36	35	1	0
12	17	17	0	0	44	44	0	0
13	23	23	0	0	34	34	0	0
14	21	21	0	0	26	26	0	0
15	12	12	0	0	59	59	0	0
16	33	33	0	0	38	38	0	0
17	14	14	0	0	35	35	0	0
18	26	26	0	0	37	35	2	0

Note: With regard to the column titles, a square bracket indicates boundary value inclusion, and a rounded bracket indicates exclusion of the boundary.

Group TFCE cluster Z-scores

The original ALFF and fALFF TFCE calculated clusters were also used as ROIs to determine their cluster-wide mean Z-score. The ALFF and fALFF clusters were in similar locations and in outlier Z-score severity and spontaneous BOLD signal activity. This observation was confirmed by creating histograms of the Z-scores contained within the TFCE clusters (Figure 5.5). The Z-score distributions were shifted and skewed positively (i.e., increased spontaneous signal activity) or negatively (i.e., decreased spontaneous signal activity) proportionately to the positive or negative nature of the Z-score outliers contained within that cluster. This was further confirmed by the histograms of the Z-scores within each TFCE cluster for each CFL subject (Figure 5.6).

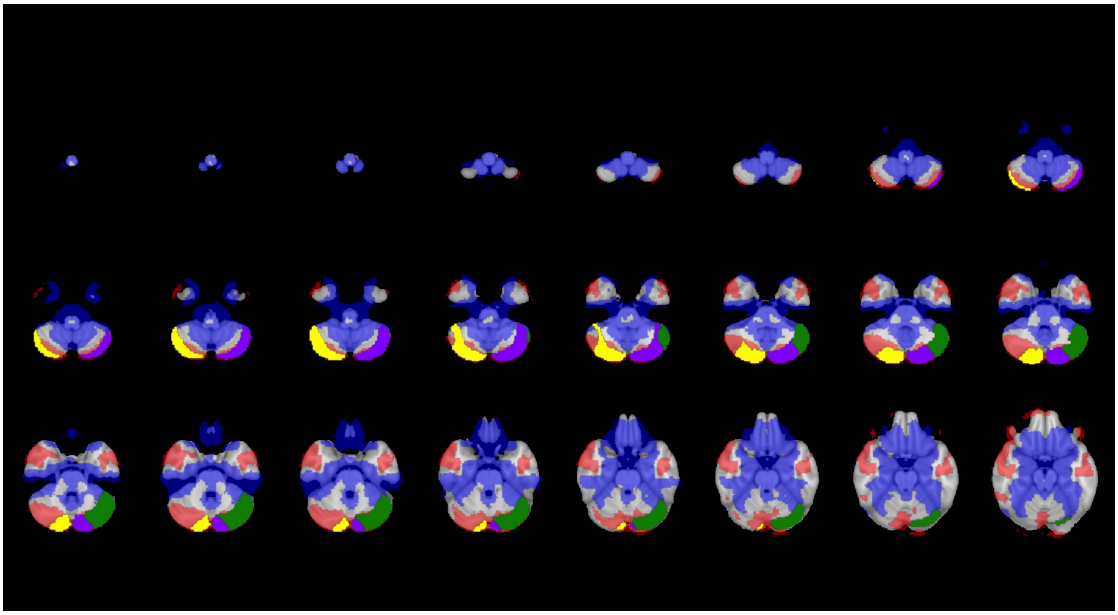

FIGURE 5.4: A representation of the cerebellar ROIs that included voxels exhibiting reduced signal spontaneity (coloured blue) and increased signal spontaneity (coloured red) based on ALFF Z-scores. There cerebellum was found to have large clusters of significantly abnormal ALFF and fALFF activity, and the cerebellum crus I and crus II were ROIs that included increased and decreased signal spontaneity. In this figure, left cerebellum crus I is coloured green, the left cerebellum crus II is coloured purple, and the right cerebellum crus II is coloured yellow. These brain slices allow for visualization of the cerebellum from the axial perspective.

Demographic and clinical correlations

The number of Z-score outliers of six ALFF and fALFF Z-score subdivisions (total ALFF, positive ALFF, negative ALFF, total fALFF, positive fALFF, and negative fALFF) were used to compare with the demographic and clinical metrics for each CFL subject. After Bonferroni correction (Demographic metrics: significance threshold $p<0.008$; Clinical test metrics: significance threshold $p<0.003$), the number of positive fALFF outliers was the only ALFF or fALFF subdivision that had a significant correlation, which was with career length ($r= 0.7$, $p= 0.0012$).

The Z-score for each of the six ROIs identified as most commonly damaged

following concussion (left and right cerebellum crus II, left and right occipital pole, right amygdala, and right thalamus) for each subject and the mean of the rCFL subjects was compared against the demographic and clinical tests. There was one significant finding using the ALFF Z-score values between the right amygdala and NPC (r= 0.639, p= 0.0078) after Bonferroni correction was applied. There were no other significant associations or correlations between ROIs and demographic and clinical test metrics. Some moderately strong, but not significant, correlations were found between the NPC and the left occipital pole (r= 0.518, p= 0.0398), right occipital pole (r= 0.586, p= 0.0171), and thalamus (r= 0.538, p= 0.0314). Additionally, the right thalamus was moderately, negatively correlated with pain (r= -0.494, p= 0.0372), and the left cerebellum crus II was moderately, negatively correlated with impulse control (r= -0.501, p= 0.0343), emotional well-being (r= 0.509, p= 0.0311) and pain (r= 0.473, p= 0.0473).

The same multiple linear regressions and Pearson's r correlation tests were replicated on the fALFF Z-score data for the six vulnerable ROIs. No significant associations or correlations were found for the left or right cerebellum crus II, left or right occipital pole, right amygdala, or the right thalamus. However, there were some non-significant moderately strong correlations between the left occipital pole and NPC (r= 0.549, p= 0.0276), the right cerebellar crus II and PHF (r= -0.471, p= 0.0487), and the right thalamus with motor speed (r= -0.488, p= 0.0399) and impulse control (r= 0.481, p= 0.0435).

5.2.5 Discussion

Based on the results of our study we found abnormalities in spontaneous brain activity in rCFL players that may have been related to their years of playing organized professional American-style football. The significant clusters calculated by the TFCE analysis showed large volumetric areas of significantly abnormal spontaneous brain activity in the rCFL subjects, however they did not provide specific enough information about brain regions or the severity of abnormality (Figure 5.1). However, by applying the Z-scoring technique significant abnormalities present within the clusters, individual voxels, and specific brain regions-of-interest (ROIs) were revealed in the rCFL subjects. As seen in Figure 5.5, the

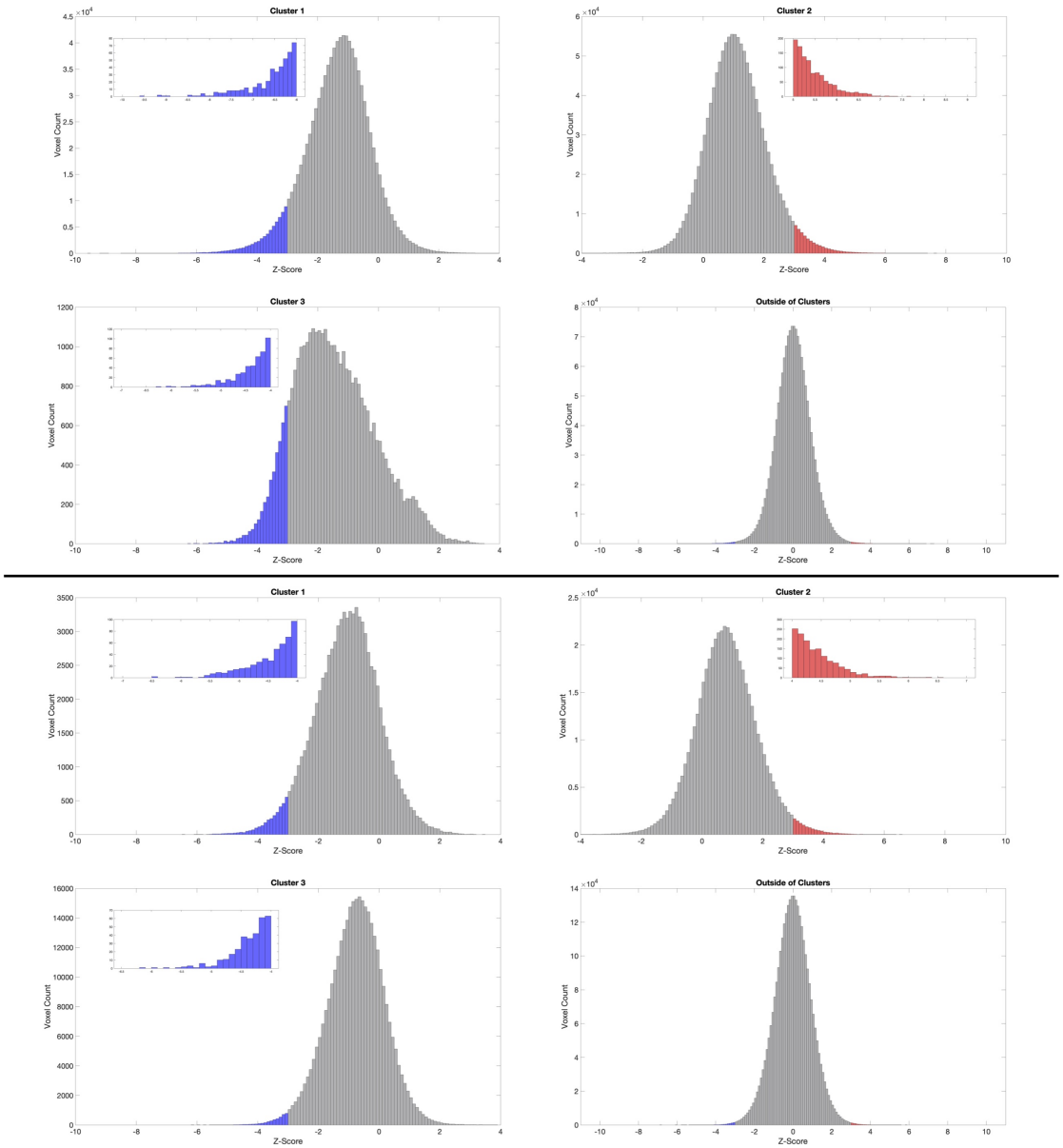

FIGURE 5.5: Histograms of the distribution of the voxel-wise Z-scores contained within the three TFCE clusters and of all the voxel-wise Z-scores within the brain but outside of the three TFCE clusters. The ALFF based Z-scores for the three clusters (top) align with the negative (coloured blue) and positive (coloured red) distribution of the fALFF based Z-scores (bottom).

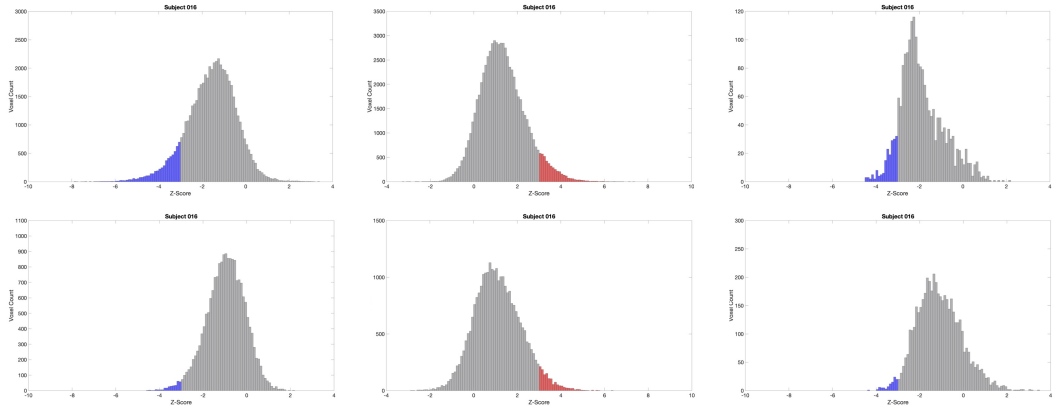

FIGURE 5.6: An example of the voxel-wise Z-score distributions contained within the three TFCE clusters for a single subject (subject 16). The ALFF based Z-scores for the three clusters (top) align with the negative (coloured blue) and positive (coloured red) distribution of the fALFF based Z-scores (bottom).

two clusters with decreased ALFF and fALFF had a negative Z-score shift, while the cluster with increased ALFF and fALFF had a positive Z-score shift. By mapping the Z-score distribution of the voxels not contained in the three TFCE calculated clusters (i.e., voxels calculated to have a Z-score between -3 and +3), the normal distribution centered at zero of the voxels provided confidence that the Z-scoring approach was robust and represented visually how abnormal the three large TFCE-identified clusters were. The increased ALFF in the frontal lobe was found in a similar study in chronic traumatic brain injury patients (Palacios et al. 2013). Also, in another comparison, decreased ALFF in the right cingulate gyrus posterior division aligned with a study on recent mTBI patients. However, our results contradict their findings of decreased ALFF in the frontal lobe and increased ALFF in the occipital gyrus (Xiong et al. 2016). There has even been evidence of functional alterations to the superior parietal lobe, precuneus, superior occipital lobe, calcarine sulcus, fusiform gyrus, supplementary motor area, cerebellum, and hippocampus that were present in collision sport athletes and not in contact or non-contact sport athletes (Churchill et al. 2017a).

From our analysis, it was apparent that centrally located subcortical brain regions were exhibiting decreased spontaneous activity in rCFL subjects (Figure

5.3), and that the cerebellum was showing distinct regions of abnormal brain activity (Figures 5.3 & 5.4). Our results also demonstrated the heterogeneity of ALFF and fALFF within each subject. Although there were several ROIs that were consistently abnormal across the rCFL group (i.e., bilateral cerebellum crus II, bilateral occipital pole, right amygdala, and right thalamus), the total number of, and location of, significantly positive (i.e., indicating increased spontaneous BOLD activity) or negative (i.e., indicating decreased spontaneous BOLD activity) ROI Z-scores was unique to each rCFL subject. This confirms the importance of doing personalized analysis from this type of research subject or head injury patient. The consistency of some regional abnormalities allows clinicians and researchers to focus their attention to certain parts of the brain for all concussion-related assessments. Therefore, if these ROIs are found to be clinically meaningful, our subject-specific analysis allowed for the personalized ALFF and fALFF, and subsequently a functional BOLD signal quantification, for each subject which was inherently unique (Tables 5.4 & 5.5).

Key findings from this study were the abnormalities found in deep brain structures and the cerebellum, compared to healthy age/sex matched controls. Deep brain structures, especially the right amygdala and thalamus, consistently exhibited significantly decreased ALFF in 17 and 18 out of 18 rCFL subjects, respectively. This was a substantial finding that was corroborated by consistently decreased fALFF values, validating those abnormalities found with ALFF were not simply a measure of unfiltered physiological noise. The medial deep brain structures seem often damaged following concussion as found in the hippocampus, cingulate, amygdala (Ford et al. 2013), and thalamus (Zhou et al. 2014). Similarly, the cerebellum was found to be an important indicator for abnormalities in rCFL subjects. Various cerebellar regions were abnormal based on ALFF and fALFF Z-scoring, and also regionally unique ALFF characteristics was found with TFCE clusters and regional Z-scores. One study on adolescent combat sport athletes (Judo and wrestling) found decreased ALFF in the inferior aspects of the cerebellum (Li et al. 2022). Our study also detected substantially reduced ALFF in the anterior and inferior aspects of the cerebellum in the rCFL subjects, but the posterior and superior aspects of the cerebellum had extensively increased ALFF and fALFF. Further research with an emphasis on the cerebellum is required to

understand the effects of concussions on this brain region more fully.

Although significant differences were found between the rCFL subjects and healthy controls, it is important to consider brain plasticity effects from years of elite athletics. There has been evidence to show that elite athletes do have structural and functional differences compared to non-athletes (Tremblay et al. 2018). Structurally, athletes have been shown to have higher than normal cortical thickness in the left superior temporal sulcus, right orbitofrontal cortex, and right parahippocampal gyrus in professional divers (Wei et al. 2011), and grey matter volume was greater in basketball athletes in their left anterior insula, inferior frontal gyrus, inferior parietal lobule, right anterior cingulate cortex, and precuneus (Tan et al. 2017). Functional changes have also been observed in female professional golfers (increased activation in the superior parietal lobe) (Milton et al. 2007), elite and professional badminton players (increased ALFF in anterior lobe of left and right cerebellum, and decreased ALFF in superior parietal lobe)(Di et al. 2012), professional ballroom dancers (increased ALFF in the left middle temporal gyrus, bilateral precentral gyrus, bilateral inferior frontal gyrus, left postcentral gyrus, left inferior temporal gyrus, right middle occipital gyrus, right superior temporal gyrus, and left middle frontal gyrus, and decreased ALFF in left lingual gyrus)(Lu et al. 2018), and in professional ice-skaters (higher fALFF in posterior cerebellar lobe)(Zhang et al. 2021). Fortunately, the ROIs that were abnormal in the majority of rCFL subjects do not align with those aforementioned brain regions that may exhibit exercise induced adaptations (except for the increased ALFF in the anterior cerebellum which we found to be the opposite, and the increased fALFF in the posterior cerebellum which aligned). Thus, the abnormalities found in our study can be more confidently understood to be likely brain injury-related and not an effect of extensive physical activity.

Although there appeared to be some correlation between ALFF and fALFF values with clinical metrics, few reached the threshold for significance. Nonetheless, there were some interesting findings. Increased ALFF Z-scores for the right amygdala were connected to more (approximated) concussions, and a greater number of ROIs with increased fALFF was correlated to a longer career length. Decreased fALFF has been shown to be linked to higher post-concussion symptoms

scores (PCSS), which return to normal with recovery (Madhavan et al. 2019). Both significant correlations in our study contradict previous findings where damage, assumed to be caused by concussions, was correlated with significantly increased spontaneous neural activity above that of normal values. Decreased ALFF and fALFF was detected in our study, but perhaps increased neural activity could be more closely linked to lasting concussion damage that is representative of a functional overcompensation or inefficiency. This possibility could be argued for, as the previous studies were based on acute concussion measurements.

The limitations of our study first include the sample size. Ideally, we would have had many more players with a wider range of years of professional play, a greater variety for positions of play, and more years since retiring. However, we were limited to performing assessment on only those who responded to our advertisements. Nonetheless, with a large control sample we were able to perform personalized analysis which does not depend on larger numbers of rCFL players. Another limitation is the lack of understanding of the freely available downloaded control data. We did our best to match that data as close to our rCFL data as possible. We believe the investigators who acquired the control data did a thorough job screening their subjects for previous brain problems and that they are truly healthy controls. However, we have no knowledge of the athleticism of this population. Despite this, because the brain regions that have different fALFF and ALFF in healthy athletes are not what we noted as being different in the rCFL players, we believe our findings hold true.

In conclusion, our study found a variety of brain regions with abnormal ALFF and fALFF Z-score values in rCFL subjects. The left and right cerebellum crus II, left and right occipital pole, right amygdala and right thalamus were found consistently abnormal across rCFL subjects based on ALFF and fALFF Z-scores. There was a general trend of being abnormally increased around the lateral aspects of the frontal, temporal and parietal lobes and posterior cerebellum, but abnormally decreased in the medial sub-cortical brain structures and anterior, inferior cerebellum. Thus, our study found that functional abnormalities, expressed as elevated and reduced BOLD signal spontaneity, was present in retired professional football players with a history of repetitive concussive head impacts.

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Conflict of interest disclosure

Dr. Noseworthy is the CEO and co-founder of TBIfinder Inc., which is not relevant to this current work. All other authors declare that they have no conflict of interest.

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Chapter 6

Conclusions

6.1 Overview

The overall aim of this work focused on novel and advanced brain MRI analyses for the identification and quantification of brain abnormalities present in retired athletes with a history of concussions. By having robust quantitative approaches, athlete safety can be improved by giving sport clinicians better tools to understand brain injury and to enhance concussion rehabilitation and recovery. The purpose of this work was not to identify risks associated with playing sports, but rather to apply diagnostic concussion tools that could be utilized in clinical practice to improve athlete safety. If clinicians could have the capability to objectively determine if an athlete is at risk of permanent brain damage from sustaining a recent or a future concussion, then athletes and teams would better understand the effects of head injuries and participate in the appropriate rehabilitation to avoid serious consequences. This is not to say that every collision sport athlete has serious concussion-related brain injuries as each concussion and person is unique. As such, improved diagnostic capabilities could reduce the risk of deleterious lasting or permanent brain changes.

Non-routine MRI techniques, as seen in this thesis, can be used to identify and quantify a range of brain alterations that may have been concussion-related. However, the exact application of MRI in sport and concussion needs to be further defined. Thus, this concluding chapter discusses the main findings of the research discussed in this thesis and outlines some future directions for this research.

6.2 Main findings and contributions to the field

Each research chapter of this thesis identified interesting abnormalities present in the rCFL subjects relative to age and sex-matched healthy controls. This was represented primarily by decreased complexity and reduced spontaneity of the BOLD rsfMRI signal, and regional increases and decreases to CBF and ASL sCoV. Across the MRI analyses applied in this study (FA, rsfMRI FD, ALFF and fALFF, and PCASL), ALFF identified the most abnormalities while FA identified the least. There were also noteworthy correlations with MRI metrics and demographic factors or clinical test scores.

6.2.1 Microstructural abnormalities

There were very few microstructural abnormalities identified in the rCFL subjects. Only 5 of the 17 rCFL subjects had one or more significant FA abnormality, where the cingulum was minorly abnormal (grade 1: -3≤Z-score≤-2) in two rCFL subjects. This suggested that microstructural injuries commonly found acutely post-concussion (Asken et al. 2018) either heal over time or that DTI was not sensitive enough to detect white matter damage that occurred many years earlier[1]. However, despite the limited amount of FA abnormalities detected, rCFL FA_{IB} was significantly correlated with emotional well-being scores ($r = -0.532$, $p=0.034$), suggesting a higher degree of white matter injury was related to a worse self-reported state of emotional health.

6.2.2 Cerebral blood flow abnormalities

With respect to CBF and tissue perfusion abnormalities, the group-wise statistical analysis revealed 48 abnormal ROIs based on CBF (left= 22, right= 26) and 43 based on ASL sCoV (left= 18, right= 25). Most notably, the caudate nucleus, cerebellum, superior parietal gyrus, and temporal occipital fusiform cortex were bilaterally abnormal based on CBF and ASL sCoV values. These regional

[1]The DTI data was analyzed as a rank-2 tensor which results in 3 orthogonal eigenvalues and corresponding eigenvectors. Simple scalar metrics like FA and MD can subsequently be calculated. A higher order tensor, e.g. rank-3, with HARDI or diffusion kurtosis needs investigation as a possible alternative with higher sensitivity.

abnormalities also correlated with demographic and clinical metrics (CBF= 50 significant correlations, ASL sCoV= 40 significant correlations). Based on CBF values, abnormal ROIs were correlated most commonly with worse physical functioning and pain experienced in daily life. Similarly, abnormal ROIs based on ASL sCoV values were frequently correlated with pain. This suggested that rCFL subjects with a greater degree of CBF abnormality were more likely to experience increases in pain while performing routine activities (i.e., walking, climbing stairs, sitting, etc.). It should be noted, however, that rCFL subjects put their bodies through high intensity exercise and countless collisions on a daily basis and would be expected to experience age-associated pain as a result. From an ROI perspective, the superior parietal gyrus had the highest number of significant correlations and was found to be bilaterally abnormal with CBF and ASL sCoV values. Thus, the superior parietal gyrus may be more vulnerable to microvascular damage as a result of concussive brain injuries and may be a reliable indicator for concussion-related CBF assessment.

6.2.3 Functional abnormalities at a resting state

Finally, rsfMRI analyses detected a substantial amount of abnormalities in the rCFL subjects that indicated significantly reduced regional neural signal complexity and spontaneous activity. Based on the FD analysis, 48 of the 91 ROIs examined had significantly reduced FD in at least one rCFL subject, with the right premotor cortex, right hippocampus dentate gyrus, right primary visual cortex, and right secondary visual cortex being the most frequently abnormal. Four rCFL subjects exhibiting a low IB (IB range= 1-6) while another four rCFL subjects exhibited high IB (IB range= 9-28). Of clinical relevance, the four rCFL subjects with a high IB all expressed motor speed, social functioning, and general health deficits worse than the other rCFL subjects. Based on the ALFF and fALFF analyses, there were 30 ROIs identified to be abnormal in more than half the rCFL sample, 7 of which were from the cerebellum, and 13 ROI that were abnormal in more than a quarter of the rCFL sample. Of particular note from an ROI perspective, the bilateral cerebellum crus II, bilateral occipital pole, right amygdala, and right thalamus were significantly abnormal based on ALFF and fALFF values. Furthermore, the thalamus was bilaterally reduced in 18/18 rCFL

subjects, the amygdala was bilaterally reduced in 17/18 rCFL subjects, the left and right putamen were reduced in 16 and 14 rCFL subjects respectively, and the hippocampus was bilaterally reduced in 15/18 rCFL subjects.

The three projects described in this thesis detected a diverse range of findings that suggested brain abnormalities may be present in this rCFL sample population due to their (likely) history of concussions and repetitive sub-concussive head impacts sustained many years earlier. Furthermore, these results highlighted the benefits of personalized brain assessment for individualized identification and quantification of abnormalities using Z-scoring analyses applied to MRI data.

6.2.4 Connection to previous work

The findings from EEG research on these same rCFL subjects closely aligns with and compliments the MRI findings discussed in this thesis. The rCFL subjects who participated in the work presented here also participated in research by our colleagues using electroencephalopathy (EEG). A study by Ruiter et al. (2019) found that relative to a healthy control group, the rCFL subjects exhibited a significantly reduced waveform amplitude and signal latency in the P300 protocol (P3a, P3b, and N2b) and Mismatch Negativity protocol components (Ruiter et al. 2019). From the work by Boshra et al. (2020), the results of abnormal P300 waveforms were repeated and shown to be different in the rCFL subjects, even relative to acutely concussed young adults (Boshra et al. 2020). The P3a response displays maximum signal amplitude over central frontal electrodes, while the P3b response displays is present over the parietal lobe (Ruiter et al. 2019). The N2b component of the N200 event-related component (ERP) displays maximum amplitudes over the central anterofrontal electrodes, similar to P3a, and in functional connection with P3b (Ruiter et al. 2019).

ROIs within the parietal lobes were also found to be abnormal based on rsfMRI and PCASL data, and the frontal lobe exhibited elevated BOLD signal spontaneity at the frontal pole and reduced BOLD signal spontaneity in other frontal ROIs based on the TFCE analysis of ALFF and fALFF data. This confirms evidence that these parts of the brain exhibit functional changes in this group of rCFL subjects with a history of concussions. However, the MRI research presented

in this thesis identified abnormalities that were more spatially accurate than the comparable EEG results, and closely examined a more comprehensive collection of brain ROIs that were found to be of significance.

6.3 Future directions

It would be incredibly beneficial to understand why some people are more susceptible to severe concussions, or prolonged recovery, and to know if there is a *concussion threshold* that once surpassed would mean that permanent changes ensue. If about 90% of people who sustain a concussion recover in 10-14 days (McCrory et al. 2017), is there something genetically, anatomically, or physiologically different in those 10% of people who don't recover quickly from concussion, and are they more likely to experience long lasting effects? What makes that 10% more vulnerable to severe concussion? Is there a *magic number* of concussions that if sustained should mean the athlete should retire for their own long term safety? Are athletes that make it to a professional level less vulnerable to concussion, while others decided or were forced to quit sports because of a concussion before reaching the professional level? Or are professional athletes simply less likely to report sustaining a concussion, better at masking post-concussion symptoms to keep playing, and willing to risk long term effects.

The results of this body of work provide evidence of concussion-related functional, perfusion, and some microstructural brain alterations in the rCFL subjects. However, the results are somewhat limited in the clinical relevance due to the few significant clinical correlations. The three projects from this thesis lay a strong foundation as preliminary studies for future research to identify the usefulness of MRI as (i) a screening and diagnostic concussion tool, and (ii) the connection between abnormalities found based on rsfMRI, ASL and DTI data relative to the clinical presentation of retired athletes in their daily life and long term implications from a history of concussions. There is continued opportunity for research to further explore these results and addressed identified limitations.

6.3.1 Follow up with the 18 rCFL subjects

It would be of interest to follow up with the 18 rCFL subjects who participated in the work in this thesis and determine if they have experienced any brain changes in the 5-7 years since their initial study visit. Having one time point limited our ability to definitively say whether the observed brain changes were consistent or changing with time (i.e. presumably getting worse).

6.3.2 Elite athletes with no history of concussion

The selection of an appropriate control group is of immense importance for research to be able to rule out biases (i.e., sex, age, ethnicity, etc.). In the case of athletes, it was discussed more explicitly in the discussion of Chapter 5. To briefly reiterate former professional athletes may have physiological differences present, compared to controls (i.e., increased perfusion, enhanced motor control, increased grey matter brain volume, increased muscular strength). Some or all of these differences could possibly propagate through to retirement and not be present in non-elite athletes or sedentary individuals. In our work, large healthy control samples that had no known history of concussions were used so that we could account for age and sex differences in the rCFL subjects. However, because the healthy control data in Chapters 3 and 5 were downloaded from online repositories, we had no information on the athleticism of the subjects. Thus, in future work on brain health of retired professional athletes it would be interesting and valuable to utilize a healthy control group comprised of elite athletes who have no history of concussion or head impacts (i.e., tennis, badminton, running, etc.). This could further solidify significant differences in retired athletes as concussion-related injuries instead of elite exercise induced adaptations.

6.3.3 Vulnerable brain regions

Compiling the results of this thesis highlighted specific brain regions that were frequently abnormal in subjects with a history of concussions and therefore may be more vulnerable to lasting changes. Across the rsfMRI and ASL data, the superior parietal lobe, the cerebellum, occipital pole, and central sub-cortical brain structures exhibited frequent differences from healthy values. It was demonstrated

that injury to the premotor cortex and superior parietal gyrus were connected to significant correlations with reduced motor speed and physical functioning, respectively. The cerebellum, which has historically been an under-studied part of the brain, had ASL sCoV abnormalities correlated with pain and exhibited a substantial amount of ALFF and fALFF abnormalities. Abnormality to the occipital pole (i.e., ALFF and fALFF TFCE clusters and ROI Z-scoring) and visual cortices (i.e., reduced BOLD signal complexity) were also interesting findings as light sensitivity and visual irregularities are common post-concussion symptoms. Finally, sub-cortical brain structures such as the amygdala, caudate nucleus, hippocampus, and thalamus were consistently abnormal in the rCFL subjects and correlated with clinical test health metrics. Consistent with common challenges related to concussion research, our findings exhibited variability through the rCFL subjects and could not definitively associate abnormalities to concussion-related damage due to single time point data collection. Further research should certainly address these challenges to better understand their influence on concussion severity and recovery.

6.3.4 Clinical symptoms and MRI findings over a lifetime

Concussion-related abnormalities were present in the rCFL subjects years after retirement and their most recent concussion. However, the progression of those abnormalities and their clinical significance could not be conclusively determined by the data collection at one time point. Furthermore, there may have been some inherent bias due to the relatively small sample size. The rCFL subjects participated in response to advertisements, but may have only done so because they suspected their own brain was damaged. There are thousands of retired CFL and National Football League (NFL) players of all ages that could be examined using the advanced quantitative MRI techniques applied in this thesis. Although the metrics assessed in the rCFL subjects were only what would be expected post-concussion (i.e., relative to healthy controls, decreased fractional anisotropy (FA), fractal dimension (FD), amplitude of low-frequency fluctuations (ALFF), and cerebral blood flow (CBF)), the clinical significance of these abnormalities were not as dramatic as was anticipated.

A proposed next step for this research would be a much larger study of several hundred active and retired professional football players who can be scanned using the same techniques utilized here. In addition it would be highly useful to have access to their complete medical history. With this proposed study, we would be able to draw more definitive and clinically relevant conclusions about the associated risks of sustaining a concussion and permanent damage. With a total sample size of about 600 subjects, we could have 100 rCFL subjects for each age group (20-29; 30-39; 40-49; 50-59; 60-69; 70+) and compare them to age and sex matched elite athlete controls for each different age group. A study of this size would face challenges with sufficient recruitment, but could be possible with collaboration with a professional league such as the CFL or NFL and their respective player associations.

There has been a surge of research on retired athletes in recent years that has connected a history of concussions and repetitive sub-concussive impacts with a neurodegenerative pathology known as chronic traumatic encephalopathy (CTE) (McKee et al. 2013; Omalu et al. 2010; Solomon 2018). Unfortunately, conclusive diagnosis of CTE has been limited to post-mortem assessments and early diagnosis has been debated without a definitive in-vivo bioindicator (Solomon 2018). There is even debate over a direct connection between sport-related concussions and CTE (McCrory et al. 2017). In addition to common post-concussion symptoms being found in other chronic TBI patients, there is an increased incidence of depression and suicide in retired high contact athletes and those who have been diagnosed with CTE (Gouttebarge et al. 2017; Montenigro et al. 2017; Solomon 2018). Thus, there is an immediate need to determine the exact timeline and damage profile of CTE to protect young and future athletes and aid in the rehabilitation of retired and aging athletes who have a high likelihood of developing CTE.

The premise of this ambitious study would be to: (i) establish a timeline for brain abnormality changes and recovery following a concussion, (ii) more accurately map concussion-related brain abnormalities seen in younger athletes and aging retired athletes to develop early CTE diagnosis metrics, and (iii) determine how those brain changes are associated with health impacts (dementia, chronic headaches, premature death, suicide, motor impairments, etc.). There may be

very limited clinically relevant risk associated with the abnormalities detected by MRI in concussed athletes with only a fraction of athletes at risk for more serious or permanent brain impairments. Until that can be confirmed the risk of sustaining concussions, repetitive sub-concussive impacts, and multiple concussions in close succession pose an immense risk to athletes in terms of their short and long term brain health.

6.3.5 Bioindicator analysis

There are known neuroprotective and neuroregenerative proteins present in the central nervous system (i.e., blood-derived neurotrophic factor (BDNF), glial fibrillary acidic protein (GFAP), and ubiquitin carboxy-terminal hydrolase L1 (UCHL1)) that are altered acutely after a concussion (Papa et al. 2016; Susa et al. 2019). There is also evidence of certain single nucleotide polymorphisms (SNPs) (i.e., apolipoprotein E4 (APOE4)) that are present in people with worse acute post-concussion symptoms (Mahley and Huang 2012; Zhou et al. 2008). However, there needs to be far more research on whether concussions have any lasting effects on regenerative protein properties (i.e., functional changes, expression levels, response efficiency) or epigenetic effects on dangerous SNPs such as APOE4. Further research into this area of concussions could lead to robust screening and diagnostic concussion tools that could be applied as point-of-care devices.

The application of such bioindicators as systemic circulating blood proteins and SNP expression into concussion assessment could be insightful supplements to measuring post-concussion symptoms and advanced MRI techniques. Setting thresholds to determine harmful deviations from healthy levels could be another diagnostic option that could indicate concussion severity, prognosis prediction, and highlight metabolic and physiological deficits. The specificity of these bioindicators for concussion-related damage would be a major challenge especially because injury location could not be determined from systemic blood collection. However, knowing that neuroregenerative proteins are still highly expressed past post-concussion symptom resolution could prevent an athlete from returning to sport prior to their brain fully recovering.

6.4 Final conclusions

As a means to assess non-acute concussion-related brain injuries, the work presented in this thesis demonstrated the effectiveness of advanced quantitative MRI techniques and the need for personalized concussion assessments. Each concussion is unique and should be treated as such. It would be a great personal success to see the implementation of DTI, rsfMRI and PCASL MRI scans into routine clinical MRI assessment of concussions, especially for athletes at a professional level. The review chapter of this thesis aimed to bridge the gap between symptom-based and medical imaging concussion assessments by discussing how concussion caused damage to specific brain regions can be connected to specific post-concussion symptoms. Furthermore, the results of the three research projects suggest that concussion-related brain abnormalities were present in athletes later in life and identified brain regions that should be areas of future research. Thus, concussion safety protocols should be enhanced with non-invasive and objective techniques, such as the MRI metrics presented in this thesis, to acutely assess current athletes and monitor those who are retired. If professional sports teams and leagues included these MRI techniques into their concussion safety protocol, this research could be a catalyst for transforming sport safety.

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