



Quantitative MRI T2 Relaxometry and Physical Activity in Acute Mild Traumatic Brain Injury: An Exploration of the Measurement and Modification of Potential Neuroinflammation

by

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Abstract

Mild traumatic brain injuries (mTBI) account for approximately 90% of all traumatic brain injuries (TBI) and are often associated with prolonged symptoms and functional impairments. Despite their prevalence and significant physical, psychosocial and financial impact, the underlying pathophysiology and factors influencing recovery remain poorly understood. mTBI typically results from a sudden impact, acceleration, deceleration, or rotational force, triggering a cascade of secondary injuries. A key component of this cascade is neuroinflammation, which, while initially protective, can lead to chronic deficits and neurodegeneration if prolonged or excessive. Despite the known role of inflammation in brain injury, significant gaps remain in understanding its influence on recovery and how it might be modulated.

This thesis aims to address these gaps by investigating a method for measuring potential neuroinflammation and exploring a behavioural approach to modifying it. Forty male athletes (aged 16-35 years) were recruited within 14 days of sports-related mTBI, along with 52 age and sex-matched controls. T2-weighted MRI data were collected using a Carr-Purcell-Meiboom-Gill (CPMG) spin-echo sequence. Preprocessing included brain extraction, normalisation, smoothing, and grey matter masking. T2 relaxation times were estimated at each voxel using a monoexponential model in qMRLab. Participants also wore Axivity AX3 wrist accelerometers continuously for 15 days to capture physical activity data. Physical activity data were analysed using the GGIR, compositions and deltacomp packages in R.

The thesis comprises three studies. Studies 1 and 2 assess the utility of MRI T2 relaxometry as a marker of neuroinflammation. Study 1 used a case series approach, statistically comparing individual mTBI participants to the control group via z-tests and voxel-wise z-maps. Results showed elevated T2 relaxation times in acute mTBI, with unique regional patterns per individual and follow-up scans in a subset of participants demonstrated reductions in T2 relaxation times, suggesting recovery. Study 2 complemented this with a group-level analysis. Independent samples t-tests with threshold-free cluster enhancement (TFCE) revealed significantly higher T2 relaxation times in the mTBI group, particularly in frontoparietal regions, as well as a negative correlation between T2 relaxation times and recovery time.

Study 3 shifted the focus to intervention, using compositional data analysis to examine physical activity patterns post-injury. No significant group differences were found, supporting the tolerability of physical activity during early recovery. Although longer sleep duration initially correlated with prolonged recovery, this effect was attenuated after adjusting for baseline symptom severity.

Together, the findings suggest that quantitative T2 relaxometry is a sensitive, non-invasive marker of brain changes potentially reflecting neuroinflammation. The correlation between T2 relaxation times and recovery time may emphasise a dual role of inflammation, beneficial in the acute phase but potentially harmful if prolonged. Study 3 supports the tolerability of physical activity during early recovery and highlights the utility of compositional analysis in understanding movement behaviours. Given the known anti-inflammatory effects of physical activity, its role in recovery may partially stem from modulating neuroinflammation.

These findings support a more individualised approach to mTBI care, integrating objective measures with clinical assessments to identify patients at risk of prolonged inflammation and neurodegeneration. Future research should focus on longitudinal designs with more diverse samples and larger activity datasets to better understand recovery trajectories and optimise intervention timing. As the first to apply quantitative T2 relaxometry and compositional data analysis in mTBI, this thesis offers novel insights into brain changes and physical activity patterns following injury.

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Abbreviations

A β	Amyloid-beta
ACRM	American Congress of Rehabilitation Medicine
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
BIDS	Brain imaging data structure
BIST	Brain injury screening tool
CA ²⁺	Calcium
C1qB	Complement C1q B chain
CAMRI	Centre for Advanced Magnetic Resonance Imaging
CoDA	Compositional data analysis
CPMG	Carr-Purcell-Meiboom-Gill
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
CTE	Chronic traumatic encephalopathy
DAMPs	Damage-associated molecular patterns
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
FA	Flip angle
FDA	Food and Drug Administration
FDR	False Discovery Rate
FOV	Field of view
FWHM	Full width half maximum
fMRI	Functional magnetic resonance imaging
FSH	Follicle stimulating hormone
GFAP	Glial fibrillary acidic protein

GSH	Glutathione
HCQ	Hydroxychloroquine
HDCZA	Heuristic algorithm looking at change of z-angle
HDEC	Health and Disability Ethics Committee
IFN- γ	Interferon-gamma
Ilr	Isometric logarithmic ratios
K ⁺	Potassium
LH	Luteinizing hormone
MANOVA	Multivariate analysis of variance
MNI	Montreal Neurological Institute
MPRAGE	Magnetisation-prepared rapid gradient echo
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
Na ⁺	Sodium
NF-L	Neurofilament light
NK cells	Natural killer cells
NOX2	NADPH oxidase 2
PA	Physical activity
QSM	Quantitative susceptibility mapping
RF	Radiofrequency
SBP	Sequential binary partition
SD	Standard deviation
SNC	Scandinavian Neurotrauma Committee
SNR	Signal-to-noise ratio
TBI	Traumatic brain injury
TDP-43	TAR DNA-binding protein 43
TE	Echo time
TFCE	Threshold free cluster enhancement
TGF- β	Transforming growth factor beta
TIV	Total intracranial volume
TNF- α	Tumor necrosis factor-alpha

TR	Repetition time
Tregs	Regulatory T cells
TUG	Timed up and go
SCAT-5	Sport Concussion Assessment Tool 5 th Edition
SCD	Subjective cognitive decline
SCF	Stem cell factor
SE	Spin echo
SWI	Susceptibility weighted imaging
UCH-L	Ubiquitin-C-terminal hydrolase 1
VEGF	Vascular endothelial growth factor

Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor used artificial intelligence tools or generative artificial intelligence tools (unless it is clearly stated, and referenced, along with the purpose of use), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

A handwritten signature in black ink, appearing to read 'M Bedggood', is positioned above a horizontal line.

Mayan Joy Bedggood

Publications

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Dedication

*For my daughter, Addison Lee.
Your smile is my favourite thing in the world.*

*“Sometimes
the smallest things
take up the most room
in your heart.”
— A.A. Milne*

The Iceberg

Intimidating. Complex. Adaptive. Resilient. Fragile. *The Brain*. It is the command centre of our existence - and yet, it remains one of the final frontiers of human understanding. Within each of us lies this highly specialised organ, one we spend our lives protecting, nourishing, and seeking to comprehend. Though it accounts for just 2% of our body weight, the brain consumes approximately 20% of the body's total energy output (Balasubramanian, 2021). In return, it works tirelessly to keep us alive and connected to the world around us.

The brain is composed of approximately 170 billion cells, including about 86 billion neurons, highly specialised messengers capable of transmitting signals at speeds of up to 120 metres per second (Herculano-Houzel, 2012). These cells do not work in isolation but form complex networks that orchestrate every thought, memory, emotion, sensation, and movement. The brain governs not only conscious experience, such as perception, attention, and decision-making, but also countless unconscious processes essential for survival, including breathing, sleep regulation, hormonal balance, and thermoregulation. To protect this delicate and vital structure, the brain is encased in a triple-layered shield of meninges, which serve as shock absorbers between the soft neural tissue and the hard, bony skull. It is further cushioned by cerebrospinal fluid, which both nourishes and defends it. Yet despite these elaborate defences, the brain remains one of the most vulnerable organs in the human body.

In many ways, what we perceive of the brain is merely the tip of the iceberg. We see the skull that encases it. We observe the outward expressions of a functioning brain: movement, language, personality, behaviour, and expression. But beneath the surface lies an intricate, largely invisible world of neural activity, a web of electrical and chemical signals firing with exquisite precision, shaping everything we know, feel, and do. This hidden complexity renders the brain both awe-inspiring and elusive.

It is no surprise, then, that when the brain is injured, the effects are often misunderstood or underestimated. External trauma may be obvious and dramatic, but internal damage can be subtle, insidious, and difficult to detect. Standard imaging may reveal no abnormality, yet the individual may experience profound changes in cognition, emotion, and quality of life. We now recognise

that even injuries without clear physical signs can significantly alter lived experience. For all its vital importance, the function of the brain remains an enigma: immensely powerful, yet strikingly susceptible to disruption

There is still much to uncover about how the brain works, how it recovers, and how we can support that recovery. This mystery is not just a challenge for science; it is a source of profound hope. Within the complexity of the brain lies immense potential for discovery, for healing, and for growth. As a researcher, my aim is to help illuminate that potential. To uncover what can be repaired. To ask not only *what damage lies beneath the surface*, but, just as importantly *what can we do about it?*

Thesis Preview

This thesis aims to deepen our understanding of mild traumatic brain injury (mTBI) by investigating ways to measure and modify the brain's response to injury. mTBI is a common yet complex condition that often escapes detection using conventional diagnostic tools, and its consequences, ranging from transient symptoms to long-term impairments, are still poorly understood. To address this, the thesis will begin by examining subtle brain changes using T2 relaxometry, a quantitative magnetic resonance imaging (MRI) technique with emerging potential to detect acute neuroinflammatory processes. It then explores physical activity as a possible evidence-based intervention for supporting recovery, specifically through its known capacity to mitigate the harmful effects of chronic neuroinflammation. By targeting both the measurement and modification of inflammation, this research addresses critical gaps in our understanding of mTBI pathophysiology and recovery.

Chapter 1 introduces mTBI by outlining its primary and secondary injury mechanisms, clinical presentation, and the wider social and economic burden it imposes. This first chapter lays the foundation by contextualising the need for improved approaches to both diagnosis and recovery monitoring. **Chapter 2** then introduces the dual theme of this thesis: possible ways of *measuring* and *modifying* brain inflammation. The first half of this chapter focuses on the biological underpinnings of neuroinflammation and introduces quantitative MRI T2 relaxometry as a potential tool for detecting subtle changes in brain water content that may reflect underlying inflammatory processes. Following this, the second half of Chapter 2 presents physical activity as a promising behavioural intervention, grounded in its potential to alter inflammatory pathways and promote recovery. This dual focus, on both quantifying and influencing brain inflammation, forms the conceptual backbone for the remaining chapters of this thesis. Following these introductory chapters, **Chapter 3** outlines the overall methodological approach taken across the thesis, including participant characteristics and overall procedure. While providing a general overview, this chapter reserves detailed methods for each individual study.

The main body of the thesis is structured around three key studies, each framed by specific overviews, methods, results, and discussions. The first two studies focus on a potential way to *measure* neuroinflammation following mTBI, while the third examines one potential strategy for

modifying it. **Chapter 4** presents the first study: an MRI case series that compares 20 mTBI participants to the mean values of a healthy control group. This study investigates the utility of quantitative T2 relaxometry to measure potential neuroinflammation at the individual level. **Chapter 5** builds on these findings with a group-level analysis involving 40 mTBI participants and matched controls. This study evaluates the extent to which T2 relaxometry can detect subtle but consistent changes across a broader sample, further validating its use as a neuroimaging biomarker. In addition, this chapter explores associations between T2 relaxation estimates and clinical recovery outcomes in the mTBI group, providing a potential link between subtle brain changes and functional prognosis.

With the first two studies focused on *measuring* inflammation, **Chapter 6** shifts attention to *modifying* it. This third study investigates the relationship between different types of physical activity (light physical activity, moderate-to-vigorous physical activity, sedentary behaviour and sleep) and recovery following mTBI. It explores the use of compositional data analysis to evaluate how different combinations of these behaviours may differ between mTBI and controls and how they might relate to symptom resolution. This chapter also explores the hypothesised mechanisms through which physical activity may support recovery from mTBI, through its capacity to attenuate the inflammatory response at a cellular level. By incorporating physical activity data, this third study adds an important dimension of clinical application to the thesis.

Finally, **Chapter 7** synthesises the findings from all three studies to draw broader conclusions about the complex interplay between brain injury, subtle brain changes, potential inflammation, and recovery. This chapter highlights the contributions of each study to the overarching aims of the thesis, integrating and contextualising the findings from each study. It evaluates the strengths and limitations of the thesis overall and outlines the important clinical implications of the work. Proposed directions for future research are discussed, including recommendations for further validating T2 relaxometry as a measure of subtle neuroinflammation. The chapter concludes the thesis with final remarks that reflect on the significance of the current findings and the crucial need for continued innovation in the assessment and monitoring of mTBI. See Figure 0.1 for an overview of the thesis structure.

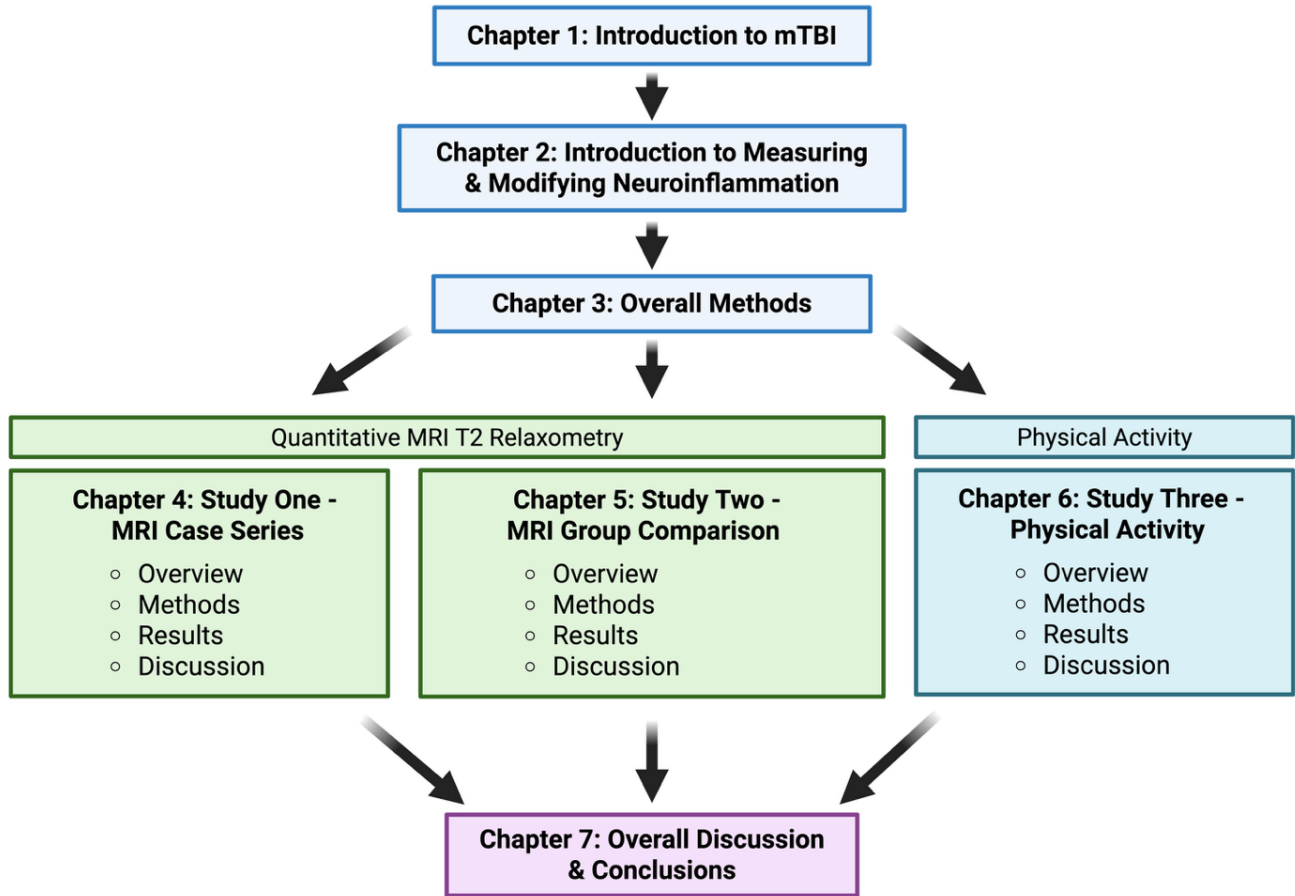


Figure 0.1 *Structure of Thesis*

1

Introduction to Mild Traumatic Brain Injury

1.1 Overview

Before delving into the intricacies of measuring and modifying potential neuroinflammation, it is important to first establish a foundational understanding of the core topic underpinning this research: mild traumatic brain injury. Gaining insight into what this type of injury entails, and how it affects individuals, is essential for appreciating the motivation behind this work. There are two key points I hope to emphasise in this opening chapter. Firstly, that much remains unknown about the pathophysiology of brain injuries, underscoring the urgent need for new tools to better understand their biological underpinnings. Secondly, that the term *mild* can be misleading, as it belies the significant and often prolonged consequences that can ensue.

This first chapter introduces how a mild traumatic brain injury occurs, and the injury evolution with regards to the cascade of cellular and molecular events that follow the initial impact. Specifically, I will outline the distinction between primary and secondary injuries, diagnostic criteria, clinical signs, and explore the wide-ranging functional, social, financial and neurological impacts associated with this type of injury. The chapter also considers the potential for long-term complications, including persistent symptoms and neurodegeneration.

Following this, the focus then narrows to the central theme of this thesis: neuroinflammation. I will describe the key cellular mechanisms involved in the brain's inflammatory response and, crucially, address the dual nature of inflammation - how it can be both protective and damaging. This distinction between adaptive and maladaptive inflammation is a recurring thread throughout this thesis, shaping the interpretation of findings and guiding the rationale for intervention.

1.2 Primary Injury and Symptoms

Mild traumatic brain injuries (mTBI) are prevalent and potentially debilitating neurological injuries that result in morphophysiological disturbances in the brain parenchyma (Freire et al., 2023). mTBI begins with a primary mechanical injury which occurs when a sudden impact, rotational force, or rapid acceleration or deceleration causes the brain to move within the skull. This movement can cause focal damage as delicate brain tissue contacts the bony skull, including coup injuries (at the site of impact), contrecoup injuries (opposite the site of impact) and side impacts to the brain. Additionally, rapid acceleration, deceleration or rotational forces can cause widespread, diffuse damage to the brain via shearing, tearing and stretching of white matter axons (see Figure 1.1) (Danielli et al., 2023; Verboon et al., 2021). The magnitude of biomechanical forces, as well as the direction, rotation and source of the forces, can differ greatly between mTBI, leading to an unpredictable nature of symptoms and long-term neurological complications (Danielli et al., 2023). The pathophysiology associated with mTBI is not fully understood, however, there seems to be a consensus that mTBI occurs due to functional disturbances as opposed to macrostructural damage (Romeu-Mejia et al., 2019).

Primary symptoms of mTBI can be broadly classified as (1) physical - e.g., headaches, neck pain, nausea, tinnitus, vertigo, photosensitivity, diplopia (double vision), sensitivity to noise, balance issues or impaired taste or smell, (2) cognitive - e.g., confusion, memory issues, disorientation, mental fog, difficulty concentrating or a brief loss of consciousness, and (3) behavioural and/or emotional - e.g., fatigue, sleep disturbances, irritability, depressive or anxious symptoms (Prince & Bruhns, 2017; Silverberg et al., 2023; Verboon et al., 2021). Current diagnostic criteria for mTBI according to the American Congress of Rehabilitation Medicine (ACRM) include (1) a plausible mechanism of injury, (2) one or more clinical signs, such as a loss of consciousness, altered mental state, or post-traumatic amnesia, (3) two or more acute symptoms, such as those listed above (4) clinical examination and laboratory findings, (5) neuroimaging (typically normal appearing on standard imaging, with obvious abnormalities suggesting a more severe brain injury), and (6) the exclusion of confounding factors. Additionally, a Glasgow Coma Scale score of less than 13, loss of consciousness for more than 30 minutes or post-traumatic amnesia for more than 24 hours would indicate a more severe injury and so the mild qualifier would not be applicable (Silverberg et al., 2023).

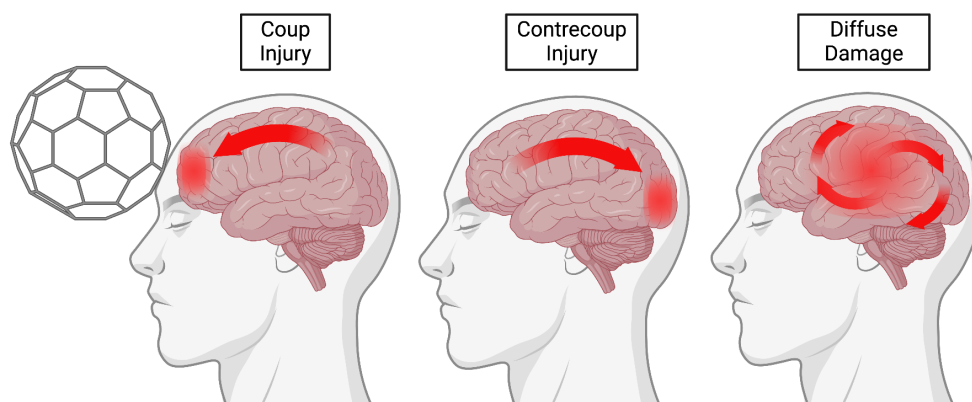


Figure 1.1 *Mechanisms of Damage in Mild Traumatic Brain Injury*

Note. The above illustration depicts a coup injury at the site of impact (left), a contrecoup injury opposite the site of impact (middle) and widespread diffuse damage (right). Created with BioRender.com.

1.3 Prevalence and Long-term Impacts

1.3.1 A Prevalent Injury

Approximately 69 million people worldwide experience a traumatic brain injury (TBI) each year (Dewan et al., 2018) with ~90% of those being classified as mild (Maas et al., 2022; Neumann et al., 2023). In Aotearoa New Zealand (NZ), a population-based study found that the incidence of TBI was 790 cases per 100,000 and for mTBI it was 749 cases per 100,000, per year (Feigin et al., 2013). In 2023 alone, approximately 10,600 Accident Compensation Corporation claims were filed for sports-related mTBI in NZ - the highest in five years. However, the actual incidence of mTBI is likely much higher (Simon et al., 2017), with up to 30% more suspected to be unreported (Accident Compensation Corporation [ACC], 2024a; ACC, 2024b), as many so-called "minor" head injuries are ignored without being medically evaluated. Under-reporting of sports-related mTBI is particularly common due to misconceptions about head injury risks, stigma surrounding injury, the desire to continue playing, or the avoidance of mandatory stand-down periods (Bretzin et al., 2022; Cusimano et al., 2017; Ledreux et al., 2020; Pennock et al., 2024). Globally, as many as 50% of mTBI cases are estimated to go unreported (Ledreux et al., 2020).

The term "mild TBI" may not accurately reflect the lived experience of many, as while some individuals with an mTBI recover within 10-14 days (Danielli et al., 2023), many individuals experience enduring symptoms. The estimated prevalence of prolonged symptoms varies widely

(Polinder et al., 2018), with some research estimating that around 20-30% of mTBI patients suffer persistent symptoms that extend beyond the expected recovery period, significantly impacting daily functioning (Hossain et al., 2022; Neumann et al., 2023; Visser et al., 2022). Other research suggests that this number is much higher. For example, Kara et al. (2020) conducted a prospective cohort study over a two-year period and found that only 45% of participants were clinically recovered from their mTBI within 14 days. Similarly, McInnes et al. (2017) found in their review that approximately half of individuals with mTBI suffered from long-term cognitive impairments. Persistent mTBI symptoms can include mild cognitive impairments, memory deficits, motor dysfunction (e.g., postural control issues), heightened mood states (e.g., anxiety and depression), as well as dizziness, headaches, excessive sympathetic nervous system activation, and sleep disturbances (Neumann et al., 2023). These long-term effects have been linked to reduced work productivity and high healthcare utilisation (Theadom et al., 2017; Wang et al., 2021).

1.3.2 Financial Impacts

The financial impact of mTBI is significant at both individual and societal levels. Globally, the economic burden of TBI is estimated at approximately US\$400 billion (Howe et al., 2022), underscoring its significant public health impact. In NZ, Accident Compensation Corporation data show that in 2023, around NZ\$64 million was spent on mTBI recovery alone, reflecting a considerable strain on the public health system. Beyond system-level costs, mTBI imposes a personal financial toll as individuals often require extended time off work to recover (Fallesen & Campos, 2020; Gaudette et al., 2022; Theadom et al., 2017). For example, Gaudette et al. (2022) reported that 59% of participants were not working two weeks post-mTBI, and 17% remained off work 12 months later. Fallesen and Campos (2020) found a 4.2% reduction in average salary following mTBI, a decline that persisted for over five years, highlighting the potential for long-term financial consequences. In addition to lost income, individuals may face out-of-pocket costs for alternative or non-publicly funded treatments. This financial burden is not evenly distributed. Although Māori and Pasifika make up approximately 17% and 9% of the population, respectively (Stats NZ Tatauranga Aotearoa, 2024), they face a 23% higher risk of mTBI than NZ Europeans, with incidence rates of 1,242 per 100,000 compared to 842 per 100,000 (Lagolago et al., 2015). This disparity reflects not only a higher health burden but also a disproportionate financial and social impact, reinforcing the need for more equitable and culturally responsive healthcare approaches.

1.3.3 Psychological Impacts

Beyond healthcare costs, the consequences of mTBI are multifaceted and impact patient lives in diverse ways, including detrimental effects on mental health (Delmonico et al., 2022; Elder et al., 2019; Gitaari et al., 2024; Howlett et al., 2022). mTBI is associated with a risk of developing depression and anxiety disorders, such as PTSD, that can develop months or years after the injury (Elder et al., 2019). For example, Delmonico et al. (2022) conducted a cohort study involving 9,428 individuals with mTBI and matched healthy controls. They found that affective disorders (including depression, anxiety, and adjustment disorders) were significantly more common in the mTBI group, with 23% receiving a diagnosis within the first 12 months compared to 14% of controls. One mechanistic explanation for the link between brain injury and psychiatric disorders is dysregulation of the inflammatory response post-injury (Risbrough et al., 2022). Neuroinflammation may heighten the risk of neuropsychiatric disorders either directly via a prolonged inflammatory response, or indirectly, via priming of the neural immune system for excessive response to subsequent disruptions to homeostasis (Risbrough et al., 2022). mTBI can be an isolating experience, as individuals may choose to stay home due to debilitating physical or cognitive symptoms such as headaches or sensitivity to light and noise (Greenberg et al., 2023; Marzolla et al., 2023; Shepherd et al., 2020). A lack of awareness and understanding about the effects of mTBI can further contribute to feelings of isolation and frustration (He et al., 2024; Karmali et al., 2022; Pappadis et al., 2011).

1.3.4 Neurodegeneration

Brain injuries, across a range of severities, have been increasingly linked to heightened vulnerability to long-term neurological complications and the development of neurodegenerative diseases, including chronic traumatic encephalopathy (CTE), Alzheimer's disease, and Parkinson's disease (Ayerra et al., 2025; Cruz-Haces et al., 2017; Dodd et al., 2022; Freire et al., 2023; Gardner & Yaffe, 2015; Hossain et al., 2022; Tagge et al., 2018). In cases of milder severity, these associations are particularly evident in individuals with repeated concussive or sub-concussive impacts, where cumulative trauma appears to amplify the risk of enduring neurodegenerative outcomes, such as CTE (Dodd et al., 2022; Fehily & Fitzgerald, 2017; Gardner & Yaffe, 2015; Neumann et al., 2023; Ntikas et al., 2022; Washington et al., 2016). The potential mechanisms underpinning these associations are diverse and complex, involving a range of neuropathological processes. These include tau and Lewy body pathology, cerebrovascular injury,

increased amyloid-beta ($A\beta$) plaque deposition, neurofibrillary tangle formation, oxidative stress, cytoskeletal disruption, glutamate excitotoxicity, and sustained inflammation (Boulton & Al-Rubaie, 2025; Dodd et al., 2022; Hossain et al., 2022; Juan et al., 2022; Ledreux et al., 2020; Tagge et al., 2018; Winston et al., 2016). Reactive astrocytes have also been shown to exacerbate chronic neuroinflammation and subsequent neuronal damage (Boulton & Al-Rubaie, 2025).

In addition to these central mechanisms, peripheral immune activity also appears to play a role. For instance, T cells recruited as part of the inflammatory response following brain injury have been implicated in contributing to long-term neurodegenerative changes (Ayerra et al., 2025). Kempuraj et al. (2020) reviewed the role of mast cells in neurodegeneration following brain injury. Mast cells, part of the innate immune system alongside macrophages, T cells, and natural killer (NK) cells, perform several protective functions, including the detection and removal of harmful pathogens and toxins. Beyond immune defence, mast cells also play an important role in neural tissue repair, scar formation and the generation of new cells (Kempuraj et al., 2020). Acutely following brain injury, mast cells are rapidly activated, releasing immune mediators and recruiting other immune cells to the central nervous system. While this acute response can support neuronal repair, persistent activation and chronic inflammation may lead to neuronal death and predispose or accelerate the onset or progression of Alzheimer's disease, a progressive neurodegenerative disease (Kempuraj et al., 2020).

Persistent neuroinflammation is now recognised as a significant risk factor for neurodegeneration, particularly among individuals with predisposing factors relating to age, sex, nutrition, stress, allergies, inflammatory disorders, and certain medications (Kempuraj et al., 2020). Importantly, even mTBIs have been associated with hallmark Alzheimer's disease pathologies, including increased amyloid-beta accumulation, neurofibrillary tangles, tau hyperphosphorylation, and Lewy body pathology (Boulton & Al-Rubaie, 2025; Ramos-Cejudo et al., 2018; Washington et al., 2016; Wilson et al., 2017). Emerging evidence also implicates cerebrovascular dysfunction as a key contributor to Alzheimer's disease-like pathology following brain injury (Ramos-Cejudo et al., 2018). A review by Washington et al. (2016) highlighted that both single and repeated mTBI events have been linked to the presence of multiple pathological markers (e.g., $A\beta$, tau, TAR DNA-binding protein 43 [TDP-43], and Lewy bodies), reflecting what has been termed a polypathology. Although growing evidence supports a link between brain injury and neurodegeneration, how *mild* TBI leads to long-term neurodegeneration remains less

well understood. Further research is needed to elucidate the role of chronic neuroinflammation in driving neurodegenerative processes after mTBI. Understanding these mechanisms will be essential for identifying early intervention strategies and preventing progressive degeneration.

Despite its significant impact, the underlying pathophysiology of persistent symptoms and prolonged recovery following mTBI remains poorly understood (Clarke et al., 2024; Visser et al., 2022). From a biopsychosocial perspective, post-concussion symptoms result from a complex interplay of biological, psychological, and social factors influencing both their onset and persistence. Biological factors may include neurological and cognitive reserve, age, sex, and the pathophysiological consequences of injury. Psychological factors encompass premorbid emotional state, personality traits, and cognitive aspects such as illness beliefs and behaviours. Social factors, including the availability of social support, access to healthcare, and welfare systems, also play a crucial role. However, the prognostic significance of biological factors, such as neuroimaging findings and biomarkers of tissue damage or inflammation, remains unclear, despite their potential role as risk factors or triggers (Clarke et al., 2024).

1.4 Invisible Injuries: The Secondary Injury Cascade

1.4.1 An Overview of the Secondary Injury Cascade

The effects of mTBI extend beyond the impact site and are often far more severe than they appear externally. Following the primary mechanical injury, a cascade of secondary injuries can be initiated that evolve in the minutes, days or even months after the primary injury (Obukohwo et al., 2024; Strogulski et al., 2023). While more prominent in moderate or severe forms of TBI, the secondary injury cascade may play a role in poor outcomes and subsequent long term neurological consequences of mTBI, particularly in cases of repeat injury (Fehily & Fitzgerald, 2017; Naumenko et al., 2023; Visser et al., 2022). Secondary injury cascades can include the instigation of an inflammatory response, disruption of the blood-brain barrier (BBB), excitotoxicity, oxidative stress, metabolic disturbances, vascular damage, brain oedema, cytoskeletal degradation, activation of microglia and astrocytes, and apoptotic cell death (Alam et al., 2020; Freire et al., 2023; Kim et al., 2023; Naumenko et al., 2023; Slavoaca et al., 2020; Soltani et al., 2020; Visser et al., 2022).

1.4.2 Ionic Imbalance, Excitotoxicity and the Metabolic Crisis

Three key interrelated processes unfold as part of the secondary injury cascade following mTBI: ionic imbalance, excitotoxicity and a resulting metabolic crisis. Ionic imbalance involves a disruption in the normal distribution of ions such as potassium (K^+), sodium (Na^+), calcium (Ca^{2+}), and glutamate. The mechanical forces involved in mTBI, particularly the stretching of axons and cell membranes, can compromise the structural integrity of neuronal and glial membranes. This disruption impairs the function of ion channels and pumps, such as the Na^+/K^+ -ATPase pump, which are essential for maintaining ionic gradients across the cell membrane. Increased membrane permeability allows for the uncontrolled movement of ions, disturbing cellular homeostasis (Barkhoudarian et al., 2016; Naumenko et al., 2023). For example, excessive efflux of K^+ into the extracellular space leads to membrane depolarisation, triggering neuronal hyperexcitability. Simultaneously, there is an influx of Na^+ and Ca^{2+} into neurons, which disrupts osmotic balance and contributes to cytotoxic oedema and the activation of calcium-dependent enzymatic cascades (Naumenko et al., 2023; Romeu-Mejia et al., 2019).

This depolarisation also results in the excessive release of glutamate, the brain's primary excitatory neurotransmitter, into the synaptic cleft. Under normal conditions, glutamate is rapidly cleared from the extracellular space, however, the energy crisis that follows mTBI impairs this reuptake mechanism, leading to an accumulation of glutamate (Thapa et al., 2021). The resulting excitotoxic environment over activates glutamate receptors, particularly NMDA and AMPA receptors, which further amplifies calcium influx and initiates a cascade of damaging processes, including oxidative stress, mitochondrial dysfunction, and ultimately, cell death (Barkhoudarian et al., 2016; Naumenko et al., 2023; Thapa et al., 2021).

The culmination of these processes is a metabolic crisis, in which the brain's energy demands during the recovery period exceed its available resources (Naumenko et al., 2023; Romeu-Mejia et al., 2019). Ionic disturbances and neurotransmitter release necessitate large amounts of adenosine triphosphate (ATP), produced via glucose metabolism, to restore ionic gradients and maintain cellular function. However, mTBI also impairs mitochondrial function, reduces cerebral blood flow, and disrupts glucose metabolism, severely limiting ATP production (Freire et al., 2022; Strogulski et al., 2023). The resulting energy deficit leaves neurons unable to repair damage or sustain normal function, prolonging dysfunction and increasing vulnerability to

further injury. Thus, the mismatch between energy supply and demand contributes to a prolonged period of metabolic vulnerability following mTBI.

1.4.3 Oedema

Another feature of the secondary injury cascade following mTBI can be the formation of oedema, characterised by increased extracellular and/or intracellular water content in the brain (Freire et al., 2023). Cerebral oedema can present in multiple forms, one of which is termed vasogenic oedema. When the forces suffered during brain injury damage cerebral blood vessels, the damage triggers an inflammatory response that releases chemical mediators (such as cytokines) that increase vascular permeability. This facilitates the leakage of fluid from blood vessels into surrounding tissues (plasma extravasation) and leads to the accumulation of extravascular fluid in the extracellular space and the formation of oedema. One of the detrimental consequences of this type of cerebral oedema is increased intracranial pressure (ICP). While mTBI generally presents a low risk of raised ICP, transient elevations may still occur and should be acknowledged in clinical assessment (Haider et al., 2018). A different but no less risky form of cerebral oedema is cytotoxic oedema, characterised by an accumulation of fluid within brain cells (Freire et al., 2023). This results from cell membrane dysfunction and the disruption of ionic homeostasis, particularly involving the sodium potassium pump.

1.5 Response to Injury: Neuroinflammation

1.5.1 An Overview of Neuroinflammation and the Blood-brain Barrier

Neuroinflammation is a dynamic response of the brain to harmful stimuli and is a crucial component of the secondary injury cascade following mTBI. Importantly, substantial research has highlighted that this response can be both protective and harmful, depending on its timing, intensity, and duration (Ayerra et al., 2025; Freire et al., 2023; Markovic et al., 2021; Naumenko et al., 2023; Neumann et al., 2023; Obukohwo et al., 2024; Pasternak et al., 2012; Pasternak et al., 2016; Piao et al., 2013; Rosen, 2024). Neuroinflammation involves a complex interplay between central and peripheral immune responses, shaped by numerous individual factors such as age, sex, injury mechanism, severity, and genetic predisposition (Simon et al., 2017).

A key structure in the initiation and regulation of the neuroinflammatory response is the BBB. This is a selectively permeable interface between the blood and the brain that tightly regulates the passage of cells, molecules and ions between the bloodstream and the brain

parenchyma, protecting the brain by signalling the presence of inflammation or infection (Galea, 2021). The BBB plays an essential role in maintaining cerebral homeostasis, including the regulation of intracranial pressure by restricting the excessive movement of water and ions (Alahmari, 2021; Galea, 2021). One of the earliest immune responses following mTBI is the disruption of the BBB, which allows blood-derived components, such as plasma proteins and immune cells, to enter the brain, thereby triggering a neuroimmune response (Risbrough et al., 2022). Following BBB disruption, the release of signalling molecules rapidly occurs, including cytokines, chemokines and damage-associated molecular patterns (DAMPs). Glial cells, such as microglia and astrocytes are then activated and involved in coordinating the neuroinflammatory response (Freire et al., 2023).

1.5.2 Microglia

Microglia make up 5-10% of adult brain cells and have a quintessential role in surveying brain parenchyma, showing functional plasticity and modifying their morphology in response to changes in their microenvironment (Neumann et al., 2023; Simon et al., 2017). Microglial activation is a key pathological marker in animal models of mTBI (Neumann et al., 2023). Within hours of the initial damage, microglia become polarised along an activation spectrum with their phenotypes being characterised into two subtypes with disparate functions (Mira et al., 2021; Simon et al., 2017). M1-type microglia serve a pro-inflammatory purpose and can be beneficial initially, but in excess or with a prolonged response, can be detrimental and facilitate a hyperinflammatory state post-injury. Therefore, M1 microglia are often considered to be neurotoxic.

In contrast, M2-type microglia are associated with the production of anti-inflammatory cytokines as well as phagocytic activity. In their M2 phenotype, microglia can contribute to repair and remodelling of the brain in response to injury and are therefore seen as being neuroprotective (Boulton & Al-Rubaie, 2025; Mira et al., 2021; Neumann et al., 2023; Simon et al., 2017). The degree to which microglia assume either an M1 or M2 activated phenotype is dependent on several factors, such as changes in their microenvironment as well as genetic and epigenetic factors (Simon et al., 2017). However, this categorisation may not accurately account for the diverse range of phenotypes that microglia can possess, and a paradigm shift away from this classification may be warranted to recognise their dynamic and complex activation (Boulton & Al-Rubaie, 2025; Neumann et al., 2023).

Phagocytosis is the cellular digestion of particles, such as dying cells and pathogens, in the extracellular space (Yu et al., 2022). In their neuroprotective capacity, microglia can play a crucial role in responding to inflammatory events as they survey the brain, phagocytose debris to dispose of neurotoxic material and aid in homeostasis (Alam et al., 2020; Bolte & Lukens, 2021; Mira et al., 2021; Obukohwo et al., 2024; Strogulski et al., 2023). Following injury, damaged cells and debris accumulate at the site of injury, resulting in further damage and inhibiting the healing process. Activated, neuroprotective microglia migrate towards the injury site, engulfing and digesting cellular debris and creating a barrier around the damaged area. This helps to reshape the extracellular matrix, preventing further tissue damage and creating an efficient environment for tissue repair (Obukohwo et al., 2024; Risbrough et al., 2022; Yu et al., 2022).

Microglia also have other beneficial roles post-injury. They can facilitate synaptic pruning and initiate synaptogenesis and neurogenesis, contributing to the neuroplasticity of the brain and its ability to repair and heal following trauma (Strogulski et al., 2023; Yu et al., 2022). Microglia also release anti-inflammatory cytokines and chemokines, such as interleukin-10, interleukin-13 and interleukin-14, that suppress the pro-inflammatory cytokines and promote survival of neurons and repair of brain tissue (Risbrough et al., 2022). Moreover, microglia can release neuroprotective factors such as brain-derived neurotrophic factor (BDNF), which promotes neuronal survival and neural plasticity (Obukohwo et al., 2024).

Conversely, neurotoxic microglia can release pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-6, interleukin-1 β and interleukin-12, as well as reactive oxygen species, that lead to the recruitment of peripheral immune cells, including monocytes and T cells, which play a key role in the inflammatory response (Ayerra et al., 2025; Bolte & Lukens, 2021; Freire et al., 2023; Obukohwo et al., 2024; Risbrough et al., 2022; Simon et al., 2017; Strogulski et al., 2023). Dysregulated microglia activation can contribute to a prolonged inflammatory response that can damage healthy brain tissue and hinder healing at the site of injury. This in turn can lead to neuronal death, axonal damage, further BBB disruption and neurotransmitter dysregulation. Therefore, excessive microglial activation can be neurotoxic and exacerbate the secondary injury cascade following brain injury (Bolte & Lukens, 2021; Obukohwo et al., 2024). In fact, activated microglia have been implicated in various neurological disorders, such as Alzheimer's disease, Parkinson's disease and multiple sclerosis, where they can cause chronic inflammation and neuronal damage (Ayerra et al., 2025; Bolte & Lukens, 2021;

Obukohwo et al., 2024). Further research is needed to understand the role of prolonged microglia activation in the development of neurodegenerative disorders, particularly for mild forms of TBI.

1.5.3 Astrocytes

Activated microglia also release signals that induce structural changes in astrocytes, facilitating a shift from their resting form to their reactive form in response to pathological events (Boulton & Al-Rubaie, 2025; Freire et al., 2023). Once in a reactive form, astrocytes upregulate proteins that control the inflammatory response. As with microglia, astrocytes can be dichotomised as A1-type reactive astrocytes, that have a neurotoxic role, and A2-type reactive astrocytes, that have an anti-inflammatory and neuroprotective role (Boulton & Al-Rubaie, 2025). Astrogliosis, the activation and proliferation of astrocytes, may contribute to the spread of secondary injury in distal regions from the initial site of brain damage (Mira et al., 2021). In addition, reactive astrocytes may be associated with the link between brain trauma and neurodegenerative diseases, such as Alzheimer's disease (Boulton & Al-Rubaie, 2025; Jamjoom, et al., 2021), although more research is warranted in this space with regards to mTBI.

1.5.4 Inflammatory Mediators

Inflammatory mediators, such as cytokines, chemokines and damage-associated molecular patterns (DAMPs), are synthesised and released by activated microglia and astrocytes following brain injury. These mediators contribute to lesion propagation by amplifying the initial damage and exacerbating secondary injury cascades. Upregulated cytokines recruit additional inflammatory molecules to the injury site, creating an inflammatory feedback loop (Freire et al., 2023). Cytokines exert complex effects, as they include both pro-inflammatory and anti-inflammatory subtypes (Naumenko et al., 2023). Pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF- α), interleukin-1 β , interleukin-6, interleukin-12, and interleukin-18, as well as reactive oxygen species (ROS) and nitric oxide (NO), promote neuroinflammatory processes. In contrast, anti-inflammatory cytokines such as transforming growth factor-beta (TGF- β), interleukin-4, interleukin-10, and interleukin-13 help resolve inflammation (Freire et al., 2023; Obukohwo et al., 2024).

Chemokines, a subclass of cytokines, also play a key role in modulating the inflammatory response and directing the migration of peripheral immune cells, including neutrophils, macrophages, and T cells, to the site of injury (Obukohwo et al., 2024). Common chemokines associated with brain injury include CXCL1, CXCL2, CXCL8, and CCL2. Lastly, DAMPs are

released from injured neurons, glial cells, and vascular endothelium, acting as endogenous danger signals that activate inflammasomes - particularly the NLRP3 inflammasome. This activation further increases the production of pro-inflammatory cytokines such as TNF- α , interleukin-1 β , and interleukin-18, and chemokines, thereby perpetuating a cycle of escalating neuroinflammation (Freire et al., 2023; Obukohwo et al., 2024). Collectively, these inflammatory mediators contribute to a neuroinflammatory environment that plays a central role in the secondary injury cascade following mTBI.

1.5.5 Peripheral Immune Cells

In addition to glial cells and inflammatory mediators, a variety of other immune cells play essential roles in the brain's inflammatory response to injury. Neutrophils are among the first peripheral immune cells to infiltrate the brain after injury and are responsible for recruiting monocytes, which differentiate into macrophages. Macrophages, a type of white blood cell, are critical for clearing pathogens, dead cells, and cellular debris through phagocytosis. In doing so, they not only help to protect the brain from further damage and infection but also stimulate the activity of other immune cells, contributing to a coordinated defence and repair response. T cells and mast cells also contribute to the inflammatory milieu, with both cell types facilitating the production of cytokines such as interleukin-4, that plays a neuroprotective role and aids in axonal growth post-injury. Regulatory T cells (Tregs) play a modulatory role by limiting excessive inflammation, supporting wound healing and tissue remodelling, and regulating astrocyte activity during astrogliosis (Kempuraj et al., 2020). Mast cells, which act as both sensors and effectors in the immune response, release a broad array of pro- and anti-inflammatory mediators upon activation. These include interleukins (e.g., interleukin-1 β and interleukin-6), TNF- α , vascular endothelial growth factor (VEGF), matrix metalloproteinases, ROS, nerve growth factor (NGF), histamine, and stem cell factor (SCF) - each contributing to inflammation, repair, angiogenesis, or neuroprotection depending on the context and timing of their release (Kempuraj et al., 2020). Ultimately, the immune response to brain injury is a highly coordinated, multi-cellular process. While essential for protecting neural tissue and initiating recovery, dysregulation of this complex response can exacerbate injury and contribute to long-term neurological dysfunction.

1.5.6 Beneficial versus Harmful Neuroinflammation

Neuroinflammation can be beneficial in the acute phase following brain injury, clearing cellular waste, reducing the risk of infection and promoting neurogenesis and the repair of

damaged tissue (Ayerra et al., 2025; Calderone et al., 2024; Monsour et al., 2022). However, aberrant regulation of the immune response can lead to deleterious neuroinflammation (see Figure 1.2) (Bolte & Lukens, 2021). The development of chronic neuroinflammation has been linked to multiple factors including injury severity, genes associated with immune response, age, sex and comorbidities such as sleep disturbances (Risbrough et al., 2022). Importantly, the activation of microglia following brain injury is shown to be a significant contributor to chronic neuroinflammation. While microglia activation begins within hours of injury, it can extend to locations beyond the focal region of initial damage and can remain active for years following injury (Bolte & Lukens, 2021; Calderone et al., 2024; Risbrough et al., 2022). Even mild forms of TBI can prime microglia activation, resulting in more exaggerated or prolonged inflammatory responses to subsequent trauma, indicating a heightened vulnerability to additional brain injuries (Risbrough et al., 2022).

Prolonged neuroinflammation can be harmful, causing BBB disruption, synaptic dysfunction, neuronal death and chronic neurodegeneration (Ayerra et al., 2025; Calderone et al., 2024; da Luz Scheffer & Latini, 2020; Kim et al., 2023; Markovic et al., 2021; Mee-Inta et al., 2019). Dysregulated neuroinflammation is linked with longer recovery trajectories and poorer long-term health outcomes following brain injury and may be a driving force behind the link between brain injury and neurodegeneration, necessitating further research (Boulton & Al-Rubaie, 2025; Di Battista et al., 2020; Risbrough et al., 2022; Simon et al., 2017). As the neuroinflammatory processes associated with secondary injury cascades begin acutely following the trauma (within hours), there is a potentially important therapeutic window of opportunity for prevention of further injury and preservation of brain function (Kim et al., 2023).

Inflammatory biomarkers (i.e., via blood, cerebrospinal fluid, or neuroimaging) could be crucial for tracking neuroinflammation and neuroplasticity during recovery from mTBI (Calderone et al., 2024). A limited number of candidate biomarkers are currently under investigation, including ubiquitin-C-terminal hydrolase 1 (UCH-L1), tau, neurofilament light (NF-L), glial fibrillary acidic protein (GFAP), and inflammatory cytokines such as interleukin-1 β , interleukin-6, and TNF- α (Tabor et al., 2022). However, very few biomarkers have been approved for clinical use in mTBI recovery. The only approved biomarkers are UCH-L1 and GFAP, which are approved by the U.S. Food and Drug Administration (FDA) for assessing the likelihood of intracranial injury, and S100B, which is recommended by the Scandinavian Neurotrauma Committee (SNC)

guidelines for triaging computed tomography (CT) scans (Clarke et al., 2024; Visser et al., 2022). More research is needed for biomarkers that can be used specifically in mild forms of TBI and those that can be used for prognostic purposes in understanding and predicting prolonged symptoms and poor outcomes. Given the critical role of brain inflammation in shaping recovery, accurate measurement of neuroinflammation is a key priority. One magnetic resonance imaging-based method showing promise is quantitative T2 relaxometry, discussed in the following chapter of this thesis.

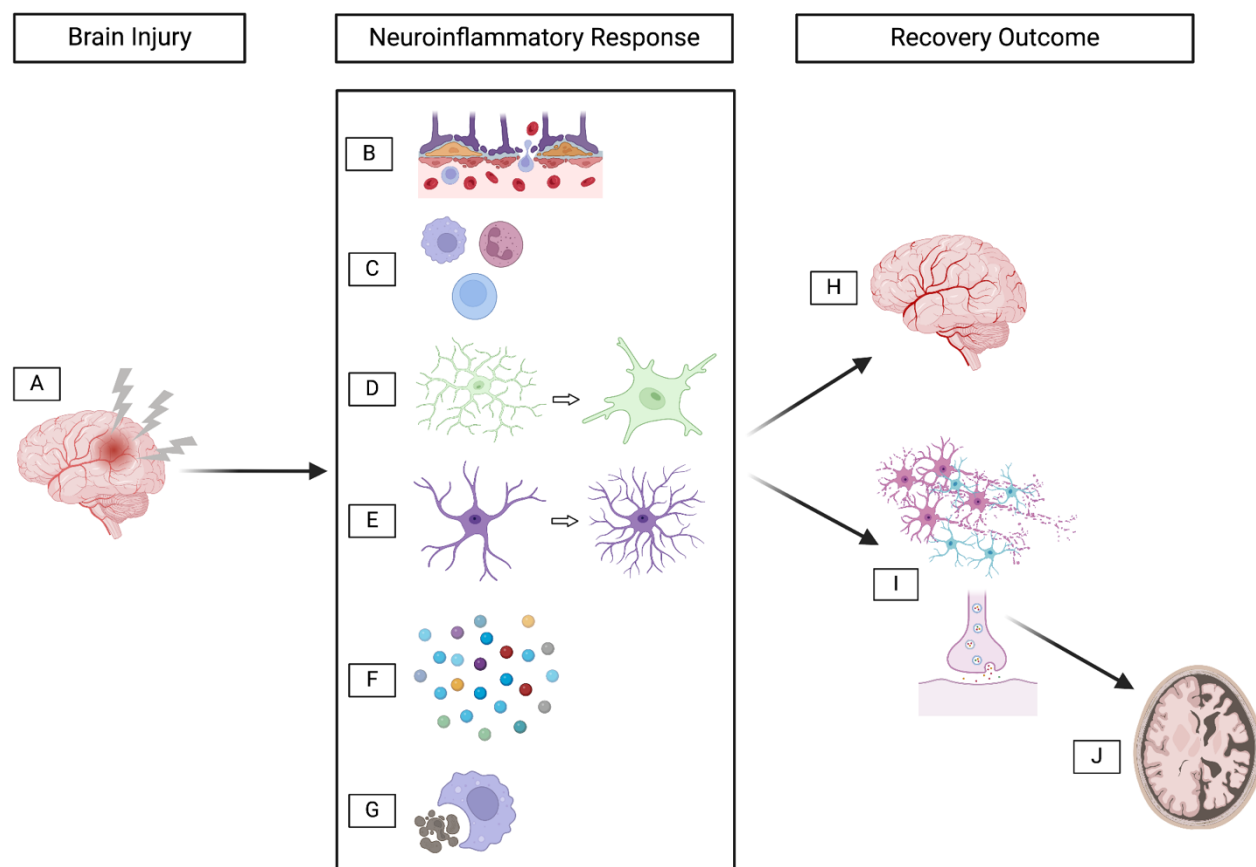


Figure 1.2 *The Neuroinflammatory Response to Brain Injury*

Note. This image depicts some of the key events involved in the brain's inflammatory response to injury. The initial brain injury (A) instigates a range of structural and functional alterations, including: (B) blood-brain barrier disruption, (C) the release of immune cells (e.g., microglia, astrocytes, neutrophils, monocytes, and macrophages), (D) activation of microglia from their resting state to their active state, (E) activation of astrocytes from their resting state to their active state, (F) the release of pro- and anti-inflammatory cytokines, and (G) phagocytosis of cellular debris. This response can be (H) neuroprotective and serve to preserve brain structure and maintain homeostasis or it can lead to (I) neuronal loss and synaptic dysfunction and subsequent (J) chronic neurodegeneration. Created with BioRender.com.

2

Potential Methods to Measure and Modify Neuroinflammation

2.1 Overview

With a general introduction to mTBI and neuroinflammation provided in Chapter 1, this second chapter shifts the focus towards the specific objectives of the thesis. While understanding the secondary injury cascade and recognising the critical role of neuroinflammation are essential, a recurring question continues to drive my curiosity and my motivation for this research, *but what now, what can we do about this?* With this line of questioning at the forefront, Chapter 2 narrows the scope of the thesis further by introducing its central dual focus on potential ways of: (1) **measuring** and (2) **modifying** the brain's inflammatory response to injury. These two points represent two sides of the same coin, and accordingly, this chapter is divided into two distinct, but interrelated sections.

The first section introduces the neuroimaging technique used in the first two studies (further elucidated in Chapters 4 and 5): **quantitative T2 relaxometry**. This technique represents one side of the coin - a potential method to detect and quantify neuroinflammation following mTBI. Here, I explain the basic physics underlying quantitative T2 relaxometry, outline the practical steps involved in acquiring and processing the images, describe how this method is linked to changes in brain water content and why this may indicate inflammatory processes. I also review previous applications of this technique to contextualise its potential utility.

Following this, the second section of this chapter turns to the other side of the coin: a possible way of modifying the brain's inflammatory response. The strategy explored in this thesis is **physical activity (PA)**. This section discusses current evidence for the beneficial role of PA in mTBI recovery, its potential to modulate inflammatory processes, and the relevance of using compositional data analysis to authentically represent and analyse time-use data involving PA. By

selecting this analytical approach, I aim to capture the interdependent nature of different types of movement behaviours in a way that reflects real-world behaviour.

Lastly, I conclude this chapter with a clear rationale for the research, along with the specific aims that the thesis sets out to address. With the foundational concepts established in Chapter 1, my goal for the current chapter is to guide the reader into the core focus of my work. By the end of this chapter, I hope the dual focus of this thesis is clear and it is evident that while measuring the brain's response to injury is critical, it is only part of the solution. To make a meaningful impact, we must also explore ways to actively influence that response and improve outcomes from mTBI.

2.2 Potentially Measuring Brain Inflammation Using Magnetic Resonance Imaging

2.2.1 Quantitative T2 Relaxometry: An Introduction

T2-weighted magnetic resonance images (MRI) can be used to detect subtle brain abnormalities, including pathological fluid accumulation. Conventional T2-weighted MRI provides a visual representation of the underlying tissue, illustrated by varying intensities of signal contrast, which is qualitative in nature and relies on subjective interpretation of the images (St-Onge, 2024). Radiologists can use these images as a basis for diagnostic recommendations by assessing the presence of abnormal fluid accumulation in the brain (Dhabalia et al., 2024). Without a quantitative metric to interpret the signal intensities it is challenging to compare MR images longitudinally or across subjects. To obtain quantitative information, the contributions of different contrast mechanisms need to be extracted (Cheng et al., 2012).

Quantitative T2 relaxometry is a novel MRI method to assess microstructural alterations in brain tissue by measuring tissue relaxation properties that can be indicative of different neurological conditions (Chekhonin et al., 2024; Deoni, 2010; Liu et al., 2018). Quantitative T2 relaxometry can overcome issues relating to conventional MR imaging, such as the qualitative visual interpretation of images or the absence of signal intensity standardisation by isolating the contributions of individual MR contrast mechanisms (i.e. T1, T2 and T2*) that are contributing to the signal and providing T2 maps (Chekhonin et al., 2024). These maps can be interpreted by absolute units, which provides a numerical measurement of the T2 relaxation time, enabling an

objective characterisation of the underlying tissue and an unbiased metric for comparisons between MRI data (Cheng et al., 2012; Deoni, 2010).

2.2.2 Quantitative T2 Relaxometry: The Physics and Signal Modelling

MRI operates based on the magnetic properties of hydrogen nuclei (protons), which are especially abundant in water and fat. When an MRI scan is initiated, a strong magnetic field, referred to as B_0 , is applied, causing the hydrogen protons in the body to align either parallel or antiparallel to the direction of this field. Because slightly more protons align with the field than against it, a small net magnetisation is produced along the z-axis (longitudinal direction) (Deoni, 2010; Pai et al., 2023). To generate a measurable signal, a 90-degree radiofrequency (RF) pulse (tuned to the Larmor frequency) is applied perpendicular to B_0 . This pulse excites the protons, tipping the net magnetisation into the transverse plane (x-y axis), where the protons begin to precess in phase with each other (Cheng et al., 2012; Deoni, 2010; Pai et al., 2023). When this excitation pulse is turned off, the protons begin to lose the energy absorbed during excitation and gradually return to their original alignment along the longitudinal axis. During this process, they lose synchrony with each other, a phenomenon known as dephasing (Deoni, 2010). This loss of phase coherence gives rise to what is known as T2 relaxation (also referred to as transverse or spin-spin relaxation). T2 relaxation reflects the rate at which hydrogen protons lose phase synchrony in the transverse plane due to microscopic magnetic field inhomogeneities caused by interactions with neighbouring spins (Cheng et al., 2012; Deoni, 2010; St Onge, 2024; Pai et al., 2023). Specifically, the time at which 63% of the transverse magnetisation has decayed is called the T2 time (Pai et al., 2023). The equation below describes how the transverse signal decays over time (Abragam, 1961):

$$M_{xy}(t) = M_{xy}(0) e^{-t/T2}$$

Where:

$M_{xy}(t)$	is the transverse magnetisation at time t after the RF pulse
$M_{xy}(0)$	is the transverse magnetisation at time $t = 0$ (i.e. immediately after the RF pulse)
$e^{-t/T2}$	is the exponential decay function representing the signal decay over time
T2	is the T2 relaxation time, specific to tissue type (in ms)

Measuring T2 relaxation times involves performing scans with long repetition times (TR) and multiple echo times (TE) (Liu et al., 2018). These scans begin with a 90-degree excitation pulse, followed by a series of 180-degree refocusing pulses (Carr & Purcell, 1954; Meiboom & Gill, 1958; St-Onge, 2024). Each refocusing pulse realigns dephasing spins, producing what is known as a spin echo. The T2 signal is measured at the mid-points between these refocusing pulses, where the spin-echo occurs. As the TE increases, more transverse signal decay has occurred, resulting in lower signal intensity (Cheng et al., 2012). T2 signal intensity varies depending on the tissue microenvironment. Tissues with higher free water content, such as cerebrospinal fluid or oedematous tissue, tend to have longer T2 relaxation times because the protons maintain transverse magnetisation for longer periods (Cheng et al., 2012; Deoni, 2010; Pai et al., 2023). These tissues therefore appear brighter on T2-weighted MR images. The loss of phase coherence is slower for water compared to fat, for example, because there is less spin-spin interaction in tissue with higher water content (Cheng et al., 2012; Deoni, 2010). In contrast, tissues with more tightly bound water, such as white matter or muscle, induce more spin-spin interactions and exhibit shorter T2 relaxation values. Pathological changes, such as inflammation, oedema, or demyelination, can alter tissue water content and thus influence T2 relaxation times and signal intensity (Cheng et al., 2012; Deoni, 2010). To quantify these changes, an exponential decay curve is fitted across the echo sequence. This curve enables voxel-wise estimation of T2 values, using the following formula (St-Onge, 2024):

$$S(TE) = S_0 \cdot e^{-TE/T2}$$

Where:

$S(TE)$	is the signal at each echo time
S_0	is the signal intensity immediately following the excitation pulse
e	is the base of the natural logarithm (Euler's number)
$T2$	is the transverse relaxation time

The output of the T2 relaxation equation provides a quantitative T2 value for each voxel, which can then be used to generate a T2 map - an image in which the signal intensity of each voxel

corresponds to its estimated T2 relaxation time, typically expressed in milliseconds. These maps can be overlaid onto structural MRI scans or standardised brain templates (e.g., the Montreal Neurological Institute [MNI] brain) to allow spatial localisation of T2 changes. A common technique for acquiring T2 relaxometry data involves using multiple single spin-echo sequences with varying echo times. However, clinical scan times are often constrained and as a result, multi-echo spin-echo sequences are more commonly used, as they allow multiple T2-weighted images to be acquired in a single scan session (Milford et al., 2015). This method for acquiring T2 maps is usually constructed as a Carr-Purcell-Meiboom-Gill (CPMG) spin-echo sequence, which samples the decaying transverse magnetisation at multiple echo times. These sampled data points are then fitted to a monoexponential decay model to estimate the T2 relaxation time at each voxel (see Figure 2.1) (Chekhonin et al., 2024; Cheng et al., 2012; Hilbert et al., 2018; Milford et al., 2015).

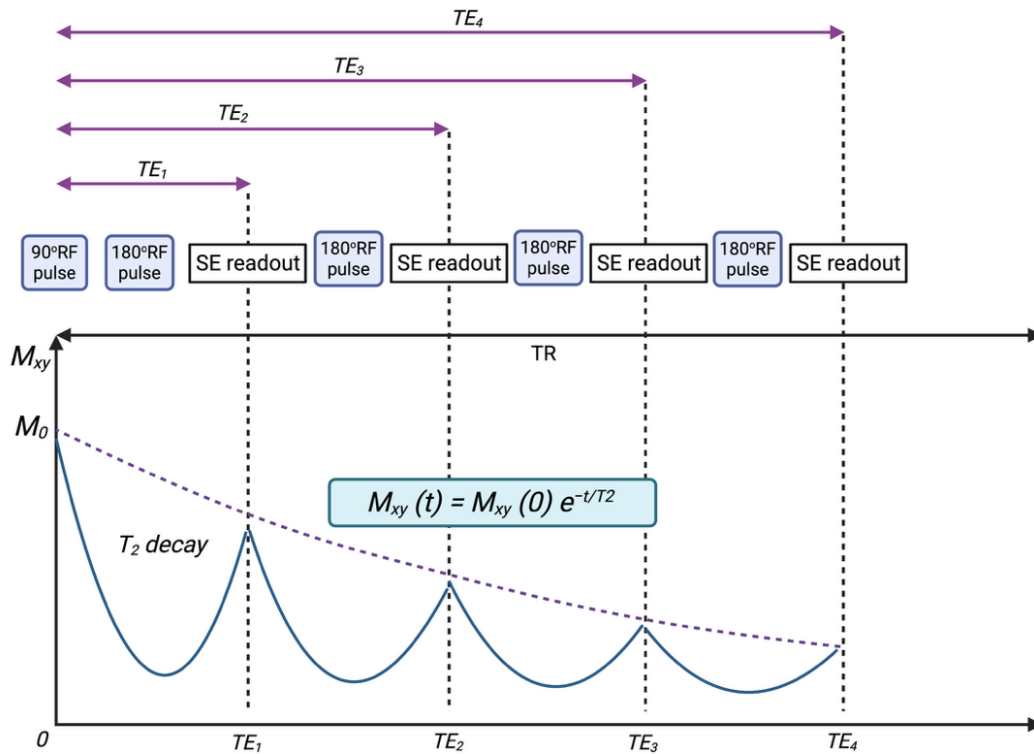


Figure 2.1 Magnetic Resonance Imaging T2 Relaxometry Acquisition and Relaxation Curve

Note. The above schematic illustrates the acquisition of MRI T2 relaxometry data using a multi-echo spin echo sequence (top). It also shows the relaxation curve (bottom) which is sampled at multiple time points (TE_1 through to TE_4) and then fitted to a monoexponential function. TE = echo time, TR = repetition time, SE = spin echo, M_{xy} represents the transverse magnetisation, M_0 represents the initial magnetisation value immediately after the RF pulse.

2.2.3 Measuring Fluid in the Brain

The most important property that impacts T2 relaxation time is the fluid content of the tissue. In the brain, free water is found within the ventricles, subarachnoid space and perivascular spaces as cerebrospinal fluid (CSF). Free water is also found outside of cells, in the extracellular space of the brain parenchyma and can accumulate here due to brain trauma or haemorrhage, for example (Pasternak et al., 2009). As a result of the inflammatory response following mTBI, a higher amount of water can accumulate in the extracellular space, increasing the free water to bound water ratio. This accumulated fluid, or free water, reflects the fractional volume of unrestricted water and is hypothesised to indicate extracellular changes driven by underlying pathological conditions (Lyall et al., 2018). Increased accumulated free water can be a result of multiple different aspects of the inflammatory response, such as inflammatory oedema, BBB breakdown, or activated microglia and astrocytes that facilitate excessive osmosis of water into the extracellular space from the BBB (Albrecht et al., 2016; Lyall et al., 2018; Pasternak et al., 2012).

T2 relaxometry is a measure of the loss of spin coherence of excited water molecules and represents the dynamic nature of water and its interaction with macromolecules in tissue (Albrecht et al., 2016). Water bound with larger macromolecules has a spin frequency comparable to the Larmour frequency (the frequency at which the magnetic moment of a charged particle precesses around an external magnetic field) and is linked with shorter T2 relaxation times. In contrast, free water molecules are smaller, with a faster spin frequency and a longer T2 relaxation time (Cheng et al., 2012; Ghugre et al., 2011; Liu et al., 2018). In healthy tissue, these two types of water exist in equilibrium. However, in many pathological conditions (e.g. inflammation), the bound water is released, and the free water ratio increases. (Cheng et al., 2012; Ghugre et al., 2011; Liu et al., 2018). This creates an inefficient medium for T2 relaxation.

As T2 relaxometry assesses microstructural tissue alterations, primarily based on water content, it is possible that it may provide a marker of inflammatory processes (Adel et al, 2023; Cheng et al., 2012; Gracien et al., 2016; Liu et al., 2018; Pell et al., 2004; Winston et al., 2017; Yang et al., 2015). In individuals with mTBI, increased T2 relaxation times may reflect fluid accumulation due to an elevated ratio of free to bound water. This rise in extracellular water content is potentially driven by inflammatory responses associated with secondary injury cascades. As mTBI typically does not involve overt bleeding or fluid-rich lesions, such changes may reflect

subtle increases in tissue water content. Accordingly, T2 relaxometry holds promise as a quantitative, evidence-based marker of neuroinflammation in mTBI.

2.2.4 Prior Research Applications of T2 Relaxometry

Quantitative T2 relaxometry has been used extensively in clinical research. A common application of this technique is within the field of epilepsy and hippocampal sclerosis research (E.g., Adel et al., 2023; Bartlett et al., 2007; Misbah et al., 2024; Rivas-Fernández et al., 2025; Sarkar et al., 2023; Winston et al., 2017). For example, Rivas-Fernández et al. (2025) used T2 relaxometry to study microstructural tissue alterations in individuals with subjective cognitive decline (SCD) with or without hippocampal atrophy. They assessed five T2 relaxometry related MRI biomarkers and found that, compared to controls, those with SCD without hippocampal atrophy had lower total water content. Furthermore, those with SCD and hippocampal atrophy showed a higher fraction of free water relative to total water content, as well as lower intra-extracellular water fraction, geometric mean of intra-extracellular water and total water content. Higher fraction of free water relative to total water content is associated with neuroinflammation and so measures of free water may serve as a biomarker for monitoring neuroinflammation in early neurodegeneration associated with the development of Alzheimer's disease (Rivas-Fernández et al., 2025). Furthermore, Adel et al. (2023) used a combination of diffusion-weighted and quantitative T2 relaxometry imaging techniques to investigate hippocampal abnormalities in temporal lobe epilepsy. They found that regions of elevated mean diffusivity and T2 relaxometry correlated and were also consistent across time. They also showed that focal elevations in T2 relaxation times were able to identify neuronal loss with 75% sensitivity and 88% specificity.

Sarkar et al. (2023) found T2 relaxometry to be superior to conventional visual analysis of MR imaging in detecting cases of early hippocampal sclerosis. For most of the patients in their study, there was a correlation between T2 relaxation values and their degree of hippocampal atrophy. However, they found that 28% of patients had normal appearing MR images on visual analysis but showed elevated quantitative T2 relaxation times that correlated with the patients' clinical and EEG-based diagnoses. Therefore, they concluded that quantitative T2 relaxation was a more sensitive and specific measure for hippocampal atrophy in those with temporal lobe epilepsy compared with conventional methods. Similarly, Misbah et al. (2024) conducted a study with individuals with temporal lobe epilepsy and found that T2 relaxometry enabled quantification of hippocampal atrophy that could detect subtle alterations in signal intensity not perceivable with

visual assessment alone. Specifically, conventional MRI without T2 relaxometry had a sensitivity of 94%, however, there were two cases where only mild hippocampal atrophy was detected with an unclear diagnosis. In those cases, T2 relaxation times were increased and facilitated an official diagnosis.

Other clinical utilities of quantitative T2 MRI have also been demonstrated. Astrakas et al. (2008) used both T2 relaxometry and functional MRI to investigate restless leg syndrome. Their results showed that T2 relaxation times were higher in patients with restless leg syndrome compared to controls, specifically in the substantia nigra. In addition, Maillard et al. (2004) used T2 relaxometry to assess thigh muscles in children with juvenile dermatomyositis, a type of idiopathic inflammatory myopathy that involves autoimmune inflammatory processes that impact the muscle and skin. T2 relaxation times were significantly increased in those children with active compared to inactive juvenile dermatomyositis and healthy controls, indicating an increase in inflammation within these muscles. In addition, Liu et al. (2018) used quantitative T2 relaxometry to facilitate breast cancer diagnosis. They found that the T2 relaxation times in the 46 malignant lesions were significantly lower than the relaxation times in the 21 benign lesions. Gracien et al. (2016) used T2 relaxometry to assess cortical damage in patients with multiple sclerosis. Results showed prolonged T2 relaxation times in cortical normal appearing grey matter in the multiple sclerosis patients and they concluded that quantitative T2 relaxometry can be seen as an *in vivo* surrogate of tissue damage in multiple sclerosis. Lastly, Ghugre et al. (2011) used quantitative T2 maps, T2* maps and contrast-enhanced MRI to monitor the time course of oedema, haemorrhage and microvascular obstruction, respectively, after myocardial infarction in a porcine model. They found that quantitative T2 and T2* maps were useful in giving insights into the histological and tissue remodelling processes.

The above research highlights the existing utility of quantitative T2 relaxometry to detect abnormalities in clinical populations. While there exists limited evidence of T2 relaxometry being used as a marker of TBI in animals (e.g., Yang et al., 2015) to the best of my knowledge, only one prior study utilised MRI T2 relaxometry to investigate human brain injury. Pedersen et al. (2020) showed the potential utility of quantitative T2 relaxometry in a professional Australian Rules Football player who had incurred multiple concussions. This was a case study on one 23-year-old male who sustained seven sports-related concussions in a time frame of approximately four years. Pedersen et al. conducted MRI scans for the latter four concussions within 15 days following

injury, as well as three follow up scans during recovery. Routine T1- and T2-weighted images showed no clinically significant structural abnormalities when comparing each time point to the average of 19 healthy male controls. However, using quantitative T2 relaxometry, they found focal but transient elevations in T2 relaxation times in left frontal cortices on all three of the scans with confirmed concussion diagnosis, that recovered towards baseline between concussions. The fourth time point was a probable but not confirmed diagnosis and did not show this pattern, nor did the three follow up scans.

Standard clinical neuroimaging (e.g., in a hospital emergency department setting) post-mTBI is often negative, with no clinically significant findings (Mayer et al., 2015). This can perpetuate the “invisible” nature of mTBI and the notion that the injury did not result in neuronal pathology despite the patient presenting as symptomatic. Advanced neuroimaging techniques are required to uncover subtle brain abnormalities that may be missed on standard neuroimaging. Furthermore, mTBI diagnosis and prognosis rely primarily on subjective self-report, which can be susceptible to inaccuracies or reporting bias. Therefore, there is a need for objective, evidence-based markers of injury to facilitate diagnosis and aid recovery monitoring. Specifically, markers of neuroinflammation could be crucial in understanding the pathophysiology of mTBI and delineating recovery trajectories. Quantitative T2 MRI methods may uncover individual abnormalities that are hypothesised to be indicative of neuroinflammation despite clinically normal radiology findings. In this context, quantitative T2 relaxometry could indicate areas of fluid accumulation, and possibly transient neuroinflammation, post-mTBI and validate subjective symptom reports or indicate pathology despite a lack of subjective symptoms. Subsequently, acute T2 relaxometry measures could be utilised to detect injury and predict recovery outcomes from mTBI based on the quantified fluid and suspected inflammation in the brain.

2.3 Potentially Modifying the Inflammatory Response to Injury

2.3.1 Physical Activity and Recovery from Mild Traumatic Brain Injury

The second half of this chapter intends to guide the reader from a perspective of measuring the brain’s response to injury, to one of modifying this response. Specifically, I will now discuss the potential for physical activity (PA) to support recovery from mTBI. Since the first International Conference on Concussion in Sport in 2001, the recommendation post sports-related mTBI has generally been physical and cognitive rest until complete symptom resolution (Howell et al., 2019;

Leddy et al., 2019; Markovic et al., 2021; Micay et al., 2018; Willer et al., 2019). However, recent evidence not only highlights the lack of efficacy of prolonged rest but the potential dangers, too (Dobney et al., 2017; Lawrence et al., 2018; Leddy et al., 2019). There is little evidence that total rest for more than three days for adults is beneficial to recovery (Leddy et al., 2016; Silverberg & Iversion, 2013). Thomas et al. (2015), for example, found that those under strict rest for five days reported more daily symptoms and slower resolution of symptoms. Schneider et al. (2017) also found that only a short period of rest (between 24-48 hours), followed by a gradual increase in activity, was the best approach for recovery.

Subsequently, changes have been made to the Concussion Consensus Statement to acknowledge the emerging evidence concerning rest and the resumption of PA (Patricios et al., 2023). The guidelines now reiterate that strict rest until complete symptom resolution is not beneficial and recommends that relative rest (e.g., including activities of daily living and reduced screen time) is preferable for up to 48 hours post-injury, but that light PA can be resumed within this time (Patricios et al., 2023). Clinicians are advised to recommend daily PA be resumed following a 24- to 48-hour period of relative rest, if tolerated well (e.g., walking). Following this, the guidelines suggest patients should systematically advance their PA intensity if their symptom exacerbation does not exceed being mild and brief (Patricios et al., 2023).

The above recommendations are based on extensive research that suggests PA may constitute an effective component of recovery from mTBI. Leddy et al. (2021), for example, are among the researchers claiming to find a beneficial effect of PA. They conducted a randomised controlled trial looking at prescribed sub-symptom threshold aerobic exercise, compared to a placebo-like stretching exercise. They found that those assigned to aerobic exercise were more likely to recover within four weeks post-injury, with a 48% reduction in risk of post-concussive symptoms. Importantly, they did not discover any adverse events during their study. Chizuk et al. (2022) specifically investigated the relationship between symptom burden, exercise adherence and recovery. They found that patients who adhered the most to the exercise regime in the first week recovered faster. Interestingly, those who were more adherent were more symptomatic and more exercise intolerant at their initial visit too. They also discovered no adverse events despite exercise commencing within days of the concussion and in patients who were highly symptomatic. This not only demonstrates the value of this type of intervention, but also its apparent safety.

Seehusen et al. (2021) measured daily-life PA with a wrist-worn *Fitbit Charge-3* activity tracker in a group of adolescent athletes with mTBI. Their results indicate that the group who took longer to return to play had taken fewer steps per day, engaged in less frequent exercise per week and had a lower total exercise volume per week, on average. Similarly, Grool et al. (2016) investigated the effects of PA during the acute period of recovery (<48 hours) and assessed PA via a self-report questionnaire on day seven. Their results indicated that daily-life PA within the first week after mTBI lowered the risk of having persistent post-concussive symptoms at day 28, compared to those with no PA (24.5% versus 43.5%, respectively). Additionally, Buckley et al. (2022) found that mild to moderate daily-life PA significantly predicted time to being symptom-free as well as time to return to play. Coslick et al. (2020) also found positive benefits of PA for recovery from mTBI. Their results showed that the group who engaged in moderate-to-heavy PA recovered on average 21 days sooner than those who engaged in none-to-light PA.

Recent systematic reviews also support the beneficial effect of PA. For example, Art et al. (2023) found that early PA (and physical therapy), as soon as a couple of days following mTBI, was beneficial in reducing the severity of post-concussion symptoms, reducing the days to recovery, and allowing for an earlier return to play. Finally, Leddy et al.'s (2023) results highlighted the efficacy of early light PA (within 2 days post-injury) and prescribed aerobic exercise (between days 2 and 14), as well as reduced screen time, for shortening recovery time. Taken together, these studies provide compelling evidence for the beneficial role of PA in supporting recovery from mTBI.

2.3.2 A Possible Anti-inflammatory Effect

While the benefits of PA during mTBI recovery are increasingly supported by research, its underlying mechanisms remain less certain. One explanation is that PA enhances neuroplasticity, the brain's ability to adapt, grow, and rewire after injury, by promoting the release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF; Dech et al., 2019; Griesbach et al., 2009; Leddy et al., 2018). Another proposed mechanism is the ability of PA to help restore cerebral blood flow regulation disrupted by mTBI, whereby engaging in PA may promote vascular stability and reduce symptom duration, although the precise processes are yet to be discovered (Dech et al., 2019; Markovic et al., 2021). The key mechanism I am focusing on in this thesis for the link between PA and mTBI recovery is the modulation of inflammation. PA may aid brain injury recovery by modulating the inflammatory response that is initiated as part of the secondary injury

cascade. Specifically, PA may help maintain the balance between neuroprotective and neurotoxic inflammatory processes, thereby creating a more favourable environment for recovery (Markovic et al., 2021; Piao et al., 2013).

Research reinforces a general link between PA and inflammation, suggesting that PA could help regulate the inflammatory response following brain injury by reducing chronic microgliosis (microglial activation) and modulating cytokine levels (Ma et al., 2013; Markovic et al., 2021; Nimmo et al., 2013; Piao et al., 2013). PA has been shown to reduce pro-inflammatory cytokines, such as interleukin-1, interleukin-8, and tumor necrosis factor-alpha (TNF- α), and inflammation-related proteins like C-reactive protein (CRP), while increasing anti-inflammatory markers including interleukin-2, interleukin-6, interleukin-10, and interleukin-1 receptor antagonist (da Luz Scheffer & Latini, 2020; Godinho et al., 2021; Kreber & Griesbach, 2016; Mee-Inta et al., 2019; Mota et al., 2012; Paolucci et al., 2018; Petersen & Pedersen, 2005). PA influences inflammation through its effects on leukocytes, adipose tissue (via adipokines), and skeletal muscle (via myokines). For instance, interleukin-6 exhibits a pronounced response to PA, particularly in the acute phase post-injury, facilitating anti-inflammatory effects (Nimmo et al., 2013). During exercise, interleukin-6 is released from skeletal muscle in proportion to PA intensity, duration, fitness level, and muscle mass (Szostak & Laurant, 2011). This release initiates an anti-inflammatory cascade by inhibiting pro-inflammatory cytokines (e.g., interleukin-1 β and TNF- α) while promoting the release of interleukin-10, another key anti-inflammatory cytokine (Nimmo et al., 2013).

Furthermore, research has demonstrated a connection between PA and CRP, a key pro-inflammatory marker (Fedewa et al., 2003). For example, Ford (2002) examined the relationship between leisure-time PA (as opposed to a structured PA program) and blood CRP concentrations. Elevated CRP was defined as levels at or above the 85th percentile of a sex-specific distribution (4.4 mg/dL for men and 7.0 mg/dL for women) and PA was assessed using a one-month retrospective self-report questionnaire, which asked about participation in activities such as swimming, bicycling, and dancing. The study found an inverse relationship between CRP levels and leisure-time PA, indicating that higher PA was associated with lower CRP concentrations. Similarly, Geffken et al. (2001) examined various blood-based inflammatory markers, including CRP, and measured PA via a two-week retrospective self-report. Their findings aligned with those

of Ford (2002), showing an inverse relationship between PA and inflammatory markers, further supporting the association between engaging in PA and an anti-inflammatory effect.

Additional support for the link between PA and inflammation comes from Nigro et al. (2021), who studied interleukin-6 and TNF- α levels in patients with cystic fibrosis, a condition characterised by elevated inflammatory cytokines. Half of the participants engaged in regular PA for three years before the study, while the other half did not engage in regular PA. Their findings indicated that PA helped regulate inflammatory processes by modulating pro-inflammatory cytokines. Systematic reviews have also reinforced this link. For example, Swain et al. (2023) conducted a systematic review and meta-analysis examining the relationship between PA, inflammation, and breast cancer, concluding that exercise interventions significantly reduced CRP, TNF- α , interleukin-6, and leptin levels. Kasapis and Thompson (2005) similarly found that while PA induces a short-term pro-inflammatory response, it ultimately produces long-term anti-inflammatory benefits. Reviews by Beavers et al. (2010) and Metsios et al. (2020) further support the notion that PA has overall beneficial effects on inflammation.

Together, these studies highlight the multifaceted ways in which PA may contribute to recovery from mTBI by modulating inflammation. By reducing pro-inflammatory cytokines and C-reactive protein (CRP), while enhancing anti-inflammatory mediators such as interleukin-6 and interleukin-10, PA appears to influence key immunological pathways. This provides a plausible mechanism for its therapeutic effects. The consistent findings across experimental and observational studies reinforce the potential of PA as a powerful, non-pharmacological approach to mitigating neuroinflammation and supporting brain healing.

2.3.3 A New Way to Assess Physical Activity: Compositional Data Analysis

Research to date has largely analysed PA in isolation, investigating whether more or less PA is associated with a particular outcome. Some have separated behaviours into light PA, moderate-vigorous PA, sedentary behaviour and sleep and focused on the ways in which these varying levels of energy expenditure can impact different health-related outcomes (e.g. adiposity, fitness, cardiometabolic biomarkers or mental health) (Grgic et al., 2018). However, because the duration of a day is fixed (i.e. 24 hours), time spent in different behaviours are inherently co-dependent. Increasing time in one behaviour necessarily reduces time in at least one of the others (Pedišić et al., 2017). Therefore, since all daily activities are interrelated, the amount of time spent daily in a particular type of activity (such as light PA) cannot change without compensatory

changes in other activities during that day (such as sedentary time or sleep) to maintain the fixed daily total of 24 hours. Consequently, it is important to consider these changes holistically so that increases in one activity do not cause detrimental decreases in other activities (Dumuid et al., 2021). A meaningful way to consider elements such as light PA, moderate-vigorous PA, sedentary behaviour and sleep are as a *proportion* of a whole (see Figure 2.2).

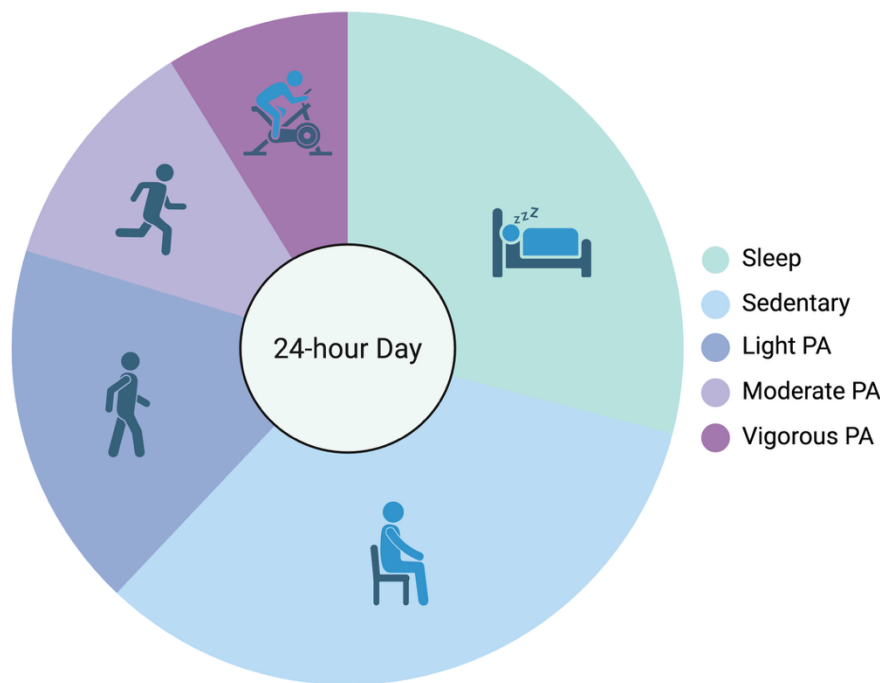


Figure 2.2 *Compositional Data Analysis Approach to Exploring Movement Behaviours*

Note. Created with BioRender.com.

Dumuid et al. (2018) describe a novel method for predicting change in a continuous outcome variable, based on relative changes in a composition. This type of data conveys relative information, as opposed to absolute information (Dumuid et al., 2020). Compositional data analysis (CoDA) was developed to be used with data that have specific properties that cannot be represented accurately with traditional statistical models. CoDA involves expressing the data as a set of logarithmic (log) ratios, which transfers them from constrained simplex space to unconstrained real space, where traditional statistical models can then be utilised, allowing the interplay between the variables to be taken into consideration (Dumuid et al., 2018; Dumuid et al., 2020; Liangruenrom et al., 2023).

Time-use epidemiology examines how the allocation of time to various daily activities influences health outcomes. This field explores the distribution and health effects of time-use patterns, aiming to identify the optimal balance of activities for promoting health. Time-use is considered one of the most relevant and modifiable behavioural risk factors across many health contexts (Pedišić et al., 2017). The primary components analysed in time-use studies are PA, sleep and sedentary behaviour, collectively known as movement behaviours (Dumuid et al., 2020). These three elements are mutually exclusive and together account for the entire 24-hour day. Research indicates that health outcomes are influenced not just by increasing or decreasing a single activity, but by how time is reallocated among these behaviours. For example, shifting time from sedentary behaviour to light or moderate-to-vigorous physical activity has been shown to improve cardiometabolic biomarkers (Grgic et al., 2018). Analysing these behaviours in isolation overlooks their compositional nature, since they are interdependent parts of a whole (Pedišić et al., 2017). CoDA provides a framework to better understand the ideal time-use composition for specific populations. This approach can help translate research findings into practical recommendations, supporting the development of actionable guidelines for healthier daily routines (Dumuid et al., 2021; Grgic et al., 2018).

PA research has begun highlighting the importance of the relative contributions of different types of activity, within a set amount of time (such as a 24-hour period). For example, Dumuid et al. (2021) examined daily composition of sleep, sedentary behaviour, light PA and moderate-vigorous PA in children. They utilised a 24-hour accelerometer over a period of eight days to study the different movement behaviours. Their results indicated that optimum time-use composition differed depending on whether the ideal outcome was optimal fitness versus optimal adiposity. Specifically, increased light PA at the expense of sleep was beneficial for fitness, in contrast with longer sleep at the expense of light PA was beneficial for adiposity. Both outcomes required maximised moderate-vigorous PA and minimised sedentary behaviour, however. This research is an example of the interrelated nature of movement behaviours and the importance of considering the desired health-related outcome when analysing what an ideal time-use composition is.

CoDA techniques have been employed in a limited number of studies involving neurological populations to date. For example, Ezeugwu and Manns (2024) explored the association between compositions of movement behaviours (sedentary behaviour, standing, stepping and sleep) and functional outcomes following stroke. Their eight-week intervention

targeted the reduction of sedentary time, and they assessed its impact on functional mobility using the Timed Up and Go (TUG) and gait speed tests. They found that reallocating 30+ or 40+ minutes per day to stepping, proportionally from other movement behaviours, was associated with a significant improvement in TUG and gait speed, respectively. Similarly, Hooker et al. (2022) examined accelerometer-measured movement behaviours (sedentary behaviour, light PA and moderate-vigorous PA) over seven consecutive days to investigate stroke incidence. Their findings suggest that replacing sedentary time with light PA or short bouts of moderate-vigorous PA may lower the risk of stroke.

Orme et al. (2020) also applied CoDA to investigate the impact of a six-week cardiac rehabilitation programme for individuals that were within six months of having had a stroke. They measured changes in step count, stationary time, light PA, and moderate-vigorous PA using accelerometers before and after the programme. Results indicated that people engage in less PA acutely following stroke and that cardiac rehabilitation was effective in increasing step count but not in increasing the overall proportion of time reallocated from sedentary behaviour to light or moderate-vigorous PA. Collectively, these studies highlight the value of CoDA in understanding movement behaviour patterns among individuals with neurological conditions. However, to the best of my knowledge, no research to date has applied CoDA to investigate PA patterns during recovery from mTBI - a gap that the current research seeks to address.

2.4 Framing the Problem: Rationale for the Current Research

The brain remains as elusive as it is complex, with most of its inner workings hidden from direct observation. Uncovering the intricacies of brain injury and repair continues to be a critical focus of research. Despite the high prevalence and substantial impact of mTBI, the biological processes that underlie prolonged recovery and adverse neurological outcomes remain poorly understood. While the key role of inflammation post-injury is well established, the complex interplay between brain injury, neuroinflammation, and recovery is not well defined, limiting the development of targeted and effective interventions. Improving our ability to **measure** and **modify** harmful neuroinflammatory responses is therefore essential for advancing recovery outcomes following mTBI. One of the major clinical challenges is the lack of reliable predictive markers to distinguish individuals who recover quickly from those who go on to experience chronic symptoms and prolonged functional deficits. This critical knowledge gap underscores the urgent need for

research exploring the role of neuroinflammation, along with the individual factors that predispose to or protect against poor recovery trajectories.

At present, no validated objective biomarkers exist for the diagnosis or monitoring of mTBI, and both clinical assessment and outcome tracking rely heavily on self-reported symptoms. This is problematic, as symptom reporting can be influenced by various cognitive, emotional, and social factors, increasing the risk of bias and inaccuracy. Despite ongoing research, progress towards clinically validated biomarkers has been limited (Danielli et al., 2023; Tabor et al., 2022). As such, there is a pressing need for minimally invasive, evidence-based biomarkers that can provide more precise, objective information to complement subjective assessments and improve diagnosis and the early identification of individuals at risk for poor recovery. Given the central role of the immune response in post-injury recovery, it is particularly important to develop methods for both measuring and modulating neuroinflammation. While the inflammatory response may be beneficial in the acute phase of injury, chronic or dysregulated inflammation has been shown to contribute to long-term dysfunction and neurodegeneration (Ayerra et al., 2025; Boulton & Al-Rubaie, 2025; Dodd et al., 2022; Freire et al., 2023; Hossain et al., 2022; Tagge et al., 2018).

Enhancing our understanding of the neuroinflammatory changes and physical activity patterns following mTBI is crucial for identifying individuals at elevated risk of adverse outcomes. Early identification of at-risk individuals would enable improved monitoring and targeted interventions to prevent cumulative injuries and support optimal recovery. These targeted treatment options could include behavioural modification of daily physical activity patterns aimed at attenuating potentially harmful inflammation. To improve outcomes from mTBI, it is crucial to develop a more nuanced understanding of: (1) the specific neurological changes that occur after injury that may reflect neuroinflammation, (2) the relationship between these changes and recovery outcomes, and (3) modifiable factors, such as physical activity, that can influence the inflammatory response and subsequent recovery, particularly for those susceptible to prolonged symptoms. As neuroinflammation is a hallmark of the secondary injury cascade, it represents a promising and actionable target for research.

2.5 Research Aims and Questions:

2.5.1 Aim 1

Address gaps in the literature regarding objective biomarkers of injury and inflammation in the acute phase following mTBI by investigating the utility of a quantitative MRI technique in detecting subtle brain abnormalities, through its novel application in this context.

Research questions:

- 1 – How can quantitative T2 relaxometry be used to explore subtle neuroinflammatory-related brain alterations in individuals acutely following mTBI?
- 2 – How do these subtle neuroinflammatory-related alterations appear at the group level when assessed with quantitative T2 relaxometry?

2.5.2 Aim 2

Advance understanding of potential strategies to mitigate neuroinflammation acutely following mTBI by evaluating the application of compositional data analysis for characterising physical activity time-use patterns in a novel clinical mTBI cohort.

Research questions:

- 1 - How do physical activity time-use compositions differ between individuals with acute mTBI and healthy controls?
- 2 - In what way do physical activity time-use compositions relate to recovery outcomes in acute mTBI?

3

Overall Methods

3.1 Overview

The following brief methods chapter provides information relevant to all three studies presented in this thesis. It is intended primarily as an overarching methodology, including participant inclusion and exclusion criteria, diagnostic procedures, and recruitment strategies. This chapter also outlines the ethics approvals obtained and the general procedures followed for both the mTBI and control groups across all studies. Study-specific methodological details will be presented separately within Chapters 4, 5, and 6.

3.2 Participants

3.2.1 *The Sample*

Two groups of participants were recruited for this research; males with acute mTBI ($N = 40$) and age and sex-matched controls ($N = 52$). Participant recruitment continued over the course of this project and so the sample size increases from Study 1 (a case series) to Study 2 (a group analysis). Study 3 then uses a subsample of the participants in Study 2 for whom physical activity data was available. Details of the samples used for each study will be outlined in the beginning of the corresponding chapters to follow. For all studies, participants were eligible to take part if they were male (further detail in *Chapter 7 Overall Discussion* with regards to the selection of only males) and aged between 16 and 35 years. Participants for either group were excluded if they had an existing significant neurological condition or were contraindicated for an MRI scan (e.g., certain metal implants, or braces).

For the mTBI group, participants were included if they had suffered an mTBI in sport (i.e., during a game or training session) within the last 14 days (inclusive). All sports were deemed eligible for recruitment purposes. To be eligible, their mTBI needed to have been diagnosed by a

medical doctor. Diagnostic decisions for most mTBI participants were based on a combination of (1) clinical history with plausible mechanism, (2) Sport Concussion Assessment Tool (SCAT-5) (Echemendia et al., 2017) or Brain Injury Screening Tool (BIST) (Theadom et al., 2021) symptoms scores, (3) clinical examination to exclude any neurological or intracranial abnormalities, (4) review of video if available, and (5) eye-witness accounts if available. For some mTBI participants, the exact diagnostic criteria used by their doctor was not known but is assumed to be similar to the above combination of criteria.

For the control group, participants were included if they had not suffered an mTBI in the last 12 months, had not suffered more than five total mTBI in their lifetime and did not have lingering symptoms from a previous mTBI, in order to minimise potential confounding effects of cumulative damage and/or chronic inflammation.

3.2.2 Ethics Approval

Ethics approval was obtained from the Health and Disability Ethics Committee (HDEC) (Reference: 2022 EXP 11078) and from the Auckland University of Technology Ethics Committee (Reference: 22/12) prior to commencing data collection (see Appendix 1 for ethics approval confirmation letters).

3.2.3 Recruitment

For participants in the mTBI group, a formal diagnosis from a medical doctor was required prior to their study visit, though not necessarily prior to recruitment. That is, individuals could be provisionally recruited during the interval between their injury and their medical consultation, provided they received a confirmed diagnosis of mTBI before participating in the study. If an individual was found not to meet the diagnostic criteria (e.g., their injury was deemed too minor to be classed as an mTBI), their study appointment would be cancelled. However, no such cases occurred. This approach facilitated the recruitment of a larger sample by allowing for flexibility in scheduling, accommodating delays in clinical assessment and study visit bookings that might otherwise have led to the exclusion of some participants.

Most of the mTBI recruitment took place at the St Johns and St Lukes, Auckland locations of the Axis Sports Concussion Clinics ($N = 35$). Participants were either recruited in person at their initial consultation at the Axis Sports Concussion Clinic or recruited remotely prior to their first consultation (by referral from the lead physician). Additionally, some mTBI participants ($N = 5$) were recruited via community links, including through physiotherapists in Auckland, via word of

mouth from the study team, and through digital and print advertisements. Overall, participants in the mTBI group were comprised of rugby players, football players, hockey players, martial artists, a futsal player, a gymnast, a surfer and a swimmer.

Control participants were recruited via print advertisements at the North campus of Auckland University of Technology and the city and Grafton campuses of The University of Auckland, in Auckland and via social media advertisements. Participant data collected for this study has been de-identified to protect participant confidentiality. All participants were given a study identification number that was used for all analyses in each of the studies of this thesis. Furthermore, efforts have been made to keep participant information confidential by simplifying injury descriptions, providing their age as a range and skull stripping the brain images to minimise the possibility of identification.

All participants were provided with a participant information sheet (see Appendix 2) and given time to consider the information and ask any questions prior to commencing their engagement in the study. All participants provided informed, written consent (see Appendix 3).

3.3 Materials

The primary materials used in this research were magnetic resonance imaging (MRI) and Axivity AX3 devices for monitoring physical activity. As these tools were employed in specific studies rather than across all three, detailed descriptions of their use and implementation are provided within the respective chapters in which each study is presented.

3.4 Procedure

Once recruited, each mTBI and control participant was scheduled to attend one in-person visit at the Centre for Advanced Magnetic Resonance Imaging (CAMRI) located at The University of Auckland in Grafton, Auckland, New Zealand. For the mTBI group, this visit was scheduled as soon as possible following recruitment, but within a maximum time of 14 days following their injury (inclusive). For most mTBI participants, a Brain Injury Screening Tool (BIST; Theadom et al., 2021) symptom questionnaire was completed remotely prior to their recruitment, as Axis Sports Concussion Clinic sends these to patients to complete prior to their first appointment.

However, for those mTBI participants without a completed BIST, one was emailed to them to complete prior to their in-person study visit at CAMRI (see Appendix 4).

A researcher from the team met each mTBI and control participant at CAMRI and provided them with (1) the CAMRI safety screening form and (2) the study intake questionnaire, to complete (see Appendix 5 and Appendix 6). Following this, each participant was directed to a private room to get changed into a clinical gown in preparation for their MRI scan. An MRI technician then ran each participant through their in-house safety questions and gave them a brief overview of what to expect before guiding the participant into the scanning room where they underwent an MRI scan that was approximately 45 minutes in duration. Upon completion, the MRI technician collected the participant from the scanning room and guided them back to get changed in a private room. Each mTBI and control participant was then fitted with a wrist-worn physical activity recording device by a member of the research team and requested to wear it for 15 days (see Chapter 6 for more information regarding this device).

Participants received a \$50 supermarket voucher and a \$20 Motor Trade Association (MTA) petrol voucher as compensation for their time. They were given these vouchers at the end of their in-person study visit. Additionally, all participants were advised in advance that a taxi could be provided to them free of charge, to and from their study visit, if they required.

3.5 Determining Recovery

Clinical recovery was determined differently depending on the method of recruitment for the mTBI participant. For the majority of the mTBI group, that were recruited via Axis Sports Concussion Clinics, their clinical recovery was determined by their sport and exercise medicine physician through a combination of methods including subjective symptom reports and repeat BISTs where appropriate (Kara et al., 2020; McGeown et al., 2020). Once recovered, the participant was discharged from their service, and the date of discharge was used by the study team to calculate their clinical recovery time (i.e. the number of days between their date of injury and date of discharge). For those mTBI participants recruited through the community, their clinical recovery time was calculated using remote follow up BISTs sent to them each week by a member of the study team. Once their BIST score reached ≤ 20 then the date of the BIST was used to calculate their recovery time (based on research suggesting that the general population experiences

some mTBI-like symptoms; Chua & Theadom, 2024; Garden & Sullivan, 2010; Zeldovich et al., 2022).

For participants who achieved clinical recovery before the conclusion of the study, a member of the research team contacted them to assess their interest in completing a follow-up MRI scan. Those who agreed returned to the same imaging facility (CAMRI) for a scan identical to their initial acute MRI. As compensation, they received an additional \$50 supermarket voucher and a \$20 MTA voucher. No questionnaires or physical activity data were required at this follow-up imaging session.

Study One: MRI Case Series

4.1 Overview

The first study of this thesis is a case series that explores the utility of quantitative T2 relaxometry in detecting subtle brain inflammation in individuals with acute mTBI. While conventional T2 images are already used by radiologists to detect fluid accumulation in the brain and facilitate diagnostic decisions (Dhabalia et al., 2024), a quantitative approach is warranted to improve cross-sectional and longitudinal comparisons. Quantitative T2 relaxometry isolates the contributions of individual magnetic resonance contrast mechanisms and attributes numerical values to the relaxation times observed in different brain tissues following injury (Chekhonin et al., 2024; Cheng et al., 2012; Deoni, 2010). With extensive use in other clinical populations, but very limited use in human mTBI (Pedersen et al., 2020), further exploration of the ability for quantitative T2 relaxometry to detect subtle brain abnormalities following mTBI is justified.

The focus on quantitative T2 relaxometry in Study 1 is based on its established sensitivity to fluid properties and potential for detecting subtle neuroinflammation. Research has strongly indicated that inflammation is a key component of the secondary injury cascade following mTBI (Alam et al., 2020; Kim et al., 2023; Markovic et al., 2021; Piao et al., 2013). While the primary injury of mTBI may be relatively well understood, there is more uncertainty regarding the secondary injury cascade, including the brain's inflammatory response. As T2 relaxometry can be used to detect fluid accumulation, it may be useful to quantify neuroinflammatory processes post-mTBI. Deepening our understanding of the inflammatory response to injury following mTBI could enable more effective and efficient rehabilitation to take place. Therefore, the intention of this case series is to further our understanding of the brain pathology specifically related to neuroinflammation, with the aim of contributing positively to clinical outcomes post-mTBI.

Standard clinical neuroimaging post-mTBI is often negative, with no clinically significant findings (Mayer et al., 2015). This can perpetuate the notion that the injury did not result in neuronal pathology despite the patient presenting as symptomatic. Therefore, there is a need for an advanced method of quantitative MRI that can detect subtle changes in the brain acutely after mTBI. In this context, T2 relaxometry may reveal areas of fluid accumulation and potentially transient neuroinflammation following mTBI. This could help validate self-reported symptoms or reveal underlying pathology even in the absence of symptoms or when standard neuroimaging appears normal. The current case series contributes substantially to the gap in the existing literature by studying quantitative T2 relaxometry in individuals with acute mTBI and comparing them to a group of healthy controls.

Finally, it is important to address the specific decision to employ a case series design. Individual-level analyses offer many strengths that warrant consideration. Firstly, they allow for detailed descriptive insight by providing rich, participant-specific data. Analysing each participant's brain scans individually ensures that subtle abnormalities are not overlooked or diluted through averaging, as may occur in group-level analyses. This granularity enhances the ability to detect unique or unexpected findings that may be clinically meaningful. Secondly, case series designs enhance clinical relevance by capturing real-world data that can uncover unexpected findings and nuances of the pathophysiology of mTBI. This aspect is particularly important given the heterogeneity of mTBI, with wide inter-individual variability in symptoms, recovery trajectories, and outcomes. Lastly, the use of an individual-level approach is particularly well suited to the exploratory, hypothesis-generating nature of this work. As quantitative T2 relaxometry has not previously been applied in an mTBI population, a case series provides a valuable opportunity to assess the utility of this imaging technique in detecting potential brain abnormalities at the individual level. See Appendix 7 for the publication in *NeuroImage: Clinical* relating to this study.

4.2 Methods and Materials

4.2.1 Participants

4.2.1.1 mTBI

This case series consists of the first 20 mTBI participants that were recruited for this project. They are all male sports players ($M = 21.6$ years old [16-32], $SD = 4.76$) with acute

(≤ 14 days) sports-related mTBI. Injuries were sustained from participation in rugby union ($N=13$), football ($N=2$), hockey ($N=1$), futsal ($N=1$), gymnastics ($N=1$), surfing ($N=1$), and jiu-jitsu ($N=1$). Participants were also contacted after clinical recovery and invited to participate in another identical MRI scan. All mTBI participants who were eligible (i.e., clinically recovered) and interested ($N=5$), were re-scanned at a time that suited them at the Centre for Advanced MRI (CAMRI) using the same scanning parameters as their acute scans. Mean number of days between injury and MRI scan for the acute scans was 10.3 ($SD = 3.2$) and for the recovery scans was 105.6 ($SD = 47$). Recruitment and ethics are detailed in Chapter 3 and a summary of injury and symptom reports for each mTBI participant in this case series can be found below in Table 4.1.

Table 4.1 *Participant Details*

Case	Age Range	Injury Details	Prior mTBI	MRI (days)	Symptoms	BIST (/160)	Recovery (days)
1	16 - 20	Rugby - knee to head	1	5	Headaches, tiredness, emotional, feeling “in a dream”	140	20
2	21 - 25	Hockey - ball to head	1	5	Headaches, nausea, fatigue	12	31
3	30+	Football - head to ground	0	6	None reported	78	27
4	16 - 20	Rugby - head collision	1	13	Visual disturbances (seeing “stars”), unsteady, headaches, sensitivity to light	18	26
5	16 - 20	Gymnastics - head to ground	1	12	Impaired balance, disoriented, visual disturbances	61	56
6	16 - 20	Rugby - head to ground	0	13	Vomiting, ringing in ears, dizziness, headaches, neck pain, light sensitivity, difficulty focusing	42	26
7	21 - 25	Rugby - kicked in head	0	13	Impaired balance, dizziness, headaches, sensitivity to light and noise, difficulty concentrating, irritable	13	47
8	26 - 30	Rugby - knee to head	2	12	None reported	6	27

9	21 - 25	Rugby - head to ground	?	6	Double vision, mental fog, slowed thinking, indecisiveness	56	18
10	16 - 20	Surfing - board to head	10	12	None reported	54	?
11	16 - 20	Rugby - head collision	4	10	Dizziness, dazed, headaches, neck pain, sensitivity to light, mental fog, mild cognitive symptoms	52	24
12	16 - 20	Rugby - head to ground and knee/elbow	0	13	Loss of consciousness, “zoning out”, headaches/ pressure in the head, difficulty concentrating	13	23
13	26 - 30	Rugby - knee to head	?	5	Dazed, pressure in head, neck pain, mental fog, reduced cognitive sharpness	79	17
14	26 - 30	Football - ball to head	1	13	None reported	2	20
15	21 - 25	Rugby - elbow to head	?	13	Ataxia, confusion	22	18
16	16 - 20	Rugby - knee to head	4	8	Impaired balance, blurry vision, pins and needles in hands, dizziness, headaches	117	117
17	16 - 20	Rugby - shoulder to head	2	13	None reported	0	66
18	16 - 20	Rugby - knee to head	0	10	None reported	34	26
19	16 - 20	Futsal - elbow to head	0	13	None reported	28	32
20	26 - 30	Jiu-jitsu - knee to head	2	11	None reported	69	31
Mean	21.6	N/A	N/A	10.3	N/A	44.8	34.3

Note. *Age* has been provided as a range (in years) and *Injury details* have been simplified to protect the confidentiality of participants. *Prior mTBI* refers to the total number of previous mTBI in their lifetime. *MRI* is the length of time (in days) between their injury and MRI scan. *BIST* is the total Brain Injury Screening Tool score (>24 hours) out of 160. *Recovery* is the time (in days) from their mTBI to clinical recovery. A “?” indicates that this information was not available to the research team.

4.2.1.2 Controls

The population template for individual-level comparison was derived from the first 44 healthy male controls recruited for this project ($M = 23.3$ years old [16-30], $SD = 4.38$). To accurately ascertain how many control participants were needed to detect an abnormality (i.e. a true positive finding), 3D images with Gaussian noise and 10000 voxels were simulated. A single ‘abnormality’ of connected voxels was then inserted in one of the images (the ‘ground truth’). Three different sizes of ‘abnormality’ (0.5% of the image, 2.5% of the image and 5% of the image), with five different effect sizes were used. ‘Abnormal voxels’ were made to have values 1, 2, 3, 4 and 5 standard deviations of the mean. As depicted in Figure 4.1, significant voxels start to be consistently detected with an effect size of 3 standard deviations above the mean, using between 20-30 control samples (yellow indicates significant ‘abnormal’ voxels, $p < 0.05$, False Discovery Rate corrected). Note that the effect size seemed to be more important for detecting true positive voxels than the size of the abnormality.

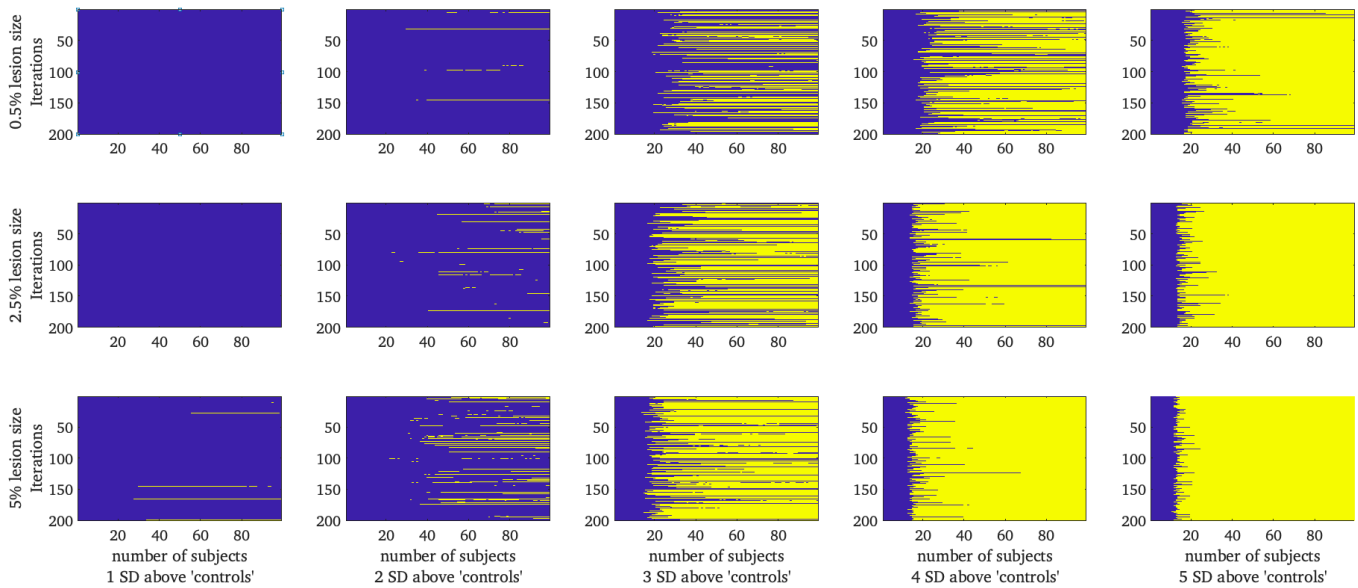


Figure 4.1 *Simulation to Estimate Appropriate Control Sample Size*

4.2.2 Magnetic Resonance Imaging

Magnetic resonance images were acquired using a 3T Siemens MAGNETOM Vida Fit scanner (Siemens Healthcare, Erlangen, Germany) located at CAMRI at The University of

Auckland, New Zealand, using a 20-channel head coil. A T2-weighted sequence was collected to investigate quantitative T2 relaxometry. T2 maps were acquired using an 8 echo Carr-Purcell-Meiboom-Gill (CPMG) sequence (TEs = 28.9, 57.8, 86.7, 115.6, 144.5, 173.4, 202.3 and 231.2 ms; TR = 6s; slice thickness = 2.0mm; voxel size = 2.0 x 2.0 x 2.0mm; matrix size = 112 x 128 x 63; flip angle (FA) = 180°; base resolution = 128; phase resolution = 100%; phase field of view (FOV) = 87.5%). Total T2 mapping acquisition time was 12:02 min. T1-weighted anatomical images were also collected for quality control purposes. T1 weighted images were acquired using a magnetisation-prepared rapid gradient echo (MPRAGE) sequence (TR = 1.9s; TE = 2.5ms; TI = 979ms; FA = 9°; slice thickness = 0.9mm; voxel size = 0.4 x 0.4 x 0.9 mm; matrix size = 192 x 512 x 512; phase FOV = 100%). Total T1-weighted acquisition time was 4:31 min. In addition to the acute MRI scans conducted within 14 days post-mTBI, five mTBI participants were re-scanned (with an identical sequence) after they had reached clinical recovery. A hospital-based radiologist reviewed clinically relevant MRI images from each participant to check for clinically significant abnormalities that might require further attention.

4.2.3 Data Processing and Statistical Analysis

4.2.3.1 Initial Preprocessing

All MRI images were received in *DICOM* format, converted to *NIfTI* format using *dcm2nii* (Li et al., 2016) and then arranged according to the *Brain Imaging Data Structure (BIDS)* (Boré et al., 2023) guidelines. Image quality assurance checking was conducted in the *MR View* toolbox of *MRtrix3* (Tournier et al., 2019) using the participants' T1 weighted image as the underlay and their T2 map as the overlay to check for artifacts or abnormalities caused by scanning or processing. Then, preprocessing was conducted on the T2 images using *PyCharm* version 2022.2.3. This preprocessing step included brain extraction (skull stripping) using the *bet* function in FSL (Smith, 2002) before normalising each image to the MNI standard space by registering them to a MNI152 2.0 x 2.0 x 2.0mm template image using *FSL FLIRT* (Jenkinson et al., 2002). For each participant, the third T2 echo volume (86.7 ms) was extracted to generate a group average brain image. Using the group average brain image and FSL FAST (Zhang et al., 2001), grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) segmentations were generated. FAST produces probabilistic maps that assign each voxel a posterior probability of belonging to each tissue class. These were converted to binary hard segmentations by assigning each voxel to the class with the highest posterior probability, consistent with the default FAST procedure. Because

this approach selects the most probable class among three tissue types, the effective GM threshold is determined by relative probability rather than a fixed cut-off.

The first volume was then removed, using the offset as a fitting parameter to the T2 relaxation data (Milford et al., 2015) and a monoexponential function at each voxel was fitted across all eight echo-times using qMRLab (Karakuzu et al., 2020) in Matlab R2022 to calculate the T2 relaxation time for each participant. An in-house script in Matlab was then used to convert files back to *NIfTI* format and apply a smoothing of 6mm full-width-half-maximum (FWHM).

4.2.3.2 Final Processing and Statistical Analyses

Following preprocessing, z-tests were used to quantify differences between individual mTBI participants and controls. All voxels residing within the grey matter mask were considered for final analysis. Given that the main statistical assumption of a z-test is that the underlying data distribution is Gaussian with a mean of 0 and standard deviation of 1, a Rank-Based Inverse Normal Transformation (Blom, 1954) was used to normalise the data. All T2 relaxometry voxels for each image were ranked and transformed into a Gaussian shape with a distribution mean of 0 and a standard deviation of 1.

Z-score maps were obtained by subtracting voxel values between individual mTBI maps and the mean of controls divided by the standard deviation of the controls. This is a similar individual-based statistical approach to previous studies (Jolly et al., 2021; Mito et al., 2023; Pedersen et al., 2020). A one-tailed z-test was conducted, interpreting positive values only, as the biology of increased T2 relaxation times are well understood, i.e., increased water properties in tissue (Cheng et al., 2012; Ghugre et al., 2011; Liu et al., 2018), whereas the interpretation of decreased T2 relaxation times are less well understood. False Discovery Rate (FDR; Benjamini & Hochberg, 1995) was used to correct for multiple comparisons in the z-score maps using a threshold of $q < 0.05$. This method obtained z-values and relaxation times (in ms) for each FDR-based significant cluster, individually for each mTBI participant.

Lastly, for the sub-group ($N=5$) of participants that had repeat MRI scans following clinical recovery, their acute voxel-wise z-maps were subtracted from the voxel-wise z-maps of their recovery MRI scans, to determine if the significantly elevated T2 relaxation clusters had resolved with clinical recovery. See Figure 4.2 for a schematic overview of the processing and analysis pipeline.

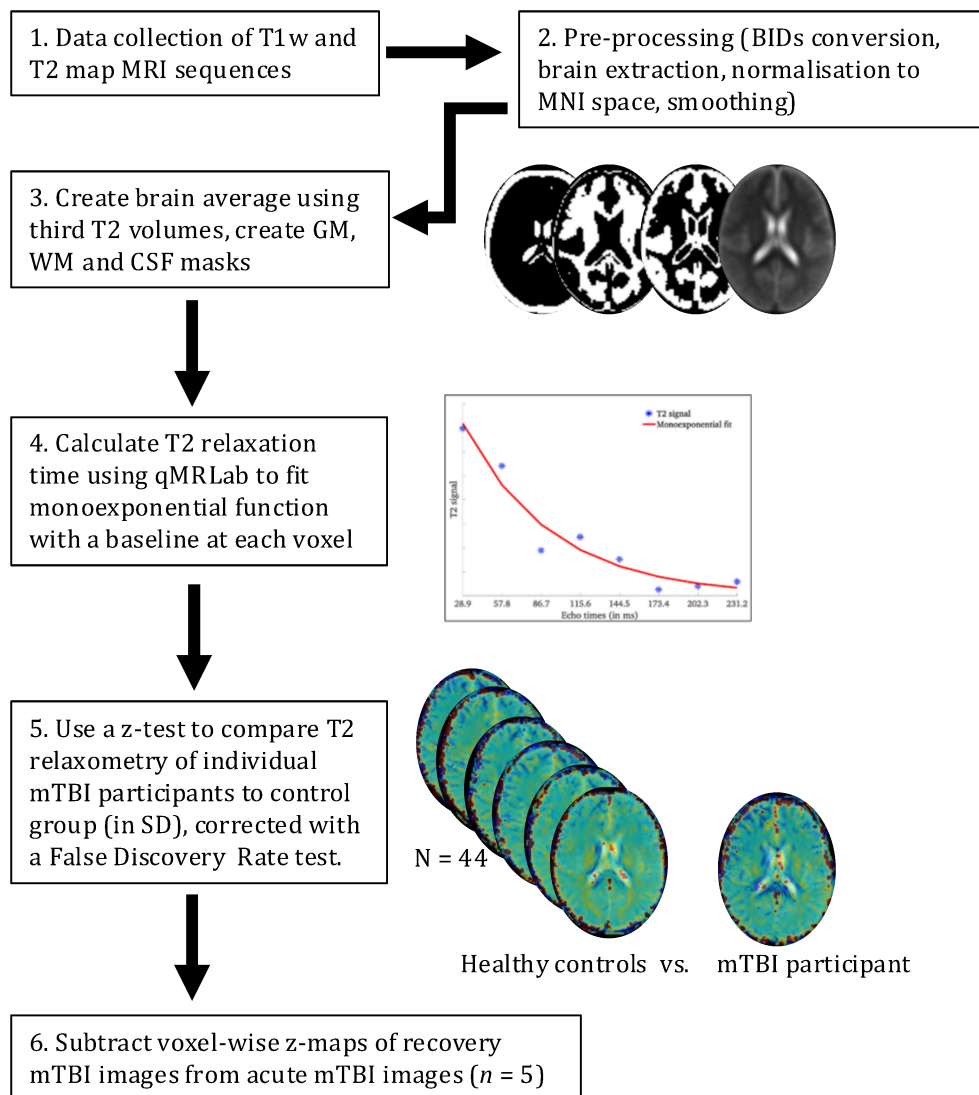


Figure 4.2 *Magnetic Resonance Imaging Processing and Data Analysis Pipeline for Study 1*

4.3 Results

4.3.1 Overall Findings

The quantitative T2 analysis indicated regions with significantly higher T2 relaxation times in 19/20 mTBI participants (95 %) (see Table 4.2). While several significant voxel clusters, such as the cingulate cortex, superior parietal cortex and insula, were shared across multiple participants (see Figure 4.3), most of the findings were individual to each case study. Recovery re-scans indicated either a full reduction (i.e. in all significant acute regions) or a partial reduction (i.e. for some areas but not others) in T2 relaxation times for all five re-scanned participants. The remainder of the Results section will provide comprehensive details about all 20 case studies, with information regarding their injury, symptoms and specific T2 relaxometry results for specific areas of their brains. The first five case studies are the participants that had follow up recovery MRI scans available (see Table 4.3), with the remaining 15 case studies only having acute scans.

Table 4.2 *Voxel Clusters with Significantly Elevated T2 Relaxation Times for mTBI*

Case	Region(s)	Raw T2 Relaxation Times (ms)	Z-score Compared to Controls (SD)
1	L superior parietal	146.50	8.40
	L lateral superior frontal	2.69×10^6 *	4.08
	L medial superior frontal	74.18	4.38
	L orbitofrontal	79.78	6.50
2	L superior parietal	63.67	9.39
	L anterior insula	63.72	18.65
	R superior frontal	72.10	6.91
3	R somatosensory	76.10	8.66
	R intraparietal sulcus	51.54	15.69
4	L anterior insula	68.26	12.12
	L posterior cerebellum	66.95	7.04
5	R anterior parietal	55.86	12.83
6	L hippocampus	95.22	5.00
	L lateral occipital	71.83	9.33
7	L superior parietal	73.15×10^4 *	7.26
	R intraparietal sulcus	72.34	14.39
	R temporoparietal junction	65.49	3.40
	R superior cerebellum	89.35	8.72
8	Cingulate cortex	73.47	8.27
	L inferior supramarginal gyrus	76.10	16.31
9	L superior parietal	65.66	8.81
	R posterior insula	70.28	5.31

10	L superior parietal	54.89	15.92
	R inferior parietal	65.95	14.48
	R superior parietal	70.83	8.46
11	L parahippocampal	76.46	10.37
	L orbitofrontal	6.50	4.83
	R anterior occipital	79.23	10.22
	R orbitofrontal	74.74	4.34
12	R superior cerebellum	79.46	13.15
	R superior temporal sulcus	69.54	10.23
13	L anterior temporal	125.00	4.70
14	L inferior supramarginal gyrus	70.15	25.44
	L anterior occipital	57.68	13.83
	L hippocampus	274.06	8.38
	R premotor	87.64	19.60
15	R inferior parietal	70.64	12.33
	R posterior parietal	66.73	19.85
	R superior cerebellum	104.69	5.78
	R medial prefrontal	83.92	8.13
16	R sensorimotor	74.02	14.86
17	Cingulate cortex	99.04	11.08
	L superior frontal	259.39	6.05
	L posterior cerebellum	1.61×10^8 *	5.37
18	L superior frontal	303.65	5.28
19	None	N/A	N/A
20	L anterior cingulate cortex	66.32	17.51
	L medial frontal	121.10	5.68
	L sensorimotor	79.65	4.57
	L precuneus	38.98	5.49
	L temporoparietal junction	100.25	5.60
	R anterior cingulate	73.53	15.48
	R superior parietal	22.05	4.89

*As these peak relaxation values are very high, they could be coming from voxels outside the brain, in the cerebrospinal fluid. However, parts of the clusters appear to be situated within the brain, so they have been included in the analyses.

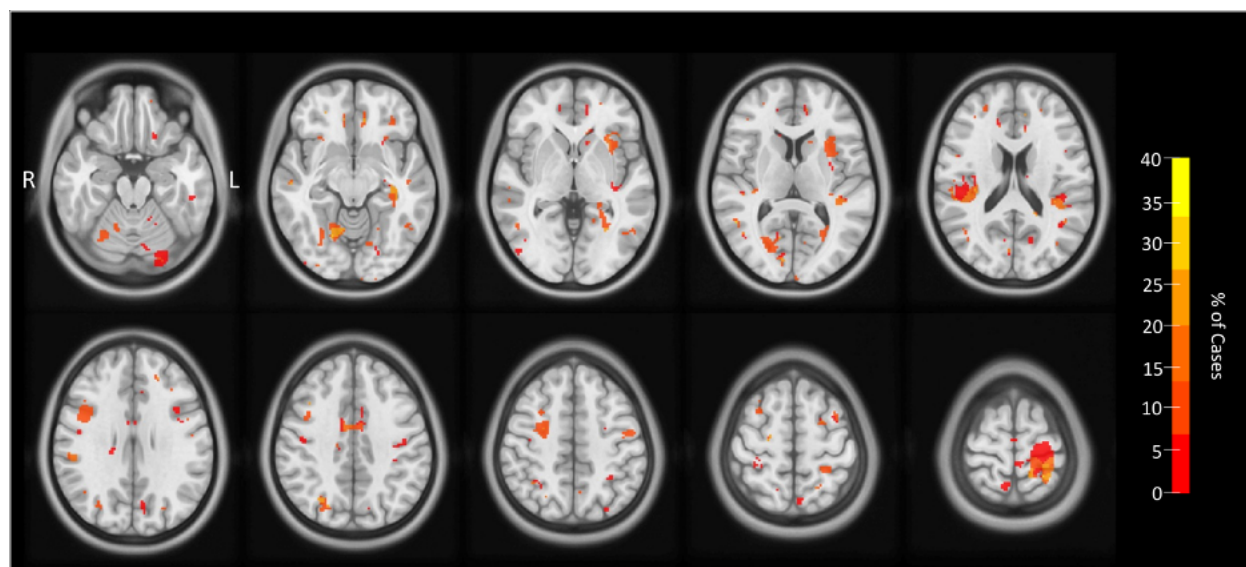


Figure 4.3 *Common Regions of Significantly Elevated T2 Relaxation Times*

Note. This is a penetrance map where binarised significant voxels for each participant are overlaid. The colour bar refers to the percentage of participants having significantly increased T2 relaxation times in specific regions, compared to controls. For all images presented in this paper, the colour bars vary between images as they have been scaled to the minimum and maximum relaxation values.

4.3.2 Case 1 - Recovery Scan Available

Case study one suffered an mTBI as a result of a knee to the head during a rugby game. He experienced headaches, tiredness, abnormal emotional expression and feeling like he was in a dream. These symptoms largely settled at the clinical assessment four days post-injury, with only mild headaches and tiredness being experienced at that point. Brain Injury Screening Tool (BIST) scores were low, with no individual statements obtaining abnormally high scores and an initial total score of 12/160. This participant had experienced one other mTBI in his life, during primary school. Recovery time for the current mTBI was recorded as 20 days. Four significant voxel clusters are apparent when assessing the T2 relaxometry images (see Figure 4.4). There is a significant cluster in the left superior parietal region, with relaxation times up to 8.40 SD higher than the controls (peak relaxation value = 146.5 ms). Two significant clusters are found in the left superior frontal region, the first more laterally with relaxation times up to 4.08 SD higher than controls (peak relaxation value = 2.7×10^6 ms). As noted above in Table 4.2, since this peak relaxation value is unusually high, it may indicate that this peak value is coming from a voxel that is situated outside the brain (i.e. in the cerebrospinal fluid). However, as some parts of the cluster appear to be located within the superior frontal region of the brain, it has been included in this case

description. The second left superior frontal region is more medial, with relaxation times up to 4.38 SD higher than controls (peak relaxation value = 74.2 ms). Lastly, there is a significant cluster in the left orbitofrontal cortex, with relaxation times up to 6.50 SD higher than controls (relaxation value = 79.8 ms). After recovery, re-scans indicated that T2 relaxation times were reduced by 14.09 SD in the left superior parietal region, by 2.01 SD in the left lateral superior frontal region, and by 4.52 SD in the left orbitofrontal cortex. No significant reduction was found for the left medial superior frontal region cluster.

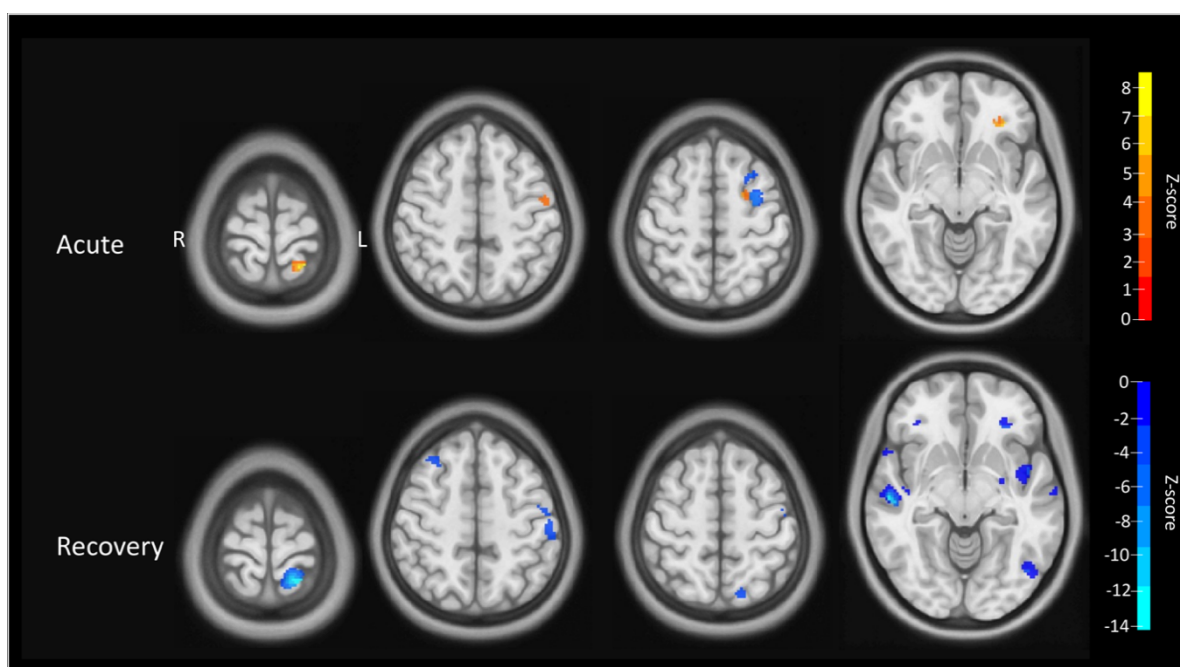


Figure 4.4 Case 1: T2 Relaxometry Acutely Following mTBI and at Recovery (in SD)

Note. The top row indicates increased T2 relaxation times in the left superior parietal, left superior frontal and left orbitofrontal regions acutely following mTBI. Note that the third cluster shows positive and negative values, as these clusters could not be visually separated. The bottom row indicates the difference in T2 relaxation times between acute and recovery scans, with negative values in the left superior parietal, left lateral superior frontal and left orbitofrontal regions indicating lower T2 relaxation times in the recovery compared to acute scans.

4.3.3 Case 2 - Recovery Scan Available

Case study two suffered an mTBI when a ball hit his left eye during a hockey game. He experienced developing headaches and nausea after the match and reported mild headaches and fatigue at his clinical assessment nine days post-injury. The participant's BIST scores were low, with no symptom domains or individual statements obtaining abnormally high scores and an initial total score of 6/160. Recovery time for this injury was recorded as 31 days. Furthermore, he suffered one previous mTBI in the year prior. Three significant voxel clusters were identified when

analysing the T2 relaxometry images (see Figure 4.5). The first is in the left superior parietal region, with relaxation times up to 9.39 SD higher than controls (peak relaxation value = 63.7 ms). There are also significant clusters in the left anterior insula, with relaxation times up to 18.65 SD higher than controls (peak relaxation value = 63.7 ms) and in the right superior frontal region, with relaxation times up to 6.91 SD higher than controls (peak relaxation value = 72.1 ms). After clinical recovery, re-scans indicated that T2 relaxation times were reduced by 8.66 SD in the left superior parietal region, by 40.88 SD in the left anterior insula, and by 6.15 SD in the right superior frontal region.

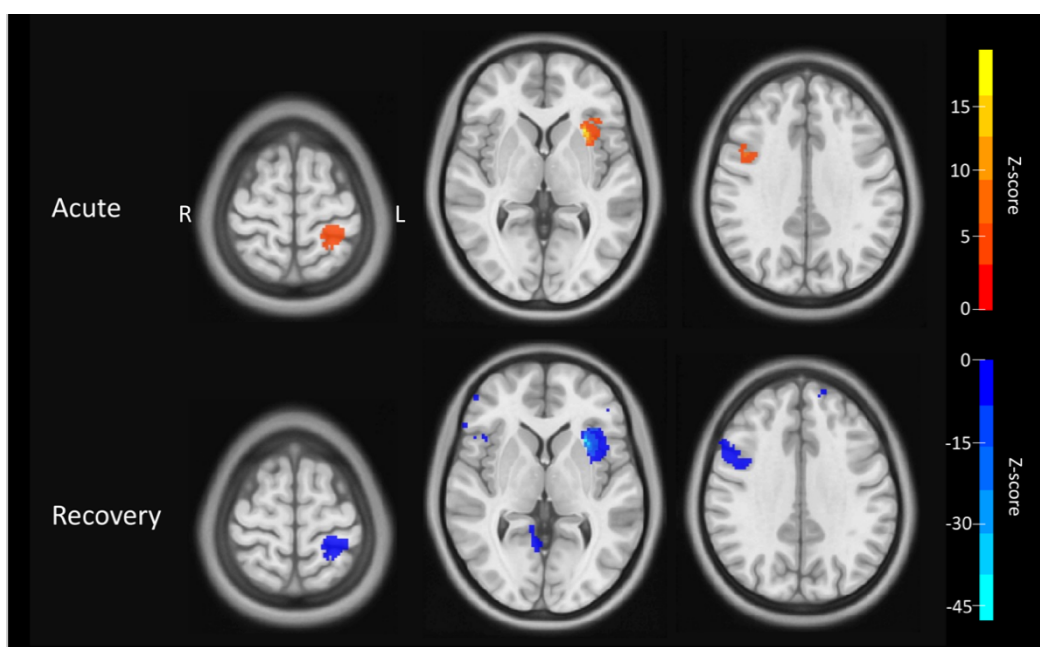


Figure 4.5 *Case 2: T2 Relaxometry Acutely Following mTBI and at Recovery (in SD)*

Note. Top row indicates increased T2 relaxation times in the left superior parietal, left anterior insula and right superior frontal regions acutely following mTBI. The bottom row indicates the difference in T2 relaxation times between acute and recovery scans, with negative values in all three regions showing lower T2 relaxation in the recovery compared to acute scans.

4.3.4 Case 3 - Recovery Scan Available

Case study three suffered an mTBI when he collided with another player during a football game. The participant did not report any specific symptoms during his clinical assessment 11 days post-injury. The participant's BIST scores were low with no symptom domains or individual statements obtaining abnormally high scores and an initial total score of 13/160. The participant reported no previous mTBIs and the recovery time for the current mTBI was recorded as 27 days.

Two significant voxel clusters are identified when analysing the T2 relaxometry images (see Figure 4.6). The first is in the right somatosensory cortex in the parietal lobe, with relaxation times up to 8.66 SD above controls (peak relaxation value = 76.1 ms) and the second is in the right intraparietal sulcus, with relaxation times up to 15.69 SD higher than controls (peak relaxation value = 51.5 ms). After clinical recovery, re-scans indicated that T2 relaxation times were reduced by 1.54 SD in the right somatosensory cortex and by 0.06 SD in the right intraparietal sulcus.

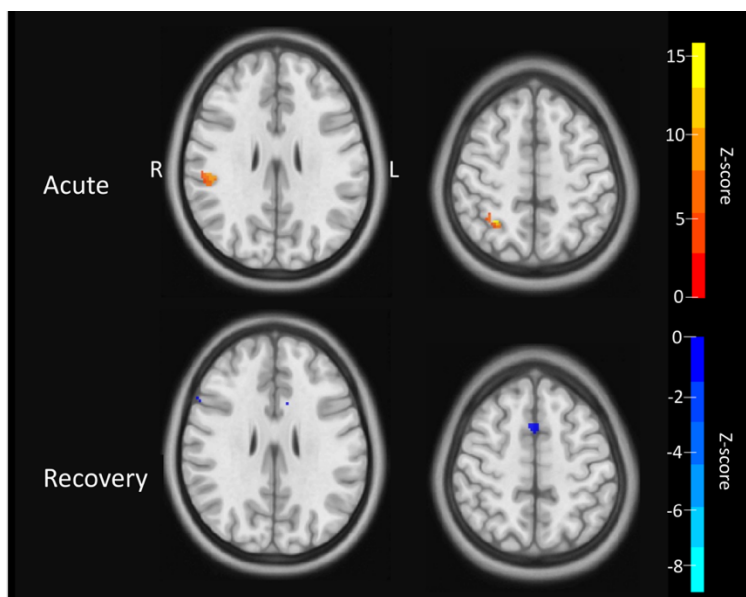


Figure 4.6 Case 3: T2 Relaxometry Acutely Following mTBI and at Recovery (in SD)

Note. The top row indicates increased T2 relaxation times in the right somatosensory cortex and right intraparietal sulcus acutely following mTBI. The bottom row indicates the difference in T2 relaxation times between acute and recovery scans, with negative values too small to be visible.

4.3.5 Case 4 - Recovery Scan Available

Case study four had a head-to-head collision with a teammate during a rugby game and suffered an mTBI as a result. At the time of injury, the participant reported “seeing stars” and being unsteady, followed by headaches and sensitivity to light. Symptoms resolved within a few days but were exacerbated approximately nine days post-injury during training. At his clinical assessment, 12 days following the initial injury, the participant reported headaches and fatigue. BIST scores were low, with no symptom domains or individual statements obtaining abnormally high scores and an initial total score of 22/160. The participant has reported one previous mTBI two years prior. Recovery time for the current mTBI was recorded as 26 days. When analysing T2

relaxometry data for this participant, two significant clusters of voxels were discovered (see Figure 4.7). The first is in the left anterior insula, with relaxation times up to 12.12 SD higher than controls (peak relaxation value = 68.3 ms) and the second is in the left posterior cerebellum, with relaxation times up to 7.04 SD above controls (peak relaxation value = 67.0 ms). After clinical recovery, re-scans indicated that T2 relaxation times were reduced by 11.22 SD in the left anterior insula, but no reduction was found in the left posterior cerebellum.

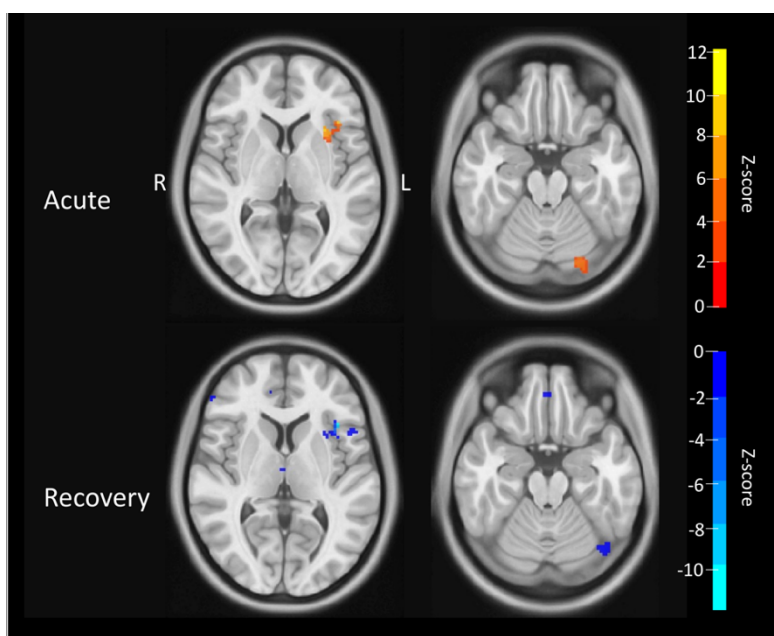


Figure 4.7 Case 4 T2 Relaxometry Acutely Following mTBI and at Recovery (in SD)

Note. The top row indicates increased T2 relaxation times in the left anterior insula and left posterior cerebellum acutely following mTBI. The bottom row indicates the difference in T2 relaxation times between acute and recovery scans, with negative values in the left anterior insula indicating lower T2 relaxation in the recovery compared to acute scans for this region.

4.3.6 Case 5 - Recovery Scan Available

Case study five sustained an mTBI during gymnastics training when he fell off a high bar. The participant reported stumbling when returning to his feet but not experiencing any other symptoms at the time of injury. The following day, he reported feeling disoriented and unwell. Two days after the first injury, the participant again fell on his head during gymnastics training. This time, the participant reported seeing flashes of colour and blurred vision. No additional symptoms are reported during his clinical assessment seven days post-injury. BIST scores were low with no symptom domains or individual statements obtaining abnormally high scores and an

initial total score of 34/160. Recovery time for this injury was recorded as 56 days and this participant has suffered one previous mTBI approximately five to six years prior. When analysing the T2 relaxometry, one significant cluster of voxels was found in the right anterior parietal lobe (see Figure 4.8), with relaxation times of up to 12.83 SD above controls (peak relaxation value = 55.9 ms). After clinical recovery, re-scans indicated that T2 relaxation times were reduced by 12.68 SD in this region.

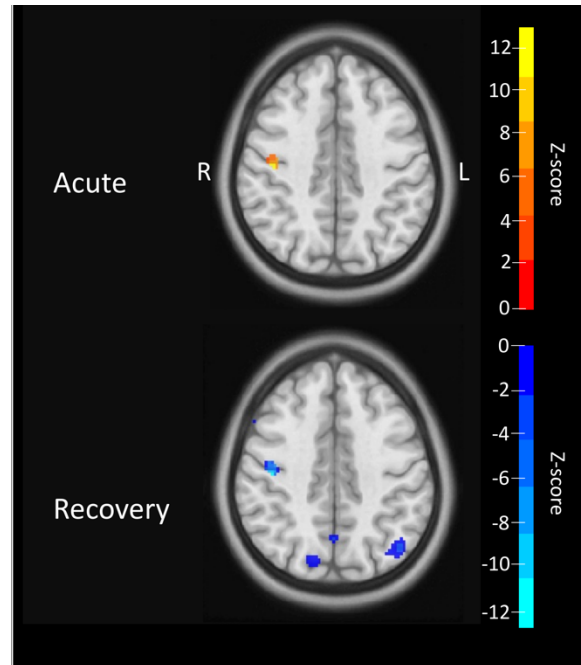


Figure 4.8 *Case 5 T2 Relaxometry Acutely Following mTBI and at Recovery (in SD)*

Note. The top row indicates increased T2 relaxation times in the right anterior parietal lobe acutely following mTBI. The bottom row shows the difference in T2 relaxation times between acute and recovery scans, with negative values in the right anterior parietal lobe indicating lower T2 relaxation times in the recovery compared to acute scans for this region.

Table 4.3 *Change in T2 Relaxation Times in Recovery Compared to Acute Scans*

Case	Region	Acute – Recovery (SD)
1	left superior parietal region	14.09
	left superior frontal region (lateral)	2.01
	left superior frontal region (medial)	N/A
	left orbitofrontal cortex	4.52
2	left superior parietal region	8.66
	left anterior insula	40.88
	right superior frontal region	6.15
3	right somatosensory cortex (parietal lobe)	1.54
	right intraparietal sulcus	0.06
4	left anterior insula	11.22
	left posterior cerebellum	N/A
5	right anterior parietal region	12.68

Note. The *Acute - Recovery* values represent the difference between acute and recovery scans, in the specific regions that were elevated in acute scans, with positive values indicating higher T2 relaxation times in acute versus recovery. N/A indicates that T2 relaxation times were not reduced in that region. All T2 relaxation time differences are indicated in standard deviations.

4.3.7 Case 6

Case six suffered an mTBI resulting from a rugby tackle where he was dropped on his neck. Clinical reports indicated some vomiting, dizziness and ringing in the ears immediately post-injury, as well as neck pain, headaches, light sensitivity and difficulty focusing four days post-injury. BIST scores were high and indicated a 10/10 rating for the statements “I don’t like bright lights” and “I don’t like loud noises”, as well as a 9/10 rating for the statement “I have trouble with my eyesight (vision)”, an 8/10 score for “I forget things” and a total initial BIST score of 140/160. This is the first mTBI that this participant has experienced, and recovery time was recorded as 26 days. Two significant findings are discovered after examination of T2 relaxometry MR images. Firstly, there is a significant cluster of voxels in the left hippocampal region, with relaxation times up to 5.00 SD higher than that of the control group (peak relaxation value = 95.2 ms). Secondly, there is a significant cluster in the left occipital lobe, with relaxation times up to 9.33 SD higher than controls (peak relaxation value = 71.8 ms).

4.3.8 Case 7

Case study seven received a kick to the head during a rugby tackle and suffered an mTBI as a result. Directly after the incident, the participant complained of feeling dizzy and off-balance and at his clinical assessment four days post-injury, he reported headaches, sensitivity to light and noise, as well as difficulty concentrating and some increased irritability. BIST scores indicated a

6/10 rating for the statement “I don’t like bright lights”, a 7/10 for the statement “I don’t like loud noises”, a 6/10 for the statement “It takes me longer to think” and a 7/10 rating for the statement “I have trouble concentrating”. His total initial score was 78/160. The participant had not experienced any previous mTBIs and recovery time was recorded as 47 days. Four significant voxel clusters were discovered when assessing the participant’s T2 relaxometry images. Firstly, there is a significant cluster in the left superior parietal region, with relaxation times up to 7.26 SD above the control average (peak relaxation value = 731,456 ms). As this peak relaxation value is very high, it may be coming from a voxel that is situated outside the brain, in the cerebrospinal fluid (CSF). However, a portion of the significant cluster appears to be situated within the superior parietal region of the brain and so it has been included in the case report. Secondly, there is a significant cluster in the right intraparietal sulcus, with relaxation times up to 14.39 SD higher than controls (peak relaxation value = 72.3 ms). Next, there is a significant cluster in the right temporal parietal junction, with relaxation times up to 3.40 SD above controls (peak relaxation value = 65.5 ms). Lastly, the right superior cerebellum contains a significant cluster with relaxation times up to 8.72 SD above controls (peak relaxation value = 89.4 ms).

4.3.9 Case 8

Case study eight suffered an mTBI during a rugby game, during which he lost consciousness momentarily. No additional clinical data was available for this participant regarding specific symptom complaints during or post-injury. BIST scores indicated a rating of 8/10 for the statement “I don’t like bright lights” and a total initial score of 52/160. This participant had experienced two previous mTBIs, with the last one two months prior. Recovery time for the current injury was recorded as 27 days. Upon examination of T2 relaxometry images, two significant findings were discovered. The first is in the cingulate cortex, with relaxation times up to 8.27 SD higher than controls (peak relaxation value = 73.5 ms) and the second overlaps the left superior Wernicke’s area and inferior supramarginal gyrus, with relaxation times up to 16.31 SD (peak relaxation value = 76.1 ms).

4.3.10 Case 9

Case study nine suffered an mTBI during a rugby game when he fell and hit the back of his head. The participant reported having double vision at the time of injury and then developing brain fog, slowed thinking and indecisiveness three days post-injury. At the time of his clinical assessment 12 days post-injury the participant reported no symptoms and a 0/10 rating for all BIST

statements. No available data indicated whether the participant has suffered any previous mTBIs. Recovery time for this participant was recorded as 18 days. When looking at the T2 relaxometry images, two significant voxel clusters are found. The first is in the left superior parietal lobe, with relaxation times of up to 8.81 SD higher than controls (peak relaxation value = 65.7 ms), and the second is in the right posterior insula, with relaxation times up to 5.31 SD higher than controls (peak relaxation value = 70.3 ms).

4.3.11 Case 10

Case study 10 sustained an mTBI while surfing. This participant reported experiencing a seizure and loss of consciousness. No additional clinical data was available for this participant regarding specific symptom complaints during or post-injury. The participant indicated a 7/10 BIST rating for the statement “I don’t like bright lights”, a 7/10 for “I don’t like loud noises”, a 6/10 for “I feel dizzy or like I could be sick”, an 8/10 for “I feel clumsy”, a 7/10 for “It takes me longer to think”, a 7/10 for “I forget things”, and a 7/10 for “I get confused easily”, with a total initial BIST score of 69/160. The participant reported numerous previous mTBIs, with the exact amount and timing of the most recent one being unknown. The recovery time for the current mTBI is also unknown. Three significant voxel clusters were located when examining the T2 relaxometry images. The first was a large cluster in the left superior parietal lobe, with relaxation times up to 15.92 SD higher than controls (peak relaxation value = 54.9 ms). The second was another large cluster, in the right inferior parietal lobe, with relaxation times up to 14.48 SD above controls (peak relaxation value = 66.0 ms) and the last was in the right superior parietal lobe, with relaxation times up to 8.46 SD above controls (peak relaxation value = 70.8 ms).

4.3.12 Case 11

Case study 11 suffered an mTBI during a rugby game when another player’s shoulder hit the right side of his head. At the time of the injury, the participant complained of feeling dizzy, dazed, with a headache and neck pain. At his clinical assessment 11 days post-injury, he indicated sensitivity to light and feeling “foggy” with “mild cognitive symptoms”. BIST scores were low with no symptom domains or individual statements obtaining abnormally high scores and an initial total score of 18/160. This participant had suffered four previous mTBIs, with the most recent being approximately two years prior. The recovery time for the current mTBI was recorded as 24 days. Four significant voxel clusters are apparent when assessing the T2 relaxometry images. The first is in the left parahippocampal cortex, with relaxation times up to 10.37 SD higher than controls

(peak relaxation value = 76.5 ms). Secondly, there is a significant cluster in the left orbitofrontal cortex, with relaxation times up to 4.83 SD higher than controls (peak relaxation value = 6.5 ms). Next, there is a cluster in the right anterior occipital lobe, with relaxation times up to 10.22 SD higher than controls (peak relaxation value = 79.2 ms). Lastly, there is a significant cluster in the right orbitofrontal cortex, with relaxation times up to 4.34 SD higher than controls (peak relaxation value = 74.7 ms).

4.3.13 Case 12

Case study 12 suffered an mTBI during a rugby tackle, with the left side of his head hitting the ground and the knee or elbow of another player hitting the right side of his head. At the time of injury, he lost consciousness for a few seconds, was reported to be “zoning out” and experiencing headaches. At his clinical assessment 11 days post-injury, he reported having some difficulty concentrating at school, as well as having headaches and some pressure in his head. BIST scores indicated a rating of 8/10 for the statement “I don’t like bright lights” and a 9/10 for the statement “I don’t like loud noises”, with a total initial BIST score of 61/160. This participant had not experienced any previous mTBIs and recovery time was recorded as 23 days. Two significant voxel clusters are apparent when assessing the T2 relaxometry images. These are in the right superior cerebellum, with relaxation times up to 13.15 SD higher than the control group average (peak relaxation value = 79.5 ms) and the right superior temporal sulcus, with relaxation times up to 10.23 SD higher than controls (peak relaxation value = 69.5 ms).

4.3.14 Case 13

Case study 13 sustained two separate head injuries during a rugby game; the first when his head collided with another player’s knee, and then the second when he received an elbow to the left side of his face. The participant reported feeling shocked and dazed at the time of the injuries and feeling pressure in his head as well as some neck pain, foggiess and disturbance to cognitive functions, such as memory, four days post-injury. There was no data available for this participant with regards to whether loss of consciousness occurred or whether any previous mTBIs have been suffered. BIST scores were low with no symptom domains or individual statements obtaining abnormally high scores, and an initial total score of 42/160. Recovery time for this participant was recorded as 17 days. One significant voxel cluster was identified when evaluating this participant’s T2 relaxometry images. This was in the left anterior temporal region, with relaxation times up to 4.70 SD above controls (peak relaxation value = 125.0 ms).

4.3.15 Case 14

Case study 14 suffered an mTBI during a tackle in a football game when the ball was kicked directly at his face, causing him to lose vision for a few seconds. No additional clinical data was available for this participant regarding specific symptom complaints during or post-injury. BIST scores indicated a 6/10 rating for the statement “I don’t like bright lights” and an initial total score of 61/160. This participant had suffered one previous mTBI approximately five years prior. Recovery time for the current mTBI was recorded as 20 days. Four significant voxel clusters were discovered when analysing the T2 relaxometry images. The first area overlaps the left superior Wernicke’s area and inferior supramarginal gyrus, with relaxation times up to 25.44 SD higher than controls (peak relaxation value = 70.2 ms). The next overlaps the left posterior corpus callosum and anterior occipital lobe, with relaxation times up to 13.83 SD higher than controls (peak relaxation value = 57.7 ms). In addition, there is a significant cluster in the left hippocampus, with relaxation times up to 8.38 SD higher than controls (peak relaxation value = 274.1 ms) and in the right premotor cortex, with relaxation times up to 19.60 SD higher than controls (peak relaxation value = 87.6 ms).

4.3.16 Case 15

Case study 15 was hit on the right side of his maxilla by an elbow during a rugby training session, resulting in an mTBI. The participant had ataxia (impaired coordination) and confusion directly following the incident. During his clinical assessment two days post-injury he reported a high symptom load as indicated by vision motion sensitivity testing, for example. However, the participant’s BIST scores were low with no symptom domains or individual statements obtaining abnormally high scores and an initial total score of 56/160. There is no available data for whether the participant has experienced any previous mTBIs and recovery time for this mTBI was recorded as 18 days. Four significant voxel clusters were found when analysing the T2 relaxometry images. The first is in the right inferior parietal region, with relaxation times up to 12.33 SD higher than controls (peak relaxation value = 70.6 ms). Next, there is a significant cluster in the right posterior parietal region, with relaxation times up to 19.85 SD higher than controls (peak relaxation value = 66.7 ms). Furthermore, there is a significant cluster that overlaps the right superior cerebellum and inferior occipital region, with relaxation times up to 5.78 SD higher than controls (peak relaxation values = 104.7 ms) and in the right medial prefrontal cortex, with relaxation times up to 8.13 SD higher than controls (peak relaxation value = 83.9 ms).

4.3.17 Case 16

Case study 16 suffered an mTBI during a rugby game when he was kneed in the back of the head. The participant experienced loss of balance at the time of injury and 24 hours later developed numbness in his hands, blurry vision and headaches, with pins and needles in his hands, dizziness and headaches still at his clinical assessment 11 days post-injury. BIST scores indicated a 7/10 rating for the statement “I feel dizzy, or like I could be sick” and an initial total score of 54/160. Recovery time for this mTBI was recorded as 117 days. Furthermore, the participant had suffered four previous mTBIs, with the latest one occurring approximately two years prior. When analysing the T2 relaxometry images, one significant voxel cluster was identified in the right sensorimotor cortex, with relaxation times up to 14.86 SD above controls (peak relaxation value = 74.0 ms).

4.3.18 Case 17

Case study 17 suffered an mTBI during a tackle in a rugby game. No clinical notes are available for this participant in relation to his symptoms at the time of the injury or at the time of clinical presentation. BIST scores indicated a rating of 6/10 for the statement “I don’t like loud noises”, an 8/10 for “It takes me longer to think”, a 9/10 for “I forget things”, a 6/10 for “I get confused easily”, a 6/10 for “I have trouble concentrating”, a 6/10 for “I get angry or irritated easily”, a 7/10 for “I feel tired during the day” and an 8/10 for “I need to sleep a lot more or find it hard to sleep at night”, with an initial total BIST score of 79/160. This participant reported two previous mTBIs, with the most recent mTBI only two months prior. Recovery time for the current mTBI was recorded as 66 days. Three significant voxel clusters were identified when analysing the T2 relaxometry images. Firstly, in the cingulate cortex with relaxation times up to 11.08 SD above controls (peak relaxation value = 99.0 ms). Secondly, in the left superior frontal lobe with relaxation times up to 6.05 SD above controls (peak relaxation value = 259.4 ms). Thirdly, in the left posterior cerebellum, with relaxation times up to 5.37 SD above controls (peak relaxation value = 1.6×10^8 ms). As this last value is abnormally high, it is likely that part of this peak voxel sits outside of the brain in the cerebrospinal fluid, however, it overlapped with the cerebellum and so has been included in the case study.

4.3.19 Case 18

Case study 18 suffered an mTBI during a rugby game when another player’s knee hit his head and he lost consciousness momentarily. No additional clinical data was available for this

participant regarding specific symptom complaints during or post-injury. BIST scores were low with no symptom domains or individual statements obtaining abnormally high scores and an initial total score of 2/160. This participant reported no previous mTBI and the recovery time for the current injury was recorded as 26 days. The radiologist report of this participant's scan indicated a tiny focus of susceptibility in the left superior frontal gyrus (which the radiologist noted could be vascular or represent a tiny focus of nonspecific haemosiderin deposition), which was not deemed to be clinically significant or warranting follow up. When analysing T2 relaxometry data for this participant, a significant cluster of voxels was identified in the left superior frontal lobe, with relaxation times up to 5.28 SD higher than controls (peak relaxation value = 303.7 ms).

4.3.20 Case 19

Case study 19 was elbowed in the face during a futsal game and suffered an mTBI as a result. No additional clinical data was available for this participant regarding specific symptom complaints during or post-injury. BIST scores indicated a high rating for 12 different statements, with an initial total score of 117/160. The participant reported an 8/10 for the statement "I don't like bright lights", a 9/10 for "I don't like loud noises", a 7/10 for "I feel dizzy or like I could be sick", a 10/10 for "If I close my eyes, I feel like I am at sea", a 10/10 for "It takes me longer to think", a 9/10 for "I forget things", a 9/10 for "I get confused easily", a 9/10 for "I have trouble concentrating", an 8/10 for "I get angry or irritated easily", a 7/10 for "I feel restless", an 8/10 for "I feel tired during the day", and an 8/10 for "I need to sleep a lot more or find it hard to sleep at night". The participant reported no previous mTBIs and the recovery time for the current injury was recorded as 32 days. No significant clusters of voxels were identified when analysing the T2 relaxometry images.

4.3.21 Case 20

Case study 20 sustained an mTBI while engaging in jiu-jitsu when he was kned in the head. There were no clinical notes available pertaining to his symptoms at the time of injury, only mention of headaches at his clinical presentation 11 days post-injury. BIST scores were mostly low, however, there was a rating of 6/10 for the statement "I feel tired during the day" and 6/10 for "I need to sleep a lot more or find it hard to sleep at night", with an initial total BIST score of 28/160. This participant reported two previous mTBIs, with the most recent being approximately 11 years prior. The recovery time for the current mTBI was reported as 38 days. When analysing the T2 relaxometry images, seven significant voxel clusters were identified. One in the left anterior

cingulate cortex, with relaxation times of up to 17.51 SD above controls (peak relaxation value = 66.3 ms), one in the left medial frontal lobe with relaxation times up to 5.68 SD above controls (peak relaxation value = 121.1 ms), one in the left sensorimotor cortex with relaxation times up to 4.57 SD above controls (peak relaxation value = 79.7 ms), one in the left precuneus of the parietal lobe with relaxation times up to 5.49 SD above controls (peak relaxation value = 39.0 ms) and one in the left temporoparietal junction with relaxation times up to 5.60 SD above controls (peak relaxation value = 100.3 ms). Furthermore, there was a significant cluster in the right anterior cingulate cortex with relaxation times up to 15.48 SD higher than controls (peak relaxation value = 73.5 ms) and lastly, in the right superior parietal lobe with relaxation times up to 4.89 SD higher than controls (peak relaxation value = 22.1 ms).

4.3.22 T2 Maps Coefficient of Variation

A further test was conducted to add confidence in the meaning behind the T2 relaxometry findings (See Figure 4.9). First, the eight T2-map echoes for all participants (mTBI and controls) were averaged. The mean (top row), coefficient of variation, in % (middle row), and coefficient of variation overlaid with the grey matter mask used in this study (bottom row) were then calculated. This demonstrated that the most variability across participants is seen proximate to the edges of the brain and ventricles. However, these voxels were not included in the case series due to the grey matter mask that was used. The results of this additional computation illustrate further support for the fact that the significantly elevated T2 relaxation times identified on an individual level are indeed biological in nature and not due to artefacts or noise that would increase the variation.

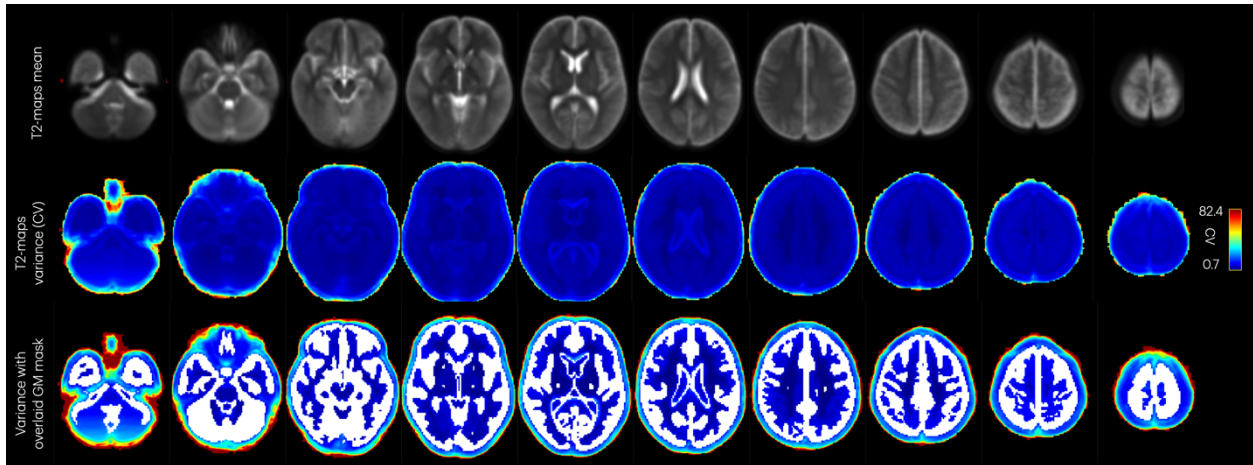


Figure 4.9 *T2 Maps Coefficient of Variation*

4.4 Discussion

4.4.1 Overall Findings

This case series investigated the utility of quantitative T2 relaxometry in detecting subtle brain abnormalities potentially indicative of neuroinflammation in individuals with acute mTBI. T2 relaxometry maps from each mTBI participant were compared against the average of all healthy controls, allowing for a detailed voxel-wise analysis of significant differences at the individual level. The results revealed that 19 out of 20 mTBI participants exhibited significantly elevated T2 relaxation times compared to the control group. Regions on the left side of the brain with significantly higher T2 relaxation times included the hippocampus, superior parietal and frontal cortices, orbitofrontal cortex, supramarginal gyrus, anterior insula, and posterior cerebellum. On the right, regions included the right temporoparietal junction, superior cerebellum, medial prefrontal cortex, somatosensory cortex, and the cingulate cortex. These widespread alterations suggest that even in the acute phase of mTBI, there may be diffuse neurobiological changes not visible on conventional hospital-based imaging.

4.4.2 Common Regions

In addition to individual variability in T2 relaxation times, several significant voxel clusters that were consistently observed across multiple participants were identified. These common regions included the cingulate cortex, anterior insula, cerebellum, and superior parietal cortex. The presence of elevated T2 relaxation times in these areas across several individuals could indicate that certain brain regions may be particularly susceptible to acute microstructural changes

following mTBI. Such vulnerability could reflect a pattern of selective regional sensitivity to neuroinflammatory or oedematous processes, positioning these areas as potential biomarkers for injury severity.

For example, meta-analytic research indicates that the insular and cingulate cortices are preferentially susceptible to grey matter loss across various conditions. This vulnerability is potentially linked to their high density of specialised, long spindle-shaped neurons, known to be particularly sensitive to neurodegeneration. (Koren et al., 2021; Månsson et al., 2022). The insular cortex's prominence in injury pathology is further underscored by its role in the inflammatory response. Rolls (2023) highlights its emerging function in forming the brain's representation of the immune state, likely facilitated by its extensive anatomical connections to peripheral sensory and autonomic nervous systems. Moreover, Månsson et al. (2022) suggest that anterior insula morphology influences sensitivity to inflammation-induced sickness and anxiety symptoms, with larger volume correlating with stronger responses. The functional connection between the insular and cingulate cortices, particularly through their shared involvement in inflammation regulation (Månsson et al., 2022; Koren et al., 2021), may explain their co-occurrence as commonly affected regions in the current study.

If regions such as these are indeed more prone to fluid accumulation in the acute phase post-mTBI, they may hold predictive value for clinical outcomes and recovery trajectories. Early identification of abnormally elevated T2 relaxation times in these regions could therefore support the development of individualised management strategies, such as tailoring return-to-play timelines, and ultimately enhance recovery and reduce the risk of prolonged symptoms. With the possibility of specific brain regions exhibiting selective vulnerability following injury, future research should investigate possible functional mechanisms underlying shared vulnerability in regions commonly found to be significant, to deepen our understanding of mTBI pathology.

4.4.3 Resolution with Recovery

For all five participants with repeat scans, this longitudinal data revealed a reduction in the elevated T2 relaxation values observed during the acute phase of mTBI (see Table 4.3). In two cases, this reduction was partial: at least one, but not all, voxel clusters with significantly increased T2 relaxation times in the acute scan showed lower values at follow-up. The remaining three cases demonstrated a full reduction, meaning all clusters with acutely elevated T2 relaxation times exhibited lower values during recovery. Specifically:

- Case one presented four clusters with T2 relaxation times significantly higher than controls in the acute phase, and three of these clusters showed reduced values upon clinical recovery.
- Case two presented three significant clusters acutely, all of which showed reduced T2 relaxation times at clinical recovery.
- Case three presented two significant clusters in the acute scan, both of which showed reduced T2 relaxation times upon recovery, though one cluster's reduction was modest (0.06 standard deviations).
- Case four also presented two significant clusters acutely, with one showing reduced T2 relaxation times in the recovery scan.
- Case five presented a single cluster with significantly elevated T2 relaxation times following injury, which also showed reduced T2 relaxation times after clinical recovery.

Overall, the reduction in T2 relaxation times from the acute phase to recovery supports the interpretation that increased T2 relaxation, likely reflecting transient fluid accumulation, are injury-related rather than indicative of pre-existing conditions. These findings align with previous evidence from a case report by Pedersen et al. (2020), who also observed region-specific reductions in T2 relaxation times following clinical recovery from mTBI. This convergence of evidence prompts important questions about whether mTBI should be conceptualised primarily as an acute or chronic condition in terms of its neurobiological consequences. Expanding the longitudinal dataset to include a larger cohort will be essential for determining the generalisability of this recovery pattern. If replicated, these results could support the use of T2 relaxometry as an objective biomarker for monitoring recovery and guiding clinical decision-making following mTBI.

4.4.4 Limitations

A key limitation of Study 1 is the lack of generalisability. Although the individual-level analyses provided detailed insights into subtle brain abnormalities following mTBI, the small sample size of each analysis ($N = 1$) limits external validity and prevents broader generalisation to the wider mTBI population. Without group-level comparisons, it remains unclear whether the results reflect unique characteristics of the individuals studied or represent general trends in mTBI pathophysiology. Larger, sufficiently powered group studies are needed to extend these findings and enable their application in clinical practice.

Some results were also challenging to interpret, which can introduce a level of subjectivity. For instance, there were cases where significant voxel clusters showed implausibly high T2 relaxation values. In Case 1, a cluster in the left lateral superior frontal region had a peak T2 relaxation time of 2.69×10^6 ms, far exceeding all other values. Visual inspection revealed that the peak of this cluster was located at the very edge of the brain, likely within the cerebrospinal fluid, rather than in brain tissue. Another example is Case 3, where the difference in T2 relaxation times between the acute and recovery scans was only 0.06 standard deviations. While this does represent a reduction, it is unclear whether such a small change is clinically meaningful. These examples highlight how subjective interpretation may influence the analysis of quantitative data, and this should be carefully considered in future research.

Additionally, there are technical considerations relevant to both Study 1 in the current chapter and Study 2 in the following chapter of this thesis. T2 estimations can be affected by noise, and this can be particularly relevant at longer echo times. Moreover, partial volume effects can also distort the T2 estimates - where a single voxel contains a mix of tissue types (such as grey matter and cerebrospinal fluid). Inaccuracies may arise when voxels at tissue boundaries are included in the analysis (Cheng et al., 2012). To mitigate this, a grey matter mask was applied twice within the preprocessing steps. Firstly, in *Matlab* when each participant's average brain T2 relaxation was calculated. Secondly, using the *DPABI Statistics Tool* when the two sample t-test was conducted, to ensure that any voxels that may have been smoothed beyond the grey matter were excluded from the analysis. This helped to avoid any tissue blurring effects between tissue types and ensured that only relevant brain tissue was analysed.

4.4.5 Concluding Remarks

In summary, Study 1 was a comprehensive case series that employed the novel use of a quantitative MRI technique to investigate its utility in acute mTBI. I found that nearly all mTBI participants exhibited elevated brain T2 relaxation times following injury. These findings may reflect underlying neuroinflammatory processes and contribute to a more nuanced understanding of the pathophysiology of mTBI. However, this interpretation remains tentative and requires validation through further research. Quantitative T2 relaxometry offers high-resolution, individualised maps of subtle brain abnormalities that may not be captured by conventional imaging techniques. By detecting these changes at the individual level, this method may provide valuable insights into a patient's clinical presentation and recovery trajectory. A clearer

understanding of the role that increased T2 relaxation times - and the potential neuroinflammation it reflects - plays in the acute phase of mTBI could support more personalised treatment strategies, ultimately enhancing recovery outcomes and informing safer return-to-play decisions in sports-related contexts, for example.

5

Study Two: MRI Group Analysis

5.1 Overview

Study 2 of this thesis expands the investigation of MRI T2 relaxometry as a potential measure of neuroinflammation acutely following mTBI. It progresses the thesis from a stage of hypothesis generation to hypothesis testing. The preceding chapter was primarily exploratory, using detailed individual analyses to identify potential patterns or abnormalities in T2 relaxometry. This exploratory approach was crucial for generating preliminary evidence that T2 relaxation changes can occur post-injury and, importantly, that these changes can be detected and quantified using MRI T2 relaxometry techniques. However, exploratory case series research, by nature, is limited in its ability to distinguish between true injury-related effects and random variation or individual differences. To strengthen the findings from Study 1 and advance scientific understanding of ways to measure potential neuroinflammation post-mTBI, it is necessary to formally test these initial observations in a larger, systematically studied cohort. Accordingly, Study 2 moves the thesis from exploratory to more confirmatory research, using controlled statistical group comparisons between mTBI participants and healthy controls. This design enables an assessment of whether the differences observed in T2 relaxation times at the individual level are consistently present across the group, and whether they reach statistical significance.

In addition to this methodological progression, a second key motivation for conducting a group comparison is to address the limited generalisability of the case series findings. While Study 1 identified deviations in T2 relaxation times between individual mTBI cases and controls, case series are inherently constrained in their ability to reflect broader population trends. Case-level investigations offer detailed, personalised insights but often lack external validity, limiting their applicability beyond the immediate sample. Therefore, it is necessary to complement the case

series with a group-based case control comparison to determine whether these individual findings reflect broader, statistically significant trends that can be generalised to the wider population.

A group-level comparison is also crucial for establishing the clinical relevance and diagnostic potential of quantitative T2 relaxometry. While Study 1 provided preliminary evidence of individual deviations in T2 relaxation times relative to typical values, the case series design primarily highlights individual variability rather than establishing consistent patterns across a group. The second study builds on this by enabling direct statistical testing of whether mTBI is associated with systematic differences in T2 relaxation times detectable at a group level. Establishing reliable group differences is fundamental for assessing the clinical applicability of T2 relaxometry. If mTBI consistently alters T2 relaxation times across a cohort, this would strengthen its candidacy as an objective biomarker for brain inflammation. Clinically, having an objective biomarker of neuroinflammation could contribute to the diagnosis of mTBI, which currently relies predominantly on subjective symptom reporting, and may support monitoring recovery or guiding return-to-activity decisions (e.g., by informing a necessity for anti-inflammatory interventions). Moving from case-level observations to robust group-level analyses is, therefore, a critical step toward validating the diagnostic and prognostic utility of T2 relaxometry in mTBI care.

The specific aim of this chapter is to provide evidence supporting the use of quantitative T2 relaxometry MRI methods as an objective measure of potential neuroinflammation following mTBI. Current evidence highlights the prominent role of neuroinflammation in the acute and subacute phases after mTBI, as well as the potential consequences of chronic or excessive inflammation on prolonged recovery outcomes (Ayerra et al., 2025; Bolte & Lukens, 2021; Boulton & Al-Rubaie, 2025; Calderone et al., 2024; Freire et al., 2023; Kim et al., 2023; Markovic et al., 2021; Naumenko et al., 2023; Neumann et al., 2023; Obukohwo et al., 2024; Pasternak et al., 2012; Pasternak et al., 2016; Piao et al., 2013; Rosen, 2024; Simon et al., 2017). Prior research has also supported the capability of quantitative T2 relaxometry to detect inflammatory responses through the quantification of extracellular fluid accumulation in various conditions and diseases (Adel et al., 2023; Chekhonin et al., 2024; Cheng et al., 2012; Deoni, 2010; Dhabalia et al., 2024; Ghugre et al., 2011; Gracien et al., 2016; Liu et al., 2018; Maillard et al., 2004; Pasternak et al., 2016). However, there is a notable gap in research regarding the use of quantitative T2 relaxometry to measure neuroinflammatory responses specifically following mTBI. To address this gap, the second study of this thesis extends the first study by doubling the mTBI sample size and analysing

group comparisons with robust statistical methods. See Appendix 8 for the publication in the *Journal of Neuroscience Research* relating to this study.

5.2 Methods

5.2.1 Participants

The first group used for Study 2 consists of all 40 male mTBI participants ($M = 21.4$ years, $SD = 5.0$ years) with acute sports-related mTBI. The second group consists of 40 of the healthy male controls ($M = 22.1$ years, $SD = 3.8$ years) who were randomly selected to provide a control group with a similar mean age as the mTBI group. Additional details regarding participant recruitment, diagnostic criteria and ethics are detailed above in Chapter 3 *Overall Methods*.

5.2.2 Power Calculation

A power calculation was conducted using G*Power Version 3.1.9.6 (Erdfelder et al., 1996). Assuming a moderate effect size based on current literature and pilot data ($d = 0.6$) and a study power of 80%, a total sample size of approximately 72 (36 per group) is required to sufficiently power the analysis. While there is no previous study directly comparable to the current one, this seems to be a conservative estimate based on larger effect sizes identified in similar, previous research (Bartlett et al., 2007; Gracien et al., 2016; Jackson et al., 1993; Liu et al., 2018; Pell et al., 2004; Winston et al., 2017)

5.2.3 Magnetic Resonance Imaging

Image acquisition details are the same as Study 1 and can be found above in Chapter 4 (in section 4.2.2 *Magnetic Resonance Imaging*).

5.2.4 Data Processing and Statistical Analysis

Initial preprocessing steps for this study mirror those for Study 1 in Chapter 4 and can be found in section 4.2.3.1 *Initial Preprocessing*. For this reason, they have not been duplicated in this chapter. Following these preprocessing steps, additional processing took place that is specific to this second study and is detailed below.

Each participant's average brain T2 relaxation was extracted using an in-house script in *Matlab* that applied a grey matter mask and smoothing parameter of 6mm. For the first analysis, an independent-sample t-test was conducted in *Jamovi* version 2.3.19.0 (The Jamovi Project, 2024) to quantify whole-brain averaged differences in T2 relaxation times between mTBI and controls. For the second analysis, a two-sample t-test was conducted with a two-tailed hypothesis using the

DPABI Statistics Tool (Yan et al., 2016). A second grey matter mask was included at this stage to ensure that any voxels smoothed beyond the grey matter were excluded from the final statistical analysis. For this analysis, voxel-wise permutation testing with Threshold Free Cluster Enhancement (TFCE) was employed with 20,000 permutations to reduce the type 1 error rate and because it is relatively insensitive to varying smoothing parameters (Smith & Nichols, 2009). Default TFCE parameters in *DPABI* were applied, corresponding to *FSL* settings of $E = 0.5$, $H = 2$, and $dh = 0.1$. Significance was determined using voxel-wise family-wise error (FWE) correction at $p < 0.05$ to account for multiple comparisons. Lastly, an exploratory analysis was conducted to ascertain if there was a relationship between T2 relaxation and recovery times. To do so, a Pearson's correlation was carried out in *Jamovi* version 2.3.19.0 (The Jamovi Project, 2024) using the whole-brain average T2 relaxation value for each mTBI participant and their recovery time measured in days.

5.3 Results

5.3.1 Analysis 1: Average Whole-Brain T2 Relaxation Times between mTBI and Controls

A two-tailed independent t-test was conducted to determine if there was a difference in mean total grey matter T2 relaxation times between the mTBI and control groups. The mTBI group (70.3 ± 1.55 ms) had significantly higher average total brain T2 relaxation times compared to the control group (69.1 ± 1.48 ms), $t(78) = 3.56$, $p < 0.001$ (see Figure 5.1). To ensure that total intracranial volume (TIV) did not have an impact on group differences in T2 relaxation times, an independent samples t-test was also conducted on TIV between mTBI and controls, which was not significant, $t(78) = 1.25$, $p = 0.216$.

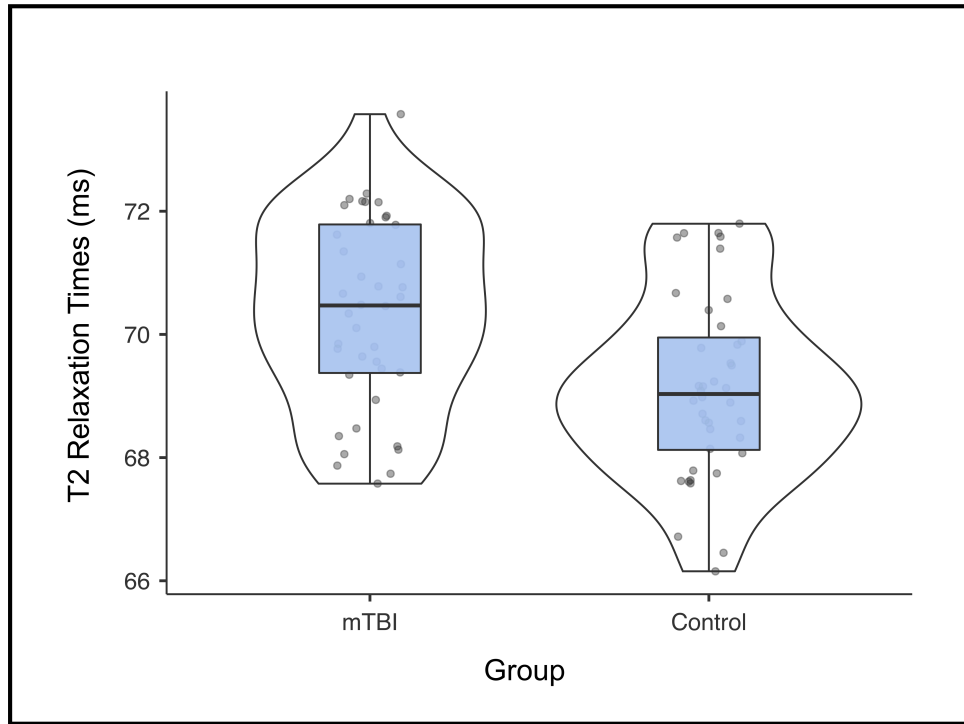


Figure 5.1 *Whole-brain T2 Relaxation Times for mTBI versus Controls (in ms)*

5.3.2 Analysis 2: Significant Voxels Compared using Threshold Free Cluster Enhancement

There were widespread significant differences found between mTBI and controls, using a TFCE permutation testing correction for multiple comparisons. These differences were driven by elevated T2 relaxation times in dorsal cortical brain regions of mTBI participants, with slightly fewer statistical differences observed in the inferior regions. Elevated T2 relaxation times in the mTBI group were observed in multiple anatomical regions, including the superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, cingulate gyrus, dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex, superior parietal lobe, precentral gyrus, postcentral gyrus, inferior parietal lobe, insula, middle temporal gyrus, superior temporal gyrus, temporoparietal junction, and cuneus of the occipital lobe (see Figure 5.2 and Table 5.1).

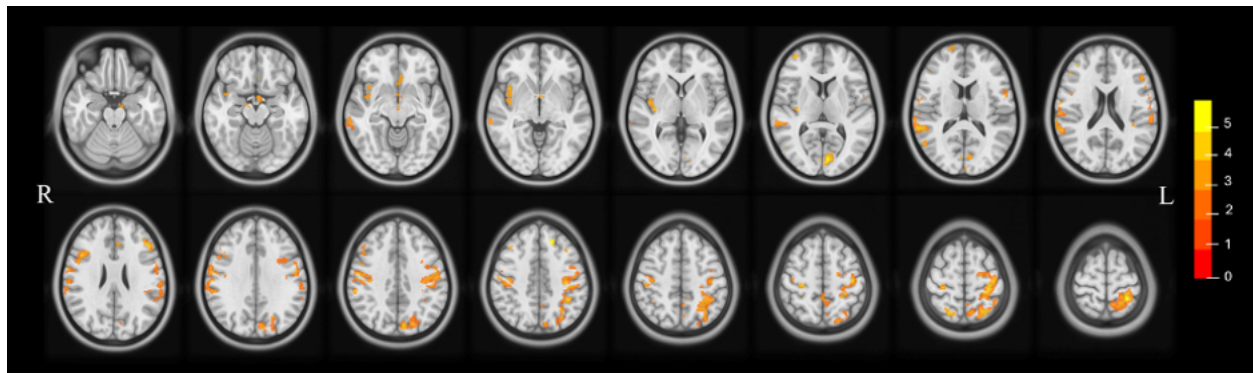


Figure 5.2 *Significantly Increased T2 Relaxation Times for mTBI versus Controls (in t-values)*

Table 5.1 *Brain Regions with Significant Group Differences in T2 Relaxation Times*

Region	Difference in T2 Relaxation Times (in t-values)
L superior frontal gyrus	5.523
L middle frontal gyrus	4.474
L paracentral lobule	3.203
L precentral gyrus	4.311
L postcentral gyrus	5.815
L postcentral gyrus	3.215
L anterior cingulate	4.034
L anterior cingulate	3.817
L hypothalamus	3.938
L medial temporal lobule	3.440
L inferior parietal lobule	4.322
L cuneus	5.257
R middle frontal gyrus	4.528
R inferior frontal gyrus	4.058
R precentral gyrus	3.674
R postcentral gyrus	4.572
R superior parietal lobule	4.486
R inferior parietal lobule	5.006
R anterior temporal lobule	4.595

Note. T2 relaxation times were calculated by subtracting the control group from the mTBI group, with positive t-values indicating higher T2 relaxation times for the mTBI group. These are examples of regions with a statistically significant difference and do not represent an all-encompassing list of brain-wide differences.

5.3.3 Analysis 3: Quantitative T2 Relaxation Times and Recovery

Given the significant difference in T2 relaxation times discovered between mTBI and control groups, it was important to understand if these elevated T2 relaxation times were associated with recovery. To investigate this association, a Pearson's correlation was conducted in Jamovi

using the average whole-brain T2 relaxation times for the mTBI group as well as their time to clinical recovery (refer to Chapter 3 *Overall Methods* for an explanation of how clinical recovery was determined). Results showed a significant, negative correlation between T2 relaxation times (in ms) and recovery (in days), with $P(38) = -0.313$, $p = 0.049$.

5.4 Discussion

5.4.1 Overall Findings

Study 2 aimed to investigate the use of quantitative MRI T2 relaxometry to measure subtle brain abnormalities potentially indicating neuroinflammation post-mTBI. Specifically, it aimed to extend the preceding study by using robust statistical analyses to compare T2 relaxation times between groups of mTBI participants and healthy controls, to examine its use as an objective marker of injury and inflammatory processes. Results showed that whole-brain quantitative T2 relaxation times were increased acutely following mTBI compared to healthy controls, as well as widespread regional elevations shown using TFCE. Furthermore, follow up correlational analyses found that T2 relaxation time was negatively correlated with days to recovery.

T2 relaxation times are influenced by the water content of tissue, with longer relaxation times observed in tissue with a higher ratio of free water molecules compared to bound water molecules. This ratio of water molecules can be observed in conditions including disease and trauma and may be reflective of the brain's inflammatory response. Inflammation encapsulates many processes that can lead to increases in extracellular free water (Albrecht et al., 2016; Lyall et al., 2017; Pasternak et al., 2012). The current findings could represent increased intracellular and/or extracellular fluid accumulation, which cannot be clarified directly with quantitative T2 methods. Intracellular fluid accumulation, where the water is building up inside the cells, is called cytotoxic oedema. This type of oedema tends to occur more in the very acute phase and in more severe trauma, where there is more cell membrane damage. Conversely, extracellular fluid accumulation, or vasogenic oedema, is when fluid is leaking out between the cells, commonly from a breakdown of the blood-brain barrier, increasing the extracellular volume (Batista et al., 2025; Freire et al., 2023).

The hypothesis here is that the increased T2 relaxation times observed in Studies 1 and 2 are likely driven by extracellular fluid accumulation, indicative of the inflammatory response. However, the voxels contain both intracellular and extracellular environments and therefore cannot

directly distinguish between these two types of oedema. A finding of increased extracellular fluid and potential neuroinflammation aligns with the well-established role of inflammation in the secondary cascade of events acutely following brain trauma, the role of the blood-brain barrier in this response, and the study timeframe (within 14 days post-injury) (Ayerra et al., 2025; Freire et al., 2023; Markovic et al., 2021; Naumenko et al., 2023; Neumann et al., 2023; Obukohwo et al., 2024; Pasternak et al., 2016; Rosen, 2024).

I observed that increased T2 relaxation times were widespread but particularly prominent in superior dorsal regions of the frontal and parietal lobes. Specific anatomical regions with elevated T2 relaxation times included areas such as the superior, middle and inferior frontal gyri, the cingulate gyrus, the DLPFC, anterior cingulate cortex, precentral and postcentral gyri, the insula, middle and superior temporal gyri, the temporoparietal junction, and cuneus (see Figure 5.2). The dorsal cortical location of increased T2 relaxation times could represent areas of increased vulnerability following mTBI. This could be due to where coup and contrecoup damage commonly occur or where there is likely to be more concentration of force in cortical sulci, for example (Drew & Drew, 2004; Kornguth et al., 2017; Toma & Nguyen, 2020). The findings overlap with existing research indicating a predictable profile of brain regions that are vulnerable in mTBI, including the frontal and temporal lobes in general and, more specifically, the DLPFC, orbitofrontal cortex, anterior cingulate cortex, temporal polar cortex, amygdala, hippocampi, cerebellum and brainstem (Bigler, 2023; McAllister, 2011). Although previous research has shown that T2 relaxation times decreased after clinical recovery, it remains unknown what the longer-term implications are, especially as cortical regions are known to be an early marker for cumulative damage and chronic injury, including neurodegenerative disease (Bieniek et al., 2021; Ghajari et al., 2017; McKee et al., 2018).

5.4.2 A Beneficial Role for Acute Inflammation

Along with the elevated T2 relaxation times in acute mTBI compared to controls, exploratory follow up analyses also indicated a significant, negative correlation between T2 relaxation times and time to clinical recovery. This finding suggests that as average whole-brain T2 relaxation times increase for the mTBI group, time to recovery decreases. It is possible that this negative correlation highlights the beneficial role of inflammation acutely post-mTBI and the impact that this process has on recovery outcomes. Specifically, this finding may reflect an initial increase in aspects of the inflammatory response that lead to increased extracellular fluid content

and elevated T2 relaxation times (such as activated microglia and astrocytes as well as the production of pro-inflammatory cytokines), that are necessary for neural repair and therefore contribute to shortened recovery times. However, as this is purely a correlational finding, I cannot ascertain causal factors in this relationship. For example, if increased T2 relaxation values, and the possible neuroinflammation that it may reflect, reduces recovery time, or if there are other factors that are influencing both T2 relaxation and recovery times. Future research is needed to extend the current exploratory analysis and directly assess the relationship between T2 relaxation and recovery. Longitudinal research that quantifies T2 relaxation times at multiple time points during recovery could help to elucidate patterns between T2 relaxation times and clinical recovery. Furthermore, obtaining existing validated measures of inflammation at each of these time points could further our understanding of a potential role for inflammation in the relationship between T2 relaxation times and clinical recovery.

5.4.3 Comparison to Prior Research

As outlined in Chapter 2, MRI T2 relaxometry has previously been utilised in various clinical research settings, including hippocampal sclerosis research (E.g., Adel et al., 2023; Bartlett et al., 2007; Jackson et al., 1993; Winston et al., 2017), juvenile dermatomyositis (E.g., Maillard et al., 2004), multiple sclerosis (E.g., Gracien et al., 2016) and in a rodent model of mTBI (E.g., Yang et al., 2015). However, only one previous study has examined T2 relaxometry in human mTBI (Pedersen et al., 2020). The current findings align with Pedersen et al. (2020)'s case study that found increased T2 relaxometry in a sports player with an acute mTBI. To the author's knowledge, however, the current study is the first research looking at the use of quantitative T2 relaxometry in a group with acute mTBI, therefore contributing to a significant gap in the literature.

5.4.4 Limitations

A key limitation of this study is the potential masking of inter-individual variability. While group-level statistics allow for robust comparisons and the generation of generalisable findings, they can obscure meaningful individual differences in brain T2 relaxation times. When data are aggregated for group comparisons, unique or potentially clinically relevant patterns may be “averaged out” and thereby overlooked. This limitation is particularly pertinent in the context of a heterogeneous condition such as mTBI, where brain pathology and recovery trajectories can vary markedly between individuals. The complementary nature of the individual-level analysis in Study 1 and the group-level analysis in Study 2 helps to mitigate this limitation. Another methodological

consideration is that both the exploratory analyses in Study 1 and the confirmatory analyses in Study 2 were conducted within the same sample. Although Study 2 included an expanded dataset, the retention of original participants may introduce confirmation bias or overfitting. Ideally, exploratory findings would be tested in a fully independent sample to strengthen the robustness and generalisability of the results.

Although the use of TFCE is generally a strength of this study, minimising the risk of false positives without requiring arbitrary thresholds, it does come with limitations. For example, it is computationally intensive due to the iterative evaluation of signal intensity across a continuum of spatial clusters, and it can remain sensitive to noise. Furthermore, the interpretability of TFCE outputs can be challenging. Rather than yielding familiar statistical values such as *t*- or *z*-scores, TFCE results reflect a combined measure of intensity and spatial extent, complicating the translation of findings into standard effect size metrics. The absence of predefined thresholds also introduces ambiguity around which regions to focus on for interpretation and what level of T2 relaxation elevation constitutes a meaningful effect.

Another limitation relevant to both Study 1 in Chapter 4 and Study 2 in the current chapter involves the interpretation of changes in T2 relaxation times. While Study 2 extended the findings of Study 1 and advanced the research toward a more confirmatory perspective regarding increased T2 relaxation times in mTBI, it remains largely hypothesis-generating in terms of interpreting these increases as indicative of neuroinflammation. Although prolonged T2 relaxation times may occur in the presence of neuroinflammation, T2 relaxometry is not a specific biomarker for this. Its lack of specificity is a central concern, as T2 relaxation can be influenced by a range of microstructural and physiological alterations - including gliosis, axonal degeneration, ischaemia or infarction (e.g., due to structural tissue loss), or increased extracellular water that is unrelated to inflammation. It is also possible that elevated T2 relaxation times reflect neuroinflammation unrelated to the mTBI itself. As this study is observational in nature, causality cannot be inferred. Nonetheless, the consistent and statistically significant prolonged T2 relaxation times among mTBI participants suggests that the differences are likely attributable to the mTBI, rather than to alternative inflammatory processes such as neurodegenerative disease, systemic inflammation, metabolic dysregulation, age-related gliosis, or prior brain injuries.

Finally, a conceptual limitation arises in the interpretation of negative T2 relaxation values when comparing mTBI participants to controls. While the interpretation of increased (i.e., positive)

T2 relaxation values is well-supported, reflecting elevated water content and slower transverse relaxation due to reduced spin-spin interactions (Albrecht et al., 2016; Cheng et al., 2012; Deoni, 2010; Ghugre et al., 2011; Liu et al., 2018; Pai et al., 2023), the physiological basis for decreased (negative) T2 relaxation values remains unclear. As this study focused on evaluating positive T2 changes, negative values were excluded from interpretation. However, this represents a valuable direction for future research to explore the mechanisms and potential implications underlying such findings.

5.4.5 Concluding Remarks

The findings of this chapter provide evidence that quantitative T2 relaxometry is a promising, non-invasive tool for detecting subtle brain changes associated with acute mTBI. The observed increases in T2 relaxation times across widespread cortical regions support the hypothesis that T2 relaxometry can be used to detect neuroinflammatory processes present following mTBI, consistent with the established pathophysiology of secondary injury cascades. Additionally, the negative correlation between T2 relaxation time and recovery suggests that acute elevations in T2 relaxation times may be linked to more rapid clinical recovery, potentially reflecting an adaptive inflammatory response, although causality cannot be established from these data alone. Overall, the results underscore the potential clinical value of quantitative T2 relaxometry as a marker for diagnosis and prognosis in mTBI, offering an objective component to complement subjective symptom reporting. Continued research is warranted to establish T2 relaxometry's specificity, validate its clinical utility, and explore its role in predicting long-term outcomes.

6

Study Three: Physical Activity

6.1 Overview

Study 3 shifts the focus from identifying potential neuroinflammatory responses to exploring strategies for their potential modification. Studies 1 and 2 established the utility of quantitative MRI T2 relaxometry in detecting subtle brain abnormalities, possibly reflecting neuroinflammation, in the acute phase following mTBI. However, detection alone is insufficient - there remains a critical need to identify modifiable behaviours that can influence these inflammatory processes and promote recovery. Physical activity (PA) has emerged as a promising candidate in this context, with growing evidence suggesting that it improves clinical outcomes following mTBI, potentially through anti-inflammatory mechanisms (Art et al., 2023; Buckley et al., 2022; Chizuk et al., 2022; Coslick et al., 2020; Leddy et al., 2021; Leddy et al., 2023; Seehusen et al., 2021).

In this chapter, I investigate the influence of different intensities of PA during a critical two-week period acutely post-mTBI, a window during which neuroinflammation may be both active and malleable. Using objective, accelerometer-based PA monitoring, this study addresses limitations of prior work that has typically relied on retrospective self-reports, which are subject to bias and imprecision. By extending the narrative of neuroinflammation introduced in the earlier chapters, this analysis considers how a modifiable behavioural factor such as PA, might interact with the biological signatures of mTBI captured by T2 relaxometry. Specifically, T2 relaxometry may help identify individuals with suspected neuroinflammation, while PA could represent a non-pharmacological strategy to mitigate these brain changes and improve recovery trajectories. This work therefore moves toward an evidence-based, personalised approach to mTBI management, informed by both neuroimaging and behavioural data.

As introduced in Chapter 2, traditional clinical guidelines have advocated physical and cognitive rest until full symptom resolution. However, this "rest-is-best" paradigm has been increasingly challenged, with studies indicating that excessive rest may hinder recovery and exacerbate symptoms (Dobney et al., 2017; Lawrence et al., 2018; Leddy, 2025; Leddy et al., 2019). The 2022 Concussion in Sport Consensus Statement reflects this shift, now recommending a brief period of relative rest followed by gradual reintroduction of PA. Activity intensity can then be progressively increased, provided any symptom exacerbation is mild and short-lived (Patricios et al., 2023). Despite these advances, the optimal timing and intensity of PA for recovery remain unclear, and the underlying neurobiological mechanisms, particularly the role of PA in modulating neuroinflammation, are not fully understood. While direct evidence linking PA to reduced neuroinflammation post-mTBI is limited, robust literature supports the anti-inflammatory effects of PA in other contexts (Fedewa et al., 2003; Ford, 2002; Geffken et al., 2001; Godinho et al., 2021; Kreber & Griesbach, 2016; Mee-Inta et al., 2019; Mota et al., 2012; Nigro et al., 2021; Nilsson et al., 2018; Nimmo et al., 2013; Paolucci et al., 2018; Petersen & Pedersen, 2005; da Luz Scheffer & Latini, 2020; Swain et al., 2023), suggesting a plausible biological pathway by which PA could facilitate neural repair and recovery (Markovic et al., 2021; Piao et al., 2013).

A novel methodological contribution of Study 3 is the application of compositional data analysis (CoDA) to PA data. CoDA acknowledges that daily time-use behaviours, such as sleep, sedentary behaviour, light PA, and moderate-to-vigorous PA, are co-dependent, as time spent in one behaviour necessarily reduces time available for others. This approach offers a more ecologically valid and holistic understanding of how daily activity patterns influence recovery. To date, CoDA has not been applied in the context of acute mTBI, a gap that Study 3 addresses.

Another major rationale for this study is the well-documented heterogeneity in mTBI recovery outcomes. While some individuals recover within days or weeks, others experience prolonged symptoms lasting for months or even years (Danielli et al., 2023; Hossain et al., 2022; Kara et al., 2020; McInnes et al., 2017; Neumann et al., 2023; Polinder et al., 2018; Slavoaca et al., 2020; Verboon et al., 2021; Visser et al., 2022). Differences in post-injury behaviour may be one possible explanatory factor in this heterogeneity. Early PA initiation may influence the neurobiological processes indicated by quantitative MRI techniques such as T2 relaxometry. If PA is shown to be associated with clinical recovery outcomes, then this could support PA as a candidate explanatory variable for why some patients recover faster or slower.

The first two studies of this thesis established the potential of quantitative MRI T2 relaxometry to detect possible neuroinflammation acutely post-mTBI. This third study builds on the neuroimaging findings of the previous chapters by investigating the role of modifiable lifestyle factors - i.e. PA time-use compositions - in shaping these neurobiological outcomes. Although time-use epidemiology and CoDA techniques have been applied in a limited number of studies involving other neurological populations, such as individuals recovering from stroke (Ezeugwu & Manns, 2024; Hooker et al., 2022; Orme et al., 2020), this is the first study to employ CoDA to examine recovery following mTBI. Specifically, Study 3 aims to (1) determine whether the time-use composition of different forms of PA differs between mTBI participants and healthy controls, and (2) explore the association between PA compositions and recovery time following mTBI. In doing so, this work contributes to the development of evidence-based, personalised recommendations for activity management in the acute phase of mTBI recovery. See Appendix 9 for the preprint article in *SportRxiv* relating to this study.

6.2 Methods

6.2.1 Participants

Data for this study was obtained from all participants recruited for this research that had sufficient PA data available. This totalled 35 of the mTBI participants ($M = 21.71$ years, $SD = 5.10$) and 45 of the control participants ($M = 23.13$ years, $SD = 4.34$). See Table 6.1 below for a breakdown of the sample. Additional details regarding participant recruitment, diagnostic and recovery criteria, as well as ethics can be found *Overall Methods* in Chapter 3.

Table 6.1 Participant Sample Information

	mTBI	Controls
Initial Sample	40	52
Devices Lost	4	0
Insufficient Data (<3 days)	1	7
Study Sample	35	45

6.2.2 Activity AX3 Devices

To record PA, wrist-worn *Activty AX3* activity tracking devices were given to each mTBI and control participant (see Figure 6.1). The device is a data logger and features MEMS 3-axis accelerometer and flash based on-board memory. It is designed to be worn at all times, which

enables the collection of continuous 24/7 movement behaviour data. Using the Open Movement Software (OMGUI, version 1.0.0.43, Open Movement, Newcastle University, UK), each device was initialised to record for 15 days (to enable 14 full days of data to be extracted after allowing for the participants to be fitted with the devices at varying times of the day) at 50 Hz sampling frequency, with a range of $\pm 8g$.



Figure 6.1 *Axivity AX3 Wrist-Worn Device*

6.2.3 Procedure

All mTBI and control participants were fitted with an Axivity AX3 device to track PA immediately following recruitment (within 14 days following their mTBI for the mTBI group). Participants were instructed to wear the device on either of their wrists for a total of 15 days. Participants were not asked by researchers to alter their PA in any way and were told that the device should ideally be worn 24/7. If the device needed to be taken off at any point during the 15-day wear time, then the participants were asked to take the device battery out of the wrist strap and secure it to their upper arm using specialised adhesive pouches that were provided to them at their study visit. Participants were asked only to do so if necessary and to return the device battery to the original wrist-worn position as soon as possible. The mTBI participants recruited through Sports Concussion Clinics ($N = 31$) underwent extensive clinical examination by a Sport and Exercise Medicine Physician. They received verbal and written education regarding physical loading to address their symptoms and were scheduled for a follow up consultation approximately 14 days post-injury (Kara et al., 2020; McGeown et al., 2020). Participants recruited through the community ($N = 4$) followed individual rehabilitation advice from their own general practitioners. Following the 15-day wear time, a member of the research team collected the devices from participants at a location convenient to them. See section 3.5 *Determining Recovery* in Chapter 3 *Overall Methods* for an overview of how clinical recovery was calculated for each participant.

6.3 Measurements

6.3.1 Movement Behaviours

Time-use behaviours were extracted from the Axivity AX3 accelerometer devices. Firstly, raw data from each device was downloaded via the *OMGUI* software in the form of .cwa files and then the *GGIR* package in R (Migueles et al., 2019) was used to determine device wear time and extract time-use behaviour variables. The variables of interest were daily time spent in sedentary behaviour, light intensity PA, moderate intensity PA, vigorous intensity PA, and sleep (all recorded in minutes). The gravity-based acceleration unit (g) thresholds used to determine cut-off points for these intensities were 40mg for light PA, 100mg for moderate PA and 400mg for vigorous PA (Hildebrand et al., 2014; Hildebrand et al., 2016). The minutes of moderate and vigorous intensity PA were combined into moderate-vigorous PA. Additionally, the sleep duration was calculated based on accumulated nocturnal sustained inactivity within a sleep period window that is identified using sustained inactivity bouts (SIB) and a Heuristic Algorithm looking at Change of Z-angle (HDCZA) (van Hees et al., 2018).

Non-wear time was detected using the GGIR default algorithm (van Hees & Migueles, 2025), defined as ≥ 60 consecutive minutes with low acceleration variability (standard deviation < 13 mg) and an acceleration range of < 150 mg per axis. Data were processed in 5-second epochs, a valid day was defined as ≥ 16 hours of wear time, and participants were required to have at least three valid days of data (Chan et al., 2022). Minutes in each behaviour of interest were averaged across valid days. The derivation of time use variables was performed in R software (version 4.2.2).

6.3.2 Covariates

Age (in years) and initial symptom burden using total Brain Injury Screening Tool (BIST) scores were included as covariates to rule out the possibility of them confounding the primary association of interest for the second analysis.

6.4 Statistical Analyses

Time-use behaviours were treated as compositional data (i.e., all behaviours sum to 24 hours) and analysed using the *compositions* (Van den Boogaart & Tolosana-Delgado, 2008) and *deltacomp* (github.com/tystan/deltacomp) R packages. No zero imputation was required as there

were no missing values in the dataset. All statistical analyses were performed using R software (version 4.2.2).

6.4.1 Analysis One: Group Comparison mTBI versus Controls

The average time spent in each movement behaviour (i.e. sedentary behaviour, light PA, moderate-vigorous PA, sleep) were reported as geometric means, which were normalised to 1440 minutes (i.e., minutes in 24 hours) in order to calculate compositional means. Compositions were created for each of the four movement behaviour variables using the *comp* function in the *compositions* package in R. The movement behaviour compositions were then expressed as isometric logarithmic-ratio (log-ratio) coordinates, which allows compositional data to be analysed using traditional statistical methods (Dumuid et al., 2018; Dumuid et al., 2020; Liangruenrom et al., 2023). To compare the time-use-composition of the mTBI group to healthy controls, a compositional multivariate analysis of variance (MANOVA) was conducted with group as the independent variable with two levels (mTBI, control) and the movement behaviour isometric log ratios as the dependent variables. Partial eta squared (η_p^2) was calculated as an indication of effect size for the model.

6.4.2 Analysis Two: Time-Use-Composition Association with Recovery

To estimate the ideal time-use-composition for optimising clinical recovery time following mTBI, a compositional isothermal substitution analysis was performed (Grgic et al., 2018). This process consisted of creating a specific set of isometric log ratio coordinates from the time-use behaviour composition and fitting a series of linear regression models. Firstly, sequential binary partition (SBP) matrices were created for the sedentary behaviour, light PA, moderate-vigorous PA and sleep variables (see Table 6.2) which are used as a series of instructions for constructing isometric log ratios (ilr).

Table 6.2 *Sequential Binary Partition Matrices for all Movement Behaviours*

(A) SBP for Sedentary Behaviour					(B) SBP for Light PA				
	<i>sed</i>	<i>lpa</i>	<i>mvpa</i>	<i>sleep</i>		<i>sed</i>	<i>lpa</i>	<i>mvpa</i>	<i>sleep</i>
<i>ilr1</i>	+1	-1	-1	-1	<i>ilr1</i>	-1	+1	-1	-1
<i>ilr2</i>	0	+1	-1	-1	<i>ilr2</i>	-1	0	+1	-1
<i>ilr3</i>	0	0	+1	-1	<i>ilr3</i>	-1	0	0	+1

(C) SBP for Moderate-Vigorous PA					(D) SBP for Sleep				
	<i>sed</i>	<i>lpa</i>	<i>mvpa</i>	<i>sleep</i>		<i>sed</i>	<i>lpa</i>	<i>mvpa</i>	<i>sleep</i>
<i>ilr1</i>	-1	-1	+1	-1	<i>ilr1</i>	-1	-1	-1	+1
<i>ilr2</i>	-1	-1	0	+1	<i>ilr2</i>	-1	-1	+1	0
<i>ilr3</i>	+1	-1	0	0	<i>ilr3</i>	-1	+1	0	0

Note. *sed* = sedentary behaviour, *lpa* = light PA, and *mvpa* = moderate-vigorous PA.

For each of the movement behaviours, only the first *ilr* (*ilr1*) is interpreted, which expresses the ratio of the behaviour of interest, relative to the others. In the SBP for sedentary behaviour, *ilr1* represents the time spent in sedentary behaviour relative to all other movement behaviours; for the SBP for light PA, *ilr1* represents the time spent in light PA relative to all other movement behaviours; for the SBP for moderate-vigorous PA, *ilr1* represents the time spent in moderate-vigorous PA relative to all other movement behaviours; and for the SBP for sleep, *ilr1* represents the time spent in sleep relative to all other movement behaviours.

A series of compositional multiple regression models were fitted to each set of *ilrs*. The *ilr1* variables for each movement behaviour were included as independent variables, while recovery time (in days) was specified as the dependent variable. Four models were fit in total, each time using a different SBP, such that each behaviour of interest was represented as *ilr1*. From these models, the coefficient for *ilr1* was extracted. Following this, adjusted models were repeated with the inclusion of age and symptom burden as covariates.

Lastly, a compositional isotemporal substitution model was run to examine theoretical changes in recovery time by reallocating time spent in different movement behaviours. Predicted changes in recovery time by increasing time spent in one behaviour (at the expense of the other three behaviours) were estimated from 0 to ± 60 minutes in 15-minute intervals. The reallocations of time were proportional to the time spent in each behaviour.

6.5 Results

6.5.1 Analysis One: Group Comparison *mTBI* versus Controls

A MANOVA was conducted to determine if the group that participants were in (*mTBI* versus control) was associated with the proportion of time spent in the four movement behaviours (sedentary behaviour, light PA, moderate-vigorous PA and sleep). The MANOVA was not statistically significant, $F(1,3) = 1.94, p = 0.13$. Results indicated that only 7.0% of the variance in the time-use-composition of participants' movement behaviours could be explained by the group that they were in ($\eta_p^2 = 0.07$). Comparative group data was generated alongside the MANOVA and can be found in Table 6.3 (a summary of average movement behaviours by group), and Figure 6.2 (log-ratio differences between groups). An illustration of the percentage differences in movement behaviours can be found in Figure S1 in Appendix 10.

Table 6.3 *Average Movement Behaviours for mTBI and Control Groups*

	Proportions					Minutes			
	<i>N</i>	Sed	LPA	MVPA	Sleep	Sed	LPA	MVPA	Sleep
<i>mTBI</i>	35	48%	13%	8%	30%	697	194	113	436
Control	45	52%	11%	7%	30%	754	161	99	426

Note. In this table *Sed* represents sedentary behaviour, *LPA* represents light PA and *MVPA* is moderate-vigorous PA. The *Proportions* section shows the percentage of time, per day, spent in each type of movement behaviour, while the *Minutes* section, shows the average amount of time spent in each behaviour per day.

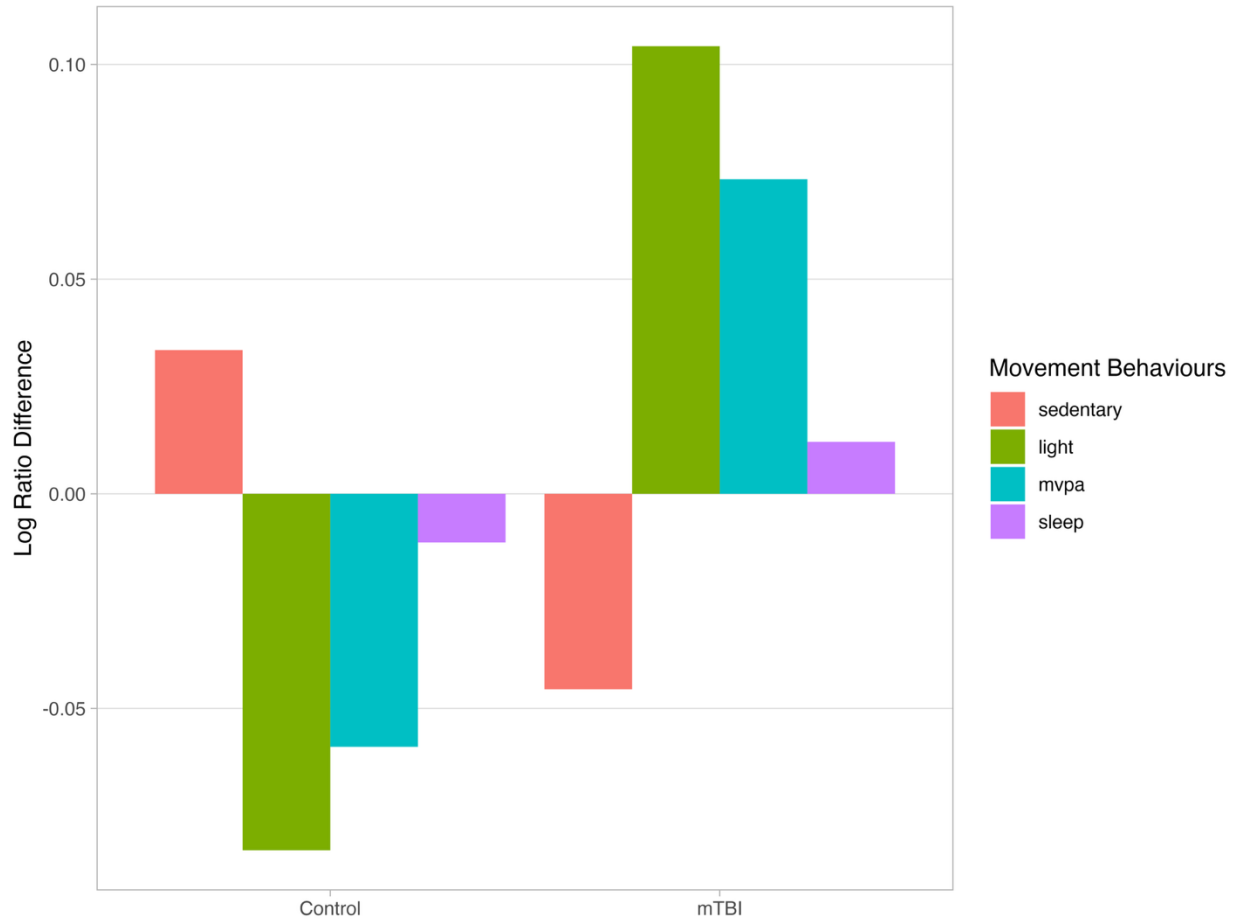


Figure 6.2 *Logarithmic Ratio Differences in Movement Behaviours for mTBI versus Controls*

Note. The above figure illustrates the between-group differences in movement behaviours (sedentary behaviour, light PA, moderate-vigorous PA, and sleep) by comparing the log ratio mean of each group to the overall log ratio mean of both groups combined. Each bar represents the difference to the overall mean of both groups, for each respective movement behaviour. i.e. the figure shows that the mTBI group engaged in less sedentary behaviour but more light PA, moderate-vigorous PA and sleep, compared to the overall mean.

6.5.2 Analysis Two: Time-Use-Composition Association with Recovery

A compositional linear regression model was used to analyse the association between time-use-composition and recovery time within the mTBI group, with participant age and initial symptom burden (total BIST scores) included as covariates. Time spent sleeping was significantly associated with recovery time ($p = 0.03$), with a positive association between sleep and recovery ($\beta = 50.54$), i.e. more sleep was associated with a longer recovery duration. This association remained significant when age was included as a covariate in the model. However, once the model was adjusted for both age and initial symptom burden, the association between sleep and recovery was no longer significant ($p = 0.06$). Time spent in sedentary, light PA and moderate-vigorous PA

were all negatively correlated with recovery, however, these associations were not statistically significant (see Table 6.4 below for a summary of results).

Table 6.4 *The Relationship Between Movement Behaviour Compositions and Recovery*

Isometric log-ratio predictor	Unadjusted Model			Adjusted Model(a) (Age)			Adjusted Model(b) (Age and BIST score)		
	β	P-value	R ²	β	P-value	R ²	β	P-value	R ²
Sed	-26.95	0.24	0.16	-28.06	0.24	0.05	-26.31	0.32	0.01
LPA	-15.02	0.42	0.16	-16.20	0.42	0.05	-13.25	0.54	0.01
MVPA	-8.58	0.64	0.16	-6.88	0.75	0.05	-9.73	0.67	0.01
Sleep	50.54	0.03*	0.16	51.15	0.03*	0.05	49.29	0.06	0.01

Note. *Sed* refers to the proportion of time spent in sedentary behaviour relative to the other movement behaviours, *LPA* refers to the proportion of time spent in light PA relative to the other movement behaviours, *MVPA* refers to the proportion of time spent in moderate-vigorous PA relative to the other movement behaviours, and *Sleep* refers to the proportion of time spent sleeping relative to the other movement behaviours. * indicates statistical significance at $p < .05$

Finally, a compositional isotemporal substitution model was also conducted, of predicted changes in recovery time when time from one movement behaviour is reallocated to/from the remaining movement behaviours (see Figure 6.3). None of the theoretical reallocations of time between different movement behaviours were statistically significant in this model. See Table 6.5 for a complete table of the theoretical reallocation results.

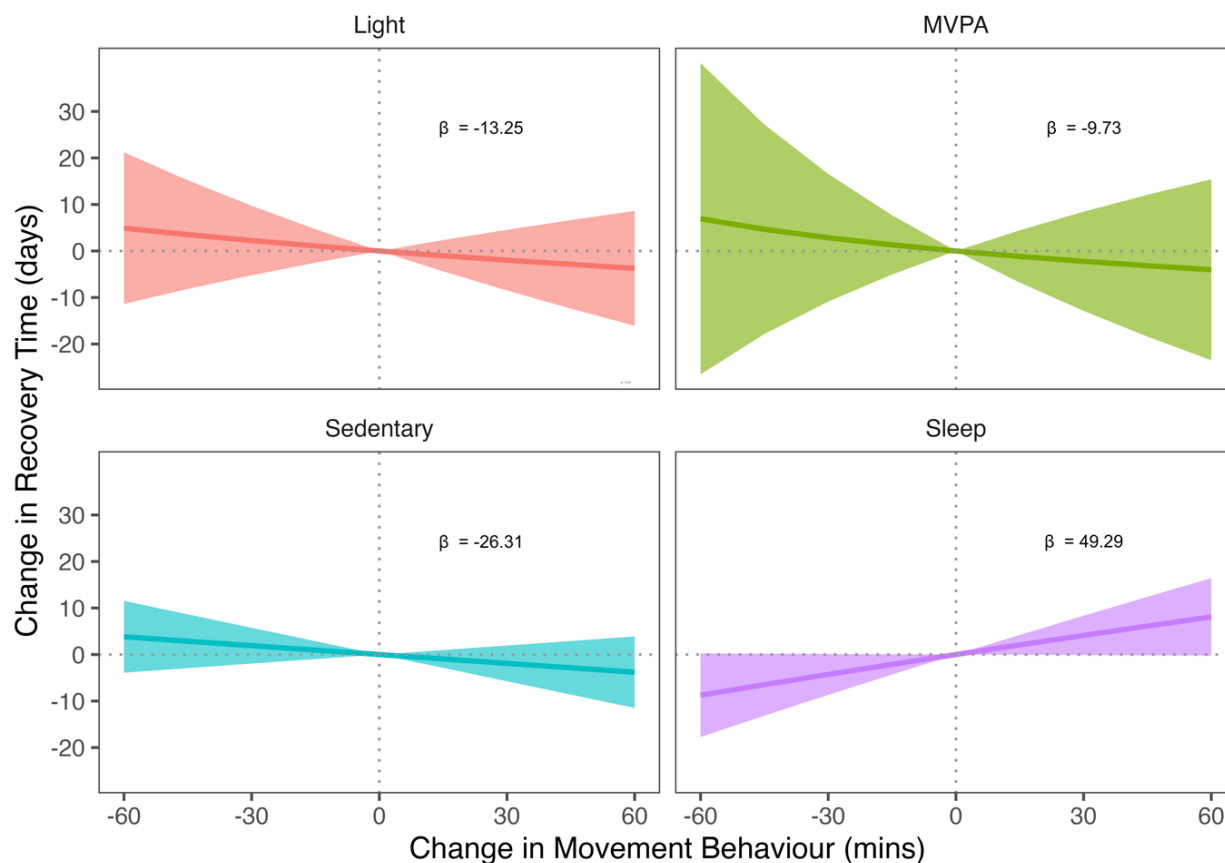


Figure 6.3 *Reallocation of Movement Behaviour Time on Recovery Time*

Note. The above figure illustrates the adjusted compositional isotemporal substitution model for the four movement behaviours; light PA (top left), moderate-vigorous PA (top right), sedentary behaviour (bottom left) and sleep (bottom right). This shows the predicted theoretical changes in recovery time (in days) when time from one movement behaviour (in minutes) is reallocated proportionately to/from the remaining movement behaviours.

Table 6.5 *Compositional Isotemporal Substitution Model of Predicted Theoretical Changes in Movement Behaviours and their Impact on Recovery from mTBI*

Movement Behaviour	Reallocated Time (mins)	Predicted Change in Recovery (days)	Lower 95% C.I.	Upper 95% C.I.
Sedentary	-60	3.82	-3.90	11.54
Light PA	-60	4.91	-11.37	21.19
MVPA	-60	6.94	-26.51	40.39
Sleep	-60	-8.74	-17.72	0.25
Sedentary	-45	2.86	-2.92	8.64
Light PA	-45	3.52	-8.15	15.19

MVPA	-45	4.67	-17.84	27.18
Sleep	-45	-6.48	-13.14	0.19
Sedentary	-30	1.90	-1.94	5.75
Light PA	-30	2.25	-5.21	9.71
MVPA	-30	2.85	-10.88	16.57
Sleep	-30	-4.27	-8.67	0.12
Sedentary	-15	0.95	-0.97	2.87
Light PA	-15	1.08	-2.51	4.68
MVPA	-15	1.32	-5.04	7.68
Sleep	-15	-2.11	-4.29	0.06
Sedentary	15	-0.95	-2.87	0.97
Light PA	15	-1.01	-4.37	2.35
MVPA	15	-1.17	-6.78	4.45
Sleep	15	2.07	-0.06	4.21
Sedentary	30	-1.90	-5.74	1.94
Light PA	30	-1.97	-8.48	4.55
MVPA	30	-2.21	-12.87	8.44
Sleep	30	4.11	-0.12	8.34
Sedentary	45	-2.85	-8.61	2.91
Light PA	45	-2.87	-12.37	6.64
MVPA	45	-3.16	-18.40	12.08
Sleep	45	6.12	-0.18	12.41
Sedentary	60	-3.80	-11.48	3.88
Light PA	60	-3.72	-16.06	8.62
MVPA	60	-4.03	-23.48	15.41
Sleep	60	8.09	-0.23	16.42

Note. For all reallocations, a negative value indicates a reduction in the corresponding movement behaviour, relative to all other movement behaviours, while a positive value indicates an increase. These theoretical allocations are calculated using the adjusted model (with both age and symptom load).

6.6 Discussion

6.6.1 Overall Findings

With the first two studies of this thesis focusing on quantitative measurements of the neurobiological consequences of mTBI, this final study aimed to address an evidence-based method of mitigating these consequences and improving recovery. Despite a growing shift toward more active, individualised approaches to mTBI management, uncertainty remains regarding the optimal timing and intensity of PA following injury. This chapter sought to address these gaps, as well as the notable limitations of previous research that has often relied on subjective and retrospective data. By investigating how objectively measured PA might influence clinical recovery - focusing on four key movement behaviours: sedentary behaviour, light PA, moderate-to-vigorous PA, and sleep - this study offers a more robust and nuanced understanding of post-injury recovery. Importantly, this is the first study to examine time-use behaviours in individuals recovering from mTBI using CoDA. This innovative approach provides novel insights into how reallocating time between different behaviours may support improved recovery outcomes.

In the group comparison, there were no statistically significant differences between the mTBI group and healthy controls in the proportion of time spent in each of the four movement behaviours. Group status accounted for only 7% of the variance in movement behaviours. Therefore, these results may indicate that those with acute mTBI were able to engage in similar proportions of movement behaviours as the group of healthy controls. Although further validation in a larger sample is needed, these initial results seem to support the potential feasibility and safety of incorporating PA into mTBI recovery interventions.

The compositional linear regression analysis showed no significant associations between moderate-to-vigorous PA, light PA, or sedentary behaviour and recovery time. However, sleep showed a significant positive correlation with recovery time, suggesting that spending more time sleeping - relative to other movement behaviours - may be linked to longer recovery durations. When the model was adjusted for age and initial symptom burden, this association was no longer significant, however. This suggests that the initial link between sleep and delayed recovery may reflect a higher acute symptom burden, with individuals requiring more sleep due to the severity of their injury. In other words, those who slept more may have also experienced more severe symptoms and, consequently, slower recovery. However, as this is a correlational finding, it remains unclear whether increased sleep contributes to prolonged recovery, or if individuals with

more severe symptoms and thus slower recovery, simply tend to sleep more. Future experimental studies are needed to investigate this relationship directly.

I also conducted an exploratory compositional isotemporal substitution analysis to examine whether theoretical changes in time-use composition were associated with recovery outcomes. While the findings did not reach statistical significance, the model provides valuable insights into potential behavioural reallocations that could hold clinical relevance. For example, the analysis suggested that reallocating time toward moderate-vigorous PA, proportionately from sedentary behaviour, light PA and sleep, could theoretically be linked to a faster recovery. Specifically, a simulated increase of 60 minutes per day in light or moderate-to-vigorous PA, relative to the other movement behaviours, was linked to an estimated reduction in recovery time of approximately four days (see Table 6.5). As these theoretical reallocations of time did not reach statistical significance they should be interpreted with caution. Nonetheless, this study demonstrates how time-use data and compositional isotemporal substitution analysis can be used to inform rehabilitation plans following mTBI. Further research with a larger sample is needed to validate the utility of this model for mTBI recovery and support its application in clinical practice.

6.6.2 The Role of Physical Activity in Recovery from Mild Traumatic Brain Injury

Deepening our understanding of the complex relationship between PA and mTBI recovery is essential, as significant uncertainty remains in this area. For decades, the standard approach involved strict physical and cognitive rest until full symptom resolution (Howell et al., 2019; Leddy et al., 2019; Markovic et al., 2021). However, growing evidence now indicates that prolonged strict rest may not only be ineffective, but also potentially harmful to recovery. Instead, current guidelines recommend a brief period of relative rest followed by a stepwise return to activity for optimal recovery outcomes (Buckley et al., 2022; Coslick et al., 2020; Leddy et al., 2019; Patricios et al., 2023; Seehusen et al., 2021; Silverberg & Iverson, 2013; Wilson et al., 2020). Multiple factors have been identified as influencing the risk of prolonged recovery. For example, McGeown et al. (2020) reported that individuals who are female, who present with a higher initial symptom burden, or exhibit cervicogenic and/or vestibulo-ocular dominant symptoms are more likely to experience extended recovery periods (>14 days). As our understanding of these risk factors continues to evolve, it becomes increasingly important to identify strategies that actively support optimal recovery - highlighting the need to refine and

individualise rehabilitation approaches through a better understanding of PA's role in mTBI recovery.

6.6.3 Strengths and Limitations

The use of CoDA is an important strength of Study 3 and facilitates clinical translation of results. Since increasing PA inherently reduces time spent in other behaviours, understanding the most beneficial time reallocations is critical for optimising recovery. For example, clinicians could engage patients in discussions about “time-use budgets” that illustrate the trade-offs between different movement behaviours on a day-to-day basis. This might involve strategies for reallocating time from sleep to light or moderate-vigorous PA at appropriate times, considering the patient's symptom exacerbation levels. If such collaborative planning between clinician and patient were implemented during the acute phase post-mTBI, it could foster individualised time-use plans that potentially shorten recovery and facilitate a more efficient return to normal activity.

Interpreting these findings requires consideration of potential limitations, particularly the limited sample size and reduced statistical power. While no significant differences were found between groups, nor significant associations between light PA, moderate-to-vigorous PA, or sedentary behaviour, and recovery, it is possible that the analyses were underpowered to detect an effect. While an a priori power analysis may not have been appropriate given the preliminary, exploratory nature of this study, a post-hoc power analysis was conducted using G*Power Version 3.1.9.6 (Erdfelder et al., 1996) to ascertain the sample size needed to detect an effect in future studies of a similar nature. Based on the effect sizes of the current findings, approximately 240 participants would be needed to detect an effect equivalent to the one observed in analysis one, while analysis two would require approximately 290 participants to detect a similar or larger R^2 value. Increasing the sample size may not only improve statistical power but may also yield larger effect sizes, better reflecting true population-level effects. While an exploratory study like the current one is valuable in providing preliminary information and generating hypotheses, it was not clear until post-analyses how large a sample would be needed to sufficiently power the study, due to the very novel nature of the research.

Moreover, PA variability may have been constrained by similar rehabilitation advice being given to participants, most of whom were recruited from the same concussion clinic. Recommendations such as daily low-intensity aerobic activity (e.g., stationary cycling) may have resulted in uniform movement patterns across participants, reducing the variability necessary to

explore meaningful associations between different PA intensities and recovery. Future work should recruit a more heterogeneous sample, from a wider range of care pathways and across extended post-injury periods, to better capture diverse movement behaviours and enhance generalisability.

Additionally, while steps were taken to improve data quality and enhance the reliability of the findings, such as the use of objective, accelerometer-based measurements, some limitations remain. For example, instances where participants removed their devices may have been inaccurately recorded as sedentary time. Furthermore, some participants reported difficulty securing the device to their arm using the provided adhesive pouches, which may have led to missed recordings of PA. This issue is particularly relevant during competitive sports that would likely contribute substantially to the participant's total moderate-to-vigorous PA, and where wrist-worn devices are often prohibited. Although competitive sport participation is less common during mTBI recovery, some participants in this study reported engaging in such activities and temporarily removing the device, potentially resulting in unrecorded high-intensity PA. To address this limitation, future studies should consider more robust and user-friendly methods for securing activity monitoring devices, particularly for use during vigorous or high-movement activities, to minimise data loss and improve the accuracy of PA estimates.

6.6.4 Concluding Remarks

This is the first study to prospectively examine movement behaviours using wearable accelerometers and time-use compositions in the acute phase following mTBI. Findings indicated that, on average, PA did not differ between the mTBI and control groups, supporting the feasibility and tolerability of PA in the early weeks after an mTBI. Additionally, increased relative time spent sleeping was associated with longer recovery times before being adjusted to initial symptom burden. Moreover, the exploratory substitution analysis, although not statistically significant, demonstrated the potential utility of this type of data analysis to inform rehabilitation recommendations. Although limited by statistical power, these findings contribute to the growing understanding of the complex interactions between PA and mTBI recovery. With further validation, CoDA could contribute to the development of personalised time-use plans in clinical settings, potentially accelerating recovery and supporting safer return to baseline activity. Finally, larger studies with more diverse mTBI cohorts are essential to validate these findings and facilitate clinical translation.

7

Overall Discussion

7.1 Overview

This final chapter aims to synthesise and contextualise the findings from all three studies presented in this thesis. Chapter 7 begins with an overview of the overarching objectives of the research and what it set out to achieve. This is followed by a summary of the key findings from the MRI case series in Study 1 (Chapter 4) and the group-level MRI analysis in Study 2 (Chapter 5). An in-depth discussion then interprets the results of these two studies, focusing on the central hypothesis that increased T2 relaxation values reflect elevated extracellular free water and may be indicative of neuroinflammation. A proposed mechanism is presented to support this hypothesis, namely, blood-brain barrier (BBB) disruption and glial cell activation. Alternative explanations for the observed T2 increases are also explored, alongside the negative correlation between T2 relaxation values and recovery outcomes found in Chapter 5.

The discussion then turns to the significance of identifying subtle brain abnormalities in individuals whose standard hospital-based imaging protocols revealed no clinically significant findings. Following this, the relationship between the MRI and physical activity (PA) data is revisited, and the key findings from Study 3 (Chapter 6) are summarised. These are interpreted in light of the proposed mechanism whereby PA supports recovery from mTBI through the attenuation of the inflammatory response. Practical considerations for translating these findings into clinical practice are also addressed at this point.

After presenting the results of all three studies, this chapter moves toward integration and synthesis, highlighting how the findings align and reinforce each other within the dual framework of this thesis: measuring and modifying potential neuroinflammation. A substantial section is then devoted to the clinical implications, including the potential for individualised treatment plans, the introduction of objective biomarkers to complement the currently subjective nature of mTBI care,

and strategies to monitor at-risk individuals to prevent long-term neurodegenerative consequences of unresolved inflammation. The final chapter concludes with a discussion of the key strengths and limitations that span the thesis, followed by recommendations for future research, such as conducting longitudinal studies and validating T2 relaxometry against established inflammatory markers. Finally, the chapter closes with some concluding reflections on the overall findings and their contribution to the field.

7.2 Research Aims Revisited

mTBIs are highly prevalent and exert considerable psychosocial, physical, and economic burdens on both individuals and society. The term *mild* can be misleading, as many individuals experience persistent symptoms and significant functional impairments post-injury (Danielli et al., 2023; Kara et al., 2020; Rosen, 2024; Slavoaca et al., 2020). Despite this substantial impact, the mechanisms underlying divergent recovery trajectories remain poorly understood and warrant further investigation. This research aimed to address key gaps in our understanding of the pathophysiology and recovery processes associated with mTBI. A dual approach was employed, focusing on both the potential of *measuring* and *modifying* neuroinflammation, a key component of the secondary cascade following mTBI. Central to this investigation were critical questions regarding whether brain inflammation can be non-invasively quantified and whether behavioural interventions, such as PA, can influence recovery trajectories. Specifically, the aims of this research were:

1 - To evaluate the utility of quantitative MRI T2 relaxometry as a sensitive, non-invasive biomarker of subtle brain abnormalities potentially indicative of neuroinflammation following mTBI, both on an individual and group level.

2 - To examine time-use behaviours and explore the role of PA in mTBI recovery using compositional data analysis (CoDA), a contemporary analytical technique in behavioural science.

These contributions are particularly pertinent in the context of Aotearoa New Zealand, where mTBI incidence is high and access to individualised care remains limited. By advancing our understanding of both the biological mechanisms and modifiable behavioural factors involved in mTBI recovery, this research seeks to improve diagnostic precision, support prognostic

assessments, and inform the development of personalised treatment strategies. Ultimately, it aims to shed light on the complex and often invisible consequences of brain injury that lie beneath the surface.

7.3 Brief Recapitulation of Key Findings from Study 1 and Study 2

Firstly, using a novel application of quantitative MRI T2 relaxometry, Study 1 (detailed in Chapter 4) compared each mTBI participant individually to the average of controls. This enabled a comprehensive analysis of significant voxel clusters for specific individuals and demonstrated the ability of this MRI technique to detect subtle brain abnormalities in 19/20 (95%) of the mTBI case studies (see Table 4.2 in Chapter 4 for a list of brain regions with significantly increased T2 relaxation times). Furthermore, for each of the five mTBI participants with longitudinal data available, their recovery scans indicated either partial or full reductions in the regions with elevated T2 relaxation times indicated by their acute scans. This provides valuable support for the idea that the increased fluid content indicated by their acute scans was indeed linked to their mTBI. Regions with increased T2 relaxation times across multiple participants could indicate that specific brain regions are more susceptible to acute brain changes following mTBI and could serve as potential biomarkers for injury and recovery prediction.

Secondly, continuing the exploration of subtle neuroinflammation post-mTBI, Study 2 (detailed in Chapter 5) employed a group-level comparison to statistically assess differences in T2 relaxation values. This analysis revealed significantly elevated average whole-brain T2 relaxation times in individuals with mTBI compared to healthy controls, as well as regional clusters of elevated T2 relaxation times using threshold free cluster enhancement (TFCE). These findings support the hypothesis that T2 relaxation time is increased acutely following mTBI and that these elevated T2 relaxation values may reflect underlying neuroinflammatory processes, likely initiated as part of the secondary injury cascade following trauma. Direct comparisons with prior studies are limited due to the novelty of applying quantitative T2 relaxometry in an mTBI sample. Nonetheless, the findings presented in Study 1 and Study 2 align with those of Pedersen et al. (2020), the only other study to date that has applied this technique in mTBI, who similarly reported elevated T2 relaxation times following acute injury.

In addition to the group comparison, Chapter 5 included an exploratory correlational analysis to investigate whether T2 relaxation times were associated with clinical recovery duration

in the mTBI group. A negative correlation was identified, suggesting that higher T2 relaxation times were associated with a shorter time to clinical recovery. This somewhat counterintuitive finding may reflect the complex, dynamic nature of the post-injury inflammatory response, potentially indicating that a robust acute inflammatory response could facilitate more effective neural repair. However, this interpretation remains speculative and requires validation through future research incorporating longitudinal designs and additional biomarkers to clarify the relationship between T2 relaxation dynamics and recovery outcomes.

7.4 Interpretation and Contextualisation of Study 1 and 2 Findings

7.4.1 Hypothesis: Increased T2 Relaxation Times Reflect Neuroinflammation

7.4.1.1 Linking Increased Fluid to Inflammation

One of the central physiological interpretations proposed in this thesis is that the increased T2 relaxation times observed in Study 1 and Study 2 reflect elevated extracellular fluid and are indicative of neuroinflammation (Albrecht et al., 2016; Lyall et al., 2017; Pasternak et al., 2012). This hypothesis is consistent with the central role inflammation plays in the secondary injury cascade, which initiates in the acute post-injury phase following brain injury (Algattas & Huang, 2013; Khatri et al., 2021; Obukohwo et al., 2024). As all participants in this study were scanned within 14 days of injury, it is reasonable to assume that the brain's inflammatory response was underway during the time of imaging (see Figure 7.1 for an illustration of the time course of the neuroinflammatory response). Therefore, the elevated T2 relaxation times may reflect this dynamic inflammatory process.

It is well established that increased T2 relaxation times indicate increased water content or changes in the microenvironment of tissue (Cheng et al., 2012; Ghugre et al., 2011; Liu et al., 2018). However, the underlying cause of this fluid accumulation remains unconfirmed. The hypothesis that neuroinflammation contributes to this increase in extracellular fluid is supported by a small but growing body of research linking elevated free water to inflammatory activity. In this context, free water refers to extracellular water molecules that are not restricted by cell membranes and do not exhibit directional flow, such as cerebrospinal fluid (Lesh et al., 2021; Pasternak et al., 2009). Supporting evidence includes findings from Lesh et al. (2021), who reported an association between elevated free water and glutathione (GSH), a metabolite involved in inflammatory processes. Additional studies have linked increased free water to small vessel

disease and elevated levels of interferon-gamma, both of which are indicators of immune activation (Duering et al., 2018; Febo et al., 2020; Sun et al., 2024).

Similar associations have also been reported in schizophrenia, a condition associated with immune dysregulation (Lyall et al., 2017; Pasternak et al., 2016). For instance, Pasternak et al. (2012) found that increased free water in early psychosis patients correlated with peripheral inflammation markers, suggesting that extracellular water may be sensitive to neuroinflammatory changes. They therefore proposed that elevated free water could serve as a surrogate biomarker for neuroinflammation. Together, this research provides some limited support for a direct link between elevated free water and inflammation. However, further research, particularly studies correlating imaging findings with histological or molecular markers of immune activity, is necessary to validate this potential biomarker.

It is important to note that much of the supporting literature, such as the studies mentioned above, relies on diffusion MRI, which, while also sensitive to extracellular water, differs from T2 relaxometry in its biophysical basis. Diffusion MRI captures the directional mobility of water molecules, making it sensitive to microstructural damage and axonal changes linked to inflammation (Neumann et al., 2023; Pasternak et al., 2012; Sun et al., 2024). In contrast, T2 relaxometry reflects water-protein interactions and properties of the broader tissue microenvironment (Albrecht et al., 2016; Cheng et al., 2012; Deoni, 2010), offering complementary insights. Therefore, while research utilising diffusion MRI techniques may help shed light on a link between free water and inflammation, direct comparisons between the two modalities should be made cautiously. Future research could aim to integrate both approaches to build converging evidence.

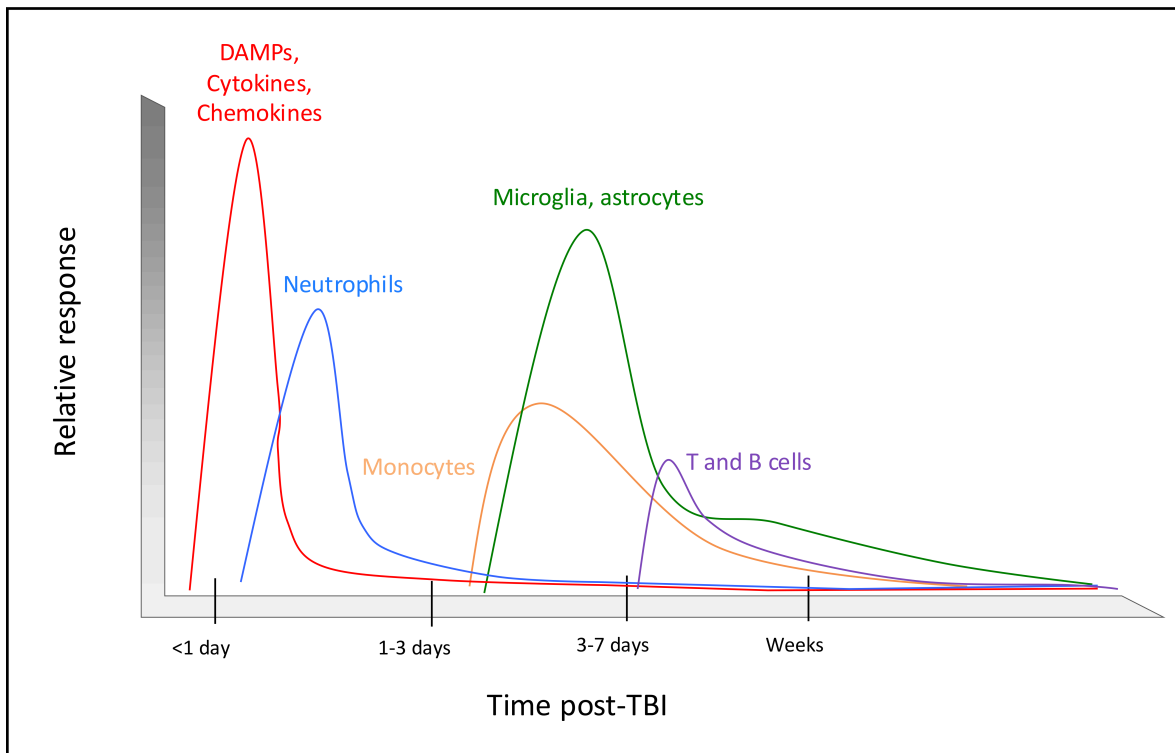


Figure 7.1 *Neuroinflammation Time Course Following Brain Injury*

Note. Reprinted from “Emerging roles for the immune system in traumatic brain injury”, by C. A. McKee and J. R. Lukens, 2016, *Frontiers in Immunology*, 7, Article 556. (<https://doi.org/10.3389/fimmu.2016.00556>) under the Creative Commons Attribution License (CC BY).

7.4.1.2 Linking Increased T2 Relaxation Times to Inflammation

As well as evidence for the link between free water and inflammation, as discussed above, it is important to consider any supporting research for the link specifically between T2 relaxometry and inflammation. Although such research is still emerging, a growing body of work supports T2 relaxometry’s potential as a non-invasive marker of inflammatory processes. For instance, Rivas-Fernández et al. (2025) found that free water estimates from T2 relaxometry may serve as early biomarkers of neuroinflammation in individuals with subjective cognitive decline. Similarly, Maillard et al. (2004) showed elevated T2 relaxation values consistent with inflammatory pathology in juvenile dermatomyositis, while Breynaert et al. (2013) reported increased T2 relaxation times during acute phases of inflammatory bowel disease in a mouse model. Kim et al. (2010) also observed rising T2 relaxation times in children with juvenile idiopathic arthritis, specifically as disease severity progressed. Collectively, these studies highlight the promise of T2

relaxometry as a sensitive marker of inflammation across various conditions, supporting its potential application in detecting neuroinflammation following mTBI.

7.4.2 Hypothesised Mechanism Behind Increased Fluid

7.4.2.1 The Blood-brain Barrier

There are several physiological explanations for why increased T2 relaxation times, indicative of increased fluid content, may indeed reflect inflammation acutely following mTBI. One of the key contributors is likely disruption of the BBB - a highly specialised, dynamic interface that regulates molecular exchange between the blood and brain parenchyma (Alahmari, 2021; Segarra et al., 2021). The human brain contains an extensive vascular network, estimated at approximately 644 kilometres in length, that supplies oxygen, nutrients, and metabolites to the brain, while facilitating waste removal (Alahmari, 2021). Under healthy conditions, the BBB maintains cerebral homeostasis by tightly regulating the transport of ions, fluids, and molecules into and out of the brain (Lacoste et al., 2025; Sweeney et al., 2018). The BBB's first line of defence is formed by endothelial cells joined by tight junctions, which selectively permit small molecules such as water and oxygen to pass while blocking larger or potentially harmful substances. These endothelial cells also produce inactivating enzymes to neutralise certain toxins (Alahmari, 2021; Lacoste et al., 2025).

Surrounding this endothelium is the second line of defence, the basal lamina membrane, housing pericytes - contractile cells that regulate capillary blood flow and act as molecular gatekeepers. Embedded macrophages provide additional protection by engulfing harmful entities (Segarra et al., 2021; Sweeney et al., 2018). The final layer of protection is formed by astrocytic end-feet, which envelop the vasculature and help regulate water and ion transport via their polarised membrane structures. Astrocytes play a crucial role in maintaining BBB function and fluid homeostasis (Alahmari, 2021; Sweeney et al., 2018). See Figure 7.2 below for an overview of the BBB structure.

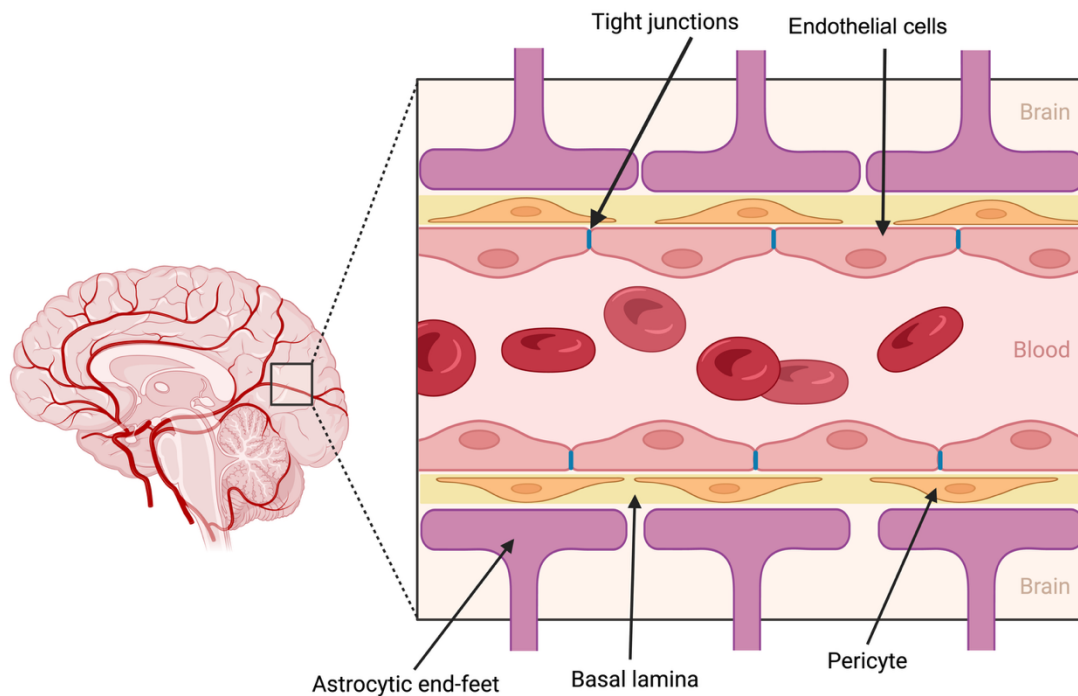


Figure 7.2 *Blood-brain Barrier Structure*

Note. Created with BioRender.com.

The BBB restricts excessive water and ion movement from the bloodstream into the brain's extracellular space, maintaining intracranial pressure and volume (Alahmari, 2021). However, following brain injury, one of the key events in the secondary injury cascade is BBB disruption. BBB compromise after brain injury typically occurs in two phases: an immediate mechanical disruption caused by vascular shearing, followed by secondary damage driven by inflammation (Sweeney et al., 2018). It may be that the consistently elevated T2 relaxation times in mTBI participants observed in the first two studies of this thesis reflect increased extracellular fluid resulting from such BBB breakdown.

Specifically, post-injury BBB disruption may allow plasma constituents to enter the brain, activate glial cells, and create a pro-inflammatory environment, which leads to fluid accumulation in the extracellular space. This disruption can result in oedema, increased intracranial pressure, and long-term changes in synaptic architecture. Furthermore, increased BBB permeability allows peripheral immune mediators (e.g., cytokines, chemokines) and leukocytes to infiltrate the brain, amplifying neuroinflammation and contributing to the dysregulation of cerebral blood flow, ionic

balance, and molecular clearance. Such pathological changes are implicated in both acute injury responses and longer-term neurodegenerative processes (Sweeney et al., 2018).

This hypothesised explanation for why increased T2 relaxation time is reflective of inflammation acutely following mTBI not only links BBB integrity to the observed imaging findings but also highlights a potential therapeutic target: restoration of vascular function. Given that even mild inflammation can compromise BBB permeability (Segarra et al., 2021), future studies should explore whether anti-inflammatory agents could help “seal” the BBB post-injury. Sweeney et al. (2018) outline promising strategies for BBB protection and restoration that could be explored further as they may hold therapeutic relevance for mild TBI.

7.4.2.2 Glial Cell Activation

In addition to BBB disturbances, other aspects of the neuroinflammatory response are likely to contribute to the increased extracellular fluid content reflected in elevated T2 relaxation times. In particular, the brain’s dynamic response to injury, such as mTBI, is mediated through the activation of glial cells, namely microglia and astrocytes. Following mTBI, cellular stress and debris trigger microglial activation (Neumann et al., 2023; Simon et al., 2017). As outlined earlier in Chapter 1, microglia play a critical role in orchestrating the inflammatory response, including the release of pro-inflammatory cytokines such as interleukin-1 β , interleukin-6, and tumor necrosis factor-alpha (TNF- α), as well as the production of reactive oxygen species and nitric oxide (Alam et al., 2020; Boulton & Al-Rubaie, 2025; Mira et al., 2021; Neumann et al., 2023; Obukohwo et al., 2024; Simon et al., 2017). These processes contribute to further BBB disruption and promote osmotic movement of water from the vasculature into the extracellular space (Pasternak et al., 2012).

Astrocytes also play a central role in the inflammatory response. In reaction to injury, astrocytes upregulate aquaporin-4 channels, specialised water channels located at their perivascular end-feet. Additionally, astrogliosis occurs, characterised by astrocyte hypertrophy, proliferation, and altered functionality in response to injury (Boulton & Al-Rubaie, 2025; Freire et al., 2023; Mira et al., 2021). The increase in astrocytes and the expression of aquaporin-4 facilitates the movement of water from the bloodstream into the extracellular space, further contributing to elevated levels of free water. This shift in the ratio of free to bound water is detectable as longer T2 relaxation times (Pasternak et al., 2012). Based on these mechanisms, I hypothesise that two key interrelated components of the neuroinflammatory response, BBB

disruption and glial cell activation, as well as the cascade of peripheral and immune cells that are upregulated or activated as a consequence, including cytokines, chemokines and damage-associated molecular patterns (DAMPs), work in tandem to increase extracellular water content, which in turn underlies the elevated T2 signals observed in Studies 1 and 2 of this thesis (see Figure 7.3).

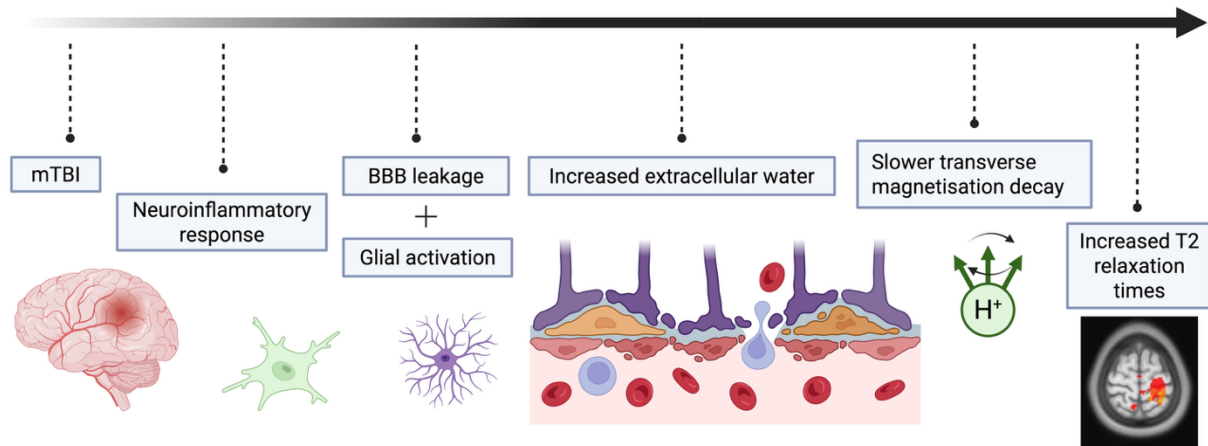


Figure 7.3 *Hypothesised Sequence of Events from mTBI to Increased T2 Relaxation*

Note. Created with BioRender.com.

7.4.3 Is Inflammation the Only Explanation?

Several alternative explanations for the increased T2 relaxation times observed in the mTBI participants across Studies 1 and 2 warrant consideration. One potential mechanism is disruption of axonal membranes or myelin sheaths, as such alterations can modify local magnetic environments and thereby affect T2 relaxation times. Well-myelinated tissue typically exhibits shorter T2 relaxation times due to the influence of macromolecular interactions and restricted water environments; conversely, demyelination can prolong T2 relaxation times (Deoni, 2010). However, given that a grey matter mask was applied twice during MRI data processing, large-scale effects of myelin disruption are less likely, as grey matter contains comparatively little myelin relative to white matter (Deoni, 2010). While subtle myelin-related changes cannot be entirely excluded, the widespread nature of the T2 alterations observed across both studies is more consistent with diffuse neuroinflammatory processes leading to increased free water content, rather than with structural myelin loss.

Another alternative explanation for the results is necrosis, the pathological death of cells, typically associated with the breakdown of cellular membranes and the subsequent dissolution of microstructural barriers that normally restrict water movement. This degradation can lead to an increase in extracellular water content, which may, in turn, prolong T2 relaxation times (Nayak & Kumar, 2023; Zhang et al., 2018). While this mechanism is conceptually plausible, it is less likely in the context of mTBI. Necrosis is more commonly associated with moderate to severe brain injuries, where extensive cell death and structural collapse are more common. In contrast, mTBI typically results in more subtle alterations in cellular physiology without significant tissue destruction. If present, necrosis would be microscopic or focal and unlikely to drive widespread elevations in T2 relaxation times. Furthermore, while limited, prior research (Pedersen et al., 2020) and findings from Cases 1 to 5 in Study 1 suggest that changes in T2 relaxation times may be transient and reversible. This supports the interpretation that increased T2 relaxation times reflect a temporary process such as neuroinflammation, rather than irreversible tissue damage.

The presence of intracranial haemorrhage is another possible explanation. Bleeding in the brain could elevate T2 relaxation times by increasing the proportion of extracellular free water relative to bound water, particularly in the acute phase of injury. However, this explanation appears unlikely for several key reasons. First, haemorrhage is relatively rare in cases of mild traumatic brain injury (Albers et al., 2013; Kwon et al., 2024). Second, no evidence of haemorrhage was identified either by MRI technicians during image acquisition or by the radiologist during formal review of the scans. Moreover, blood breakdown products, such as haemosiderin and deoxyhaemoglobin, are paramagnetic and so they distort the local magnetic field, causing more rapid dephasing of proton spins and reduced T2 relaxation times (Gaeta et al., 2021).

Another related possibility is that the observed abnormalities in T2 relaxation times reflect changes in brain iron content or distribution. Localised iron deposits (for example, due to microbleeds) would be expected to reduce T2 relaxation times, as iron's paramagnetic properties create microscopic magnetic field inhomogeneities that accelerate transverse relaxation. Conversely, reduced iron concentration or redistribution of iron could increase T2 relaxation times by decreasing local magnetic field disturbances and slowing transverse relaxation (Gaeta et al., 2021). However, widespread increases in T2 relaxation times across grey matter are unlikely to be primarily driven by iron-related mechanisms, as such effects are typically focal, most prominently

seen in iron-rich regions such as the basal ganglia, whereas the present abnormalities were diffuse and predominantly cortical (Wang et al., 2016).

Lastly, microvascular alterations may also contribute to the abnormal T2 relaxation times observed across Studies 1 and 2. Following mTBI, small cerebral vessels can be affected, leading to dysregulated cerebral blood flow and vascular reactivity. Such changes can alter tissue oxygenation and water distribution, thereby influencing T2 relaxation times. Although microvascular effects could play a role, they are generally subtle and transient after mTBI (Da Costa et al., 2016). Taken together, while alternative explanations such as demyelination, necrosis, haemorrhage, iron redistribution, and microvascular changes cannot be entirely excluded, they appear less consistent with both the imaging findings and the known pathophysiology of mTBI. The widespread pattern of elevated T2 relaxation times observed in this thesis is more plausibly explained by diffuse, low-grade neuroinflammatory processes occurring in the acute post-injury period.

While MRI findings often reflect a mixture of biological properties due to the relatively coarse spatial resolution of the technique, certain MRI modalities are well-suited to detecting specific tissue characteristics. For example, quantitative susceptibility mapping (QSM) is well-suited for detecting iron content, functional MRI (fMRI) for blood oxygenation fluctuations, and diffusion tensor imaging (DTI) for assessing white matter integrity. In the case of quantitative T2 relaxometry, there is substantial evidence supporting its utility in detecting changes associated with fluid accumulation (Haacke et al., 2015; Khanna et al., 2015; Kim & Bandettini, 2023; Tournier et al., 2011). However, to more precisely determine the biological basis of these changes, further research incorporating complementary imaging modalities or independent biomarkers is warranted.

7.4.4 Negative Correlation with Recovery

The negative correlation between T2 relaxation times and recovery observed as part of Study 2 in Chapter 5 may offer a small but meaningful insight into the complex dynamics of the brain's inflammatory response following injury. Specifically, this finding may support the hypothesis that an elevated acute inflammatory response plays a beneficial role in neural repair and can facilitate more rapid recovery. While a substantial body of research has highlighted the detrimental effects of excessive or prolonged inflammation (Ayerra et al., 2025; Bolte & Lukens, 2021; Calderone et al., 2024; Corps et al., 2015; da Luz Scheffer & Latini, 2020; Kim et al., 2023;

Markovic et al., 2021; Mee-Inta et al., 2019; Pasternak et al., 2016; Simon et al., 2017), it is also well established that an acute inflammatory response is essential for initiating tissue repair and promoting functional recovery (Ayerra et al., 2025; Boulton & Al-Rubaie, 2025; Calderone et al., 2024; Monsour et al., 2022; Neumann et al., 2023).

Although it might seem intuitive to assume that heightened inflammation would be associated with prolonged recovery given its association with poor outcomes in various clinical populations (Furman et al., 2019; Henein et al., 2022; Nishida & Andoh, 2025; Ruck et al., 2023; van Wetering et al., 2024; Xie et al., 2025; Zhang et al., 2023), this result may suggest otherwise. Instead, the data align with the broader understanding that while chronic inflammation is often linked to negative outcomes, acute inflammation is an adaptive, evolutionarily conserved response that supports survival and tissue repair (Furman et al., 2019). Nevertheless, this finding is correlational in nature and should be interpreted cautiously.

7.5 Abnormalities Found Despite Unremarkable Hospital-based Reporting

Importantly, the findings of Studies 1 and 2 suggest that subtle brain abnormalities, particularly those related to post-injury inflammatory processes, may be present despite not being detected by standard hospital-based imaging protocols. Routine clinical imaging following mTBI is frequently unremarkable (Mayer et al., 2015; Patel et al., 2020), which can be problematic. Such non-diagnostic results often do not align with patients' subjective symptom reports and may contribute to the misconception that no injury to the brain has occurred. In this study, select images (T1-weighted, susceptibility weighted imaging [SWI], diffusion weighted imaging [DWI] and limited T2-weighted sequences) were reviewed by a hospital-based radiologist for all participants, and no clinically significant abnormalities requiring follow-up were identified in either the mTBI or control groups. This suggests that participants may have experienced potentially pathological brain changes that were undetectable using conventional hospital MRI protocols. Notably, for case 18, the radiologist did report a structural change in the left superior frontal gyrus (see section 4.3.19 *Case 18* in Chapter 4). Although this finding was not deemed clinically significant and was likely unrelated to the current injury, it spatially coincided with a cluster of significantly elevated T2 relaxation times in the same region. This convergence supports the hypothesis that T2 relaxometry can identify brain abnormalities acutely post-injury.

These observations underscore a persistent and clinically relevant mismatch between subjective symptomatology and conventional imaging outcomes. This disconnect could lead to under-recognition of ongoing pathology and, in turn, inadequate management of mTBI. In some cases, the absence of abnormalities on standard scans may reinforce the misconception that mTBI causes negligible or no brain damage - an outcome which can invalidate patients' experiences, undermine the legitimacy of their symptoms and delay appropriate treatment. At its most concerning, this misalignment could contribute to misdiagnosis, or premature medical clearance for activities such as contact sport. If patients are cleared to return to sport, based on null findings from hospital neuroimaging, but have subtle, insidious neurological damage, they may be at danger of a repeat brain injury prior to their brain fully recovering from the first injury. This may lead to a significant increase in symptoms and longer lasting neural damage.

If future research confirms that quantitative T2 relaxometry reliably detects brain abnormalities in clinical populations, especially those that standard protocols overlook, it may serve as a valuable adjunct for validating symptom reports and identifying individuals at risk of poor outcomes. Integrating more sensitive, quantitative neuroimaging tools into clinical practice could significantly improve the detection of microstructural or inflammatory changes in the brain, allowing for more targeted rehabilitation. Additionally, the observation of signal hyperintensities possibly reflective of neuroinflammation, even in the absence of overt structural abnormalities, supports the notion that inflammatory processes may be an important and viable therapeutic target to promote recovery.

7.6 Re-focusing the Story: The Link between T2 Relaxometry and Physical Activity

While the two types of data analysed in this thesis may initially appear distinct, they are united by a common theme of inflammation, as my goal was to investigate both a possible way to *measure* brain inflammation as well as a possible way to *modify* it. The first two studies focused on the potential of a novel application of MRI T2 relaxometry to identify and quantify subtle brain abnormalities that may reflect acute neuroinflammation post-injury. The third study shifted focus to ways of modifying patient behaviour in a way that may attenuate the inflammatory response and enhance recovery outcomes. Given the central role of inflammation in the secondary injury cascade after brain trauma, and the well-established associations between neuroinflammation and

poor clinical outcomes (established in Chapter 2), the emphasis of this research on inflammation is both timely and warranted. With the foundation of T2 relaxometry established, I now turn to the remaining findings, which relate to physical activity and its potential relationship with recovery.

7.7 Brief Recapitulation of Key Physical Activity Findings from Study 3

Study three of this thesis continues the overarching narrative of neuroinflammation, shifting focus from its measurement to its potential modulation. Specifically, Study 3 (Chapter 6) examined time-use behaviours in individuals with mTBI compared to healthy controls and assessed the utility of CoDA techniques to identify PA patterns that may support optimal recovery. The results revealed no significant group differences in PA levels, providing preliminary support for the safety and tolerability of PA during the early post-injury period. Although most CoDA findings did not reach statistical significance, except for an association between sleep and recovery in the unadjusted model, the analyses underscored the potential of this approach to identify meaningful patterns in movement behaviours. Investigating these patterns could inform clinically relevant behavioural reallocations that promote recovery. As an exploratory study, this study makes a valuable contribution to the limited literature on objective measurement of PA following mTBI and the novel application of CoDA to recovery research. It also demonstrates the low burden and tolerability of this measurement method by participants and highlights promising methodological directions for future work aiming to refine time-use recommendations for individuals recovering from mTBI.

7.8 Interpretation and Contextualisation of Study 3 Findings

7.8.1 Overall Findings

Comparing the findings of Study 3 with existing literature is inherently challenging, as this is the first known application of CoDA to examine movement behaviours in individuals with acute mTBI. While the novelty of this approach is a key strength, it also limits direct comparability with prior work. Nevertheless, the group comparison findings were somewhat unexpected. Several previous studies have documented that individuals with acute mTBI may experience exercise intolerance, which can limit their capacity to engage in PA at levels comparable to healthy controls (Haider et al., 2021; Huber et al., 2019; Kozlowski et al., 2013; Mercier et al., 2021; Valaas et al.,

2023). Contrary to these reports, Study 3 found no significant differences in 24-hour movement behaviour compositions between the mTBI and control groups. This finding suggests that participants with acute mTBI were able to engage in PA at levels similar to healthy peers, without apparent harm to recovery, given the lack of a positive association between PA and symptom burden under the supervision of a clinician. These results support the potential feasibility and tolerability of incorporating PA into acute rehabilitation plans following mTBI. However, it is also possible that participants who were already experiencing faster recovery were more inclined or able to participate in this research. As a result, a substantial proportion of the data in Study 3 may reflect this subgroup, and caution is therefore warranted when generalising the findings to the broader mTBI population. While further validation in larger samples is needed, these preliminary findings are encouraging. If PA within 14 days post-injury is indeed safe and tolerable, future research should focus on identifying the optimal type, timing, and intensity to support recovery.

Several possible explanations may account for this somewhat unexpected finding. One plausible explanation is the quality of care provided at the concussion clinics, where most mTBI participants were recruited. It is possible that clinicians consistently delivered well-individualised rehabilitation protocols, tailoring PA recommendations to each patient's tolerance level and recovery trajectory. This may have enabled participants to safely engage in PA without exacerbating symptoms, a factor that may not have been present in other studies. Another potential factor is the pre-injury athletic background of the mTBI participants. All were classified as athletes prior to their injury, and there is growing evidence to suggest that pre-injury physical fitness may confer resilience against the negative effects of mTBI. This may occur via several mechanisms, including enhanced neuroplasticity, improved autonomic regulation, and anti-inflammatory effects (Ferguson et al., 2021; Leddy et al., 2010, 2018; Mota et al., 2012; Ntiskas et al., 2024; Taylor et al., 2015). This preconditioning could have enabled participants to resume activity levels closer to baseline without experiencing the same degree of intolerance that may be observed in more sedentary populations. Another plausible explanation is that the absence of a group difference is simply a reflection of insufficient statistical power due to the relatively small sample size or the homogeneity in PA behaviours stemming from similar PA advice being given at the primary recruitment site. Future research involving larger, more diverse cohorts will be essential to validate these findings and further investigate the potential protective role of pre-injury fitness and the effectiveness of tailored rehabilitation in mTBI recovery.

The findings from the linear regression and compositional isotemporal substitution models also cannot be aligned directly with existing literature, primarily due to the novelty of applying CoDA in this context. Rather than supporting or contradicting previous studies, these analyses extend current knowledge by illustrating the potential of CoDA to yield clinically meaningful and interpretable insights into movement behaviour and recovery. Nevertheless, even in the absence of direct comparability, the lack of a significant association between light or moderate-to-vigorous PA and recovery time, across both unadjusted and adjusted models, was an unexpected finding. A substantial body of evidence supports the role of PA in promoting recovery following mTBI, although prior studies have typically investigated individual forms of PA in isolation, rather than as part of a 24-hour time-use composition (Buckley et al., 2022; Chizuk et al., 2022; Coslick et al., 2020; Grool et al., 2016; Leddy, 2025; Leddy et al., 2021; Seehusen et al., 2021). Further support comes from a recent systematic review and meta-analysis by Kuzik et al. (2025), which found positive associations between a higher proportion of time spent in moderate-to-vigorous PA and various health and wellbeing outcomes, based on studies that also employed CoDA. Given this context, it would have been reasonable to anticipate an association between the proportion of time spent in light or moderate-vigorous PA and recovery in the current study. The absence of such a finding may reflect the exploratory nature of the research and the limited statistical power afforded by the sample size. Further investigation with larger cohorts will be necessary to clarify whether these null results persist in more robust analyses.

Another somewhat surprising result was the initially significant association between sleep and time to recovery. As this correlation was positive, it would seem to suggest that increasing time spent sleeping was associated with increased time to recovery, in other words, that more sleep was detrimental for recovery. This appears counterintuitive, given the well-established role of sleep in supporting brain health, cognitive function, and recovery from injury (Asplund, 2024; Bacaro et al., 2024; Chennaoui et al., 2021; Kuzik et al., 2025; Lim et al., 2023; McLay et al., 2023; Ramar et al., 2021; Xie et al., 2013). However, this association seemed to be explained by a third factor, the initial symptom burden of participants. Therefore, it may just be that participants who required more sleep also had more severe symptoms, which both necessitated additional rest and prolonged recovery time. Although the association was no longer significant once initial symptom burden was included in the model, the original finding warrants exploration in future research.

7.8.2 Inflammation Modulation as a Proposed Mechanism of Action

The proposed mechanism introduced in Chapter 2 underlying the beneficial effects of PA on recovery from mTBI is its ability to modulate inflammation. Although direct evidence from human studies demonstrating the ability of PA to reduce neuroinflammation and enhance recovery following mTBI remains limited, findings from animal models offer preliminary support for this hypothesis. In particular, PA has been shown to attenuate post-injury inflammatory responses by inhibiting pro-inflammatory cytokine expression, reducing reactive microglial activation, and promoting anti-inflammatory M2-type microglial phenotypes (Kim et al., 2022; Mastrorilli & Vecchioli, 2024; Piao et al., 2013). Using a rodent TBI model, Kim et al. (2022) found that early initiation of exercise (beginning one day post-injury) led to reductions in microglial activation and the expression of pro-inflammatory cytokines such as interleukin-1, interleukin-13, and interleukin-1 β . Similarly, Piao et al. (2013) demonstrated that a delayed exercise intervention - commencing five weeks post-injury and continuing for four weeks - effectively modulated neuroinflammation, reducing interleukin-1 β and markers of microglial activation (e.g., galectin-3 and C1qB), and resulted in improved working memory and reduced lesion volume. Interestingly, earlier exercise initiation in this same study (at one-week post-injury) did not produce these benefits, suggesting that timing may be a critical factor in optimising post-mTBI PA interventions. While these findings support a potential anti-inflammatory mechanism, the translation of such effects to human populations remains complex and inconsistent, underscoring the need for further research to determine optimal exercise parameters in the context of mTBI recovery (Mastrorilli & Vecchioli, 2024).

Beyond animal models, a substantial body of literature supports the general anti-inflammatory effects of PA (Fedewa et al., 2003; Ford, 2002; Geffken et al., 2001; Godinho et al., 2021; Kreber & Griesbach, 2016; Mee-Inta et al., 2019; Mota et al., 2012; Nigro et al., 2021; Nilsson et al., 2018; Nimmo et al., 2013; Paolucci et al., 2018; Petersen & Pedersen, 2005; da Luz Scheffer & Latini, 2020; Swain et al., 2023). For instance, Nilsson et al. (2018) reported that reallocating 30 minutes proportionately to moderate-to-vigorous PA was associated with a significant reduction in CRP levels. Similarly, Abramson and Vaccarino (2002) found that greater frequency of PA was linked to a lower likelihood of elevated CRP, a finding supported by Ford (2002), who observed an inverse relationship between CRP and leisure-time PA.

Paolucci et al. (2018) further demonstrated that moderate continuous training significantly reduced pro-inflammatory cytokines such as TNF- α . In a 12-week intervention study, Kumar et al. (2022) found that regular PA was associated with reductions in multiple inflammatory markers, including interleukin-6. Supporting this further, Swain et al. (2023), in a systematic review and meta-analysis concluded that exercise interventions led to decreased levels of CRP, TNF- α and interleukin-6 in breast cancer patients. Collectively, this body of research supports the role of PA as a modulator of inflammation, providing a plausible neurobiological pathway through which PA may enhance recovery following mTBI. Nevertheless, the variability of findings across human studies, particularly in those with mTBI, points to the importance of future research that carefully considers timing, intensity, and individual differences in response to PA interventions.

7.8.3 Brain Derived Neurotrophic Factor

It is important to recognise that additional mechanisms likely underlie the documented benefits of PA on recovery from mTBI, along with modulating inflammation. One such mechanism involves the stimulation of proteins associated with neural plasticity, particularly brain-derived neurotrophic factor (BDNF) (Cordingley et al., 2024; Kreber & Griesbach, 2016; Mastroioli & Vecchioli, 2024; Szuhany et al., 2015). BDNF, a key neurotrophin, is highly expressed in brain regions integral to cognitive and motor function, including the hippocampus, hypothalamus, and cerebellum (Kreber & Griesbach, 2016; Szuhany et al., 2015). It plays a crucial role in neuronal survival, differentiation, and synaptic plasticity by supporting neurogenesis, dendritic growth, and long-term potentiation (Dinoff et al., 2016; Szuhany et al., 2015).

PA has been shown to acutely elevate BDNF levels in peripheral blood, with the magnitude of increase influenced by exercise type, intensity, and duration (Bazarian et al., 2023). Even a single exercise session can raise BDNF concentrations, while regular activity produces cumulative effects over time (Szuhany et al., 2015). Aerobic exercise, in particular, is associated with increased resting BDNF levels (Dech et al., 2019). Given that BDNF expression is often reduced following concussion, PA may support brain recovery by restoring BDNF levels and promoting neuroplasticity (Cordingley et al., 2024; Dech et al., 2019). Through its involvement in ionic regulation, metabolic support, and structural repair, BDNF may play a role in facilitating neural repair and functional recovery after brain injury (Cordingley et al., 2024; Dech et al., 2019; Kreber & Griesbach, 2016).

7.8.4 Using Physical Activity to Modify Inflammation: Clinical Considerations

At this point in the discussion, it is important to reiterate the purpose of examining time-use compositions in the acute phase post-mTBI, namely, as a potential behavioural strategy to modulate the inflammatory response and thereby support neural repair and recovery. If PA is to be leveraged as a therapeutic tool in this context, careful consideration must be given to how movement behaviours are recommended. According to the Sport Concussion in New Zealand National Guidelines (ACC, 2024b), a six-stage graduated return-to-activity framework is advised. This evidence-based protocol considers time since injury, symptom load, and PA tolerance, and is designed to guide individuals through a safe reintroduction to education, work, and/or sport. For example, Stage 2 of the protocol involves the gradual reintroduction of daily activities and light PA (e.g., short walks), while Stage 3 includes increased exercise intensity tailored to the individual's symptoms and tolerance. The fundamental principle is progressive re-engagement with PA in a stepwise manner that avoids significant symptom exacerbation (ACC, 2024b). While these particular guidelines represent an example specific to Aotearoa New Zealand, similar ones in other countries exist based on common global recommendations regarding PA and mTBI (e.g., Australian Institute of Sport, et al., 2024; Centers for Disease Control and Prevention, 2024; Parachute, 2024). Therefore, should future research build upon the current exploratory analyses by using CoDA to develop specific time-use recommendations, such guidance must be framed within the existing clinical protocols. It is essential that any suggested changes to movement behaviours are contextually grounded in the individual's recovery stage, symptom presentation and PA tolerance.

This point should be considered alongside the findings from Chapter 5, which revealed a negative correlation between T2 relaxation and recovery times. This observation invites critical reflection on the role of inflammation in the early stages of injury. While excessive or prolonged inflammation can be detrimental, the acute inflammatory response may instigate crucial repair functions. Thus, modulating this process through PA presents a delicate balance between facilitating healing and avoiding harm, to avoid modifying an inflammatory process that serves an important role acutely following injury. Although evidence strongly supports the anti-inflammatory and recovery-promoting effects of PA following mTBI (Buckley et al., 2022; Chizuk et al., 2022; Coslick et al., 2020; Grool et al., 2016; Leddy, 2025; Leddy et al., 2021; Seehusen et al., 2021), the timing, intensity, and duration of PA interventions remain critical factors. Numerous

studies have demonstrated the capacity of PA to modulate inflammation (e.g., Abramson & Vaccarino, 2002; Fedewa et al., 2003; Ford, 2002; Kim et al., 2022; Ma et al., 2013; Mastroianni & Vecchioli, 2024; Metsios et al., 2020; Nimmo et al., 2013; Paolucci et al., 2018; Swain et al., 2023), yet these benefits must be harnessed strategically. As such, future research should aim to determine the optimal initiation point and "dose" of PA that maximises its anti-inflammatory and neuroreparative benefits without interfering with the potentially beneficial aspects of the initial inflammatory response. Identifying this balance will be key to safely and effectively integrating PA into recovery strategies for mTBI.

7.9 Synthesising the Story

7.9.1 *Complementary Approaches*

The main findings from both the MRI case series and the group-level comparison in Studies 1 and 2 were well aligned. In both studies, quantitative T2 relaxation was measured and found to be elevated in participants with acute mTBI compared to healthy controls. Additionally, this elevation was not localised to a single region of interest but rather appeared to be widespread across the brain in both studies (see Figures 4.3 and 5.2). Moreover, several brain regions showing significant T2 relaxation time increases in the individual analyses were also significant at the group level, including the superior frontal gyrus, anterior cingulate cortex, and superior parietal lobule. This overlap strengthens confidence that the individual-level findings are meaningfully related to the group-level effects. It suggests that while individual case analyses provide rich, person-specific insights, they also reflect broader patterns observable across the cohort. This convergence also supports the validity of group-level analyses, which might otherwise be questioned if they failed to capture effects evident at the individual level. Taken together, the consistency between individual and group findings reinforces the potential utility of quantitative T2 relaxometry as a sensitive tool for detecting possible neuroinflammation following mTBI.

Nonetheless, some subtle differences between the individual and group results warrant consideration. Although elevated T2 relaxation times were widespread in both analyses, the group-level findings appeared slightly more focused in dorsal brain regions (e.g., within the superior frontal gyrus, pre- and post-central gyri, and superior parietal lobule). These nuanced distinctions underscore the complementary nature of individual- and group-level analyses: individual assessments can reveal unique patterns that may be diluted or “averaged out” in group

comparisons, whereas group-level data capture general trends that reflect the broader population. Integrating both perspectives offers a more comprehensive understanding of the neural impact of mTBI.

While individual and group-level analyses offer distinct advantages in a research context, their combined use provides greater value and insight. The case series presented in Study 1 allowed for an in-depth exploration of the novel application of quantitative T2 relaxometry. Examining each participant individually enabled a detailed understanding of T2 relaxation patterns within the context of their unique clinical profiles - including symptom reports, history of mTBI, and individual Brain Injury Screening Tool (BIST) scores. This approach facilitated an initial investigation into the potential utility of T2 relaxometry as an objective marker of neuroinflammation. By comparing each participant's data to the average values of healthy controls, this study demonstrated the sensitivity of T2 relaxometry to subtle brain abnormalities not captured by standard clinical imaging protocols. However, the findings from the case series, while rich in detail, would lack external validity without the group-level comparison provided in Study 2. Incorporating a group analysis enabled more robust conclusions to be drawn regarding the significance of elevated T2 relaxation values and their potential physiological implications.

The Threshold Free Cluster Enhancement (TFCE) permutation testing conducted in Study 2 (with 20,000 permutations) added a substantial strength to the research that would not have been possible with the case series alone. This statistical analysis involved calculating a T2 value for each voxel in each participant's T2 map and comparing these to a null distribution generated through 20,000 random permutations of the data. In doing so, it can identify significant clusters of voxels based on both their signal intensity (i.e. higher t-values) and spatial extent (i.e. contiguous areas) and is relatively robust to smoothing, outliers and has minimal underlying assumptions about the data (such as normality) (Smith & Nichols, 2009). The method takes raw T2 maps and outputs an image whereby the voxel-wise values represent the extent of cluster-like local spatial support. While many techniques use spatial information about neighbouring voxels to boost confidence in significant clusters, cluster-based thresholding techniques are limited by needing to arbitrarily assign the initial cluster-forming threshold that may end up having a substantial impact on the results (Smith & Nichols, 2009). Instead, TFCE essentially integrates information across all thresholds and notes both their intensity and the spatial extent.

Together, the complementary strengths of the analytical approaches taken in Studies 1 and 2 enabled this research to provide both nuanced, individual-level insight and generalisable evidence regarding the brain's inflammatory response following mTBI. This integrated analysis strengthens the case for T2 relaxometry as a clinically meaningful tool in the assessment of brain injury.

7.9.2 *The Dual Focus*

While this thesis had two central themes - potential ways of (1) *measuring* neuroinflammation and (2) *modifying* it - it is important to highlight the interrelated nature of these objectives. I like to conceptualise this thesis as examining two sides of the same coin. In scientific research, we often ask how we can measure or monitor a phenomenon, or how we can change an outcome. This thesis asks both questions. The first two studies explored how neuroinflammation may be measured, while the third study investigated how it might be modified. Although the studies are largely exploratory in nature, particularly Study 1 (the MRI case series) and Study 3 (the PA analysis), they offer valuable insights. Only by improving our ability to measure and monitor biological processes can we begin to meaningfully intervene when they are maladaptive. Together, the findings presented in Chapters 4, 5, and 6 contribute to our understanding of recovery following mTBI by addressing two sides of a core pathophysiological process: exploring a way to quantify potential neuroinflammation and then exploring the allocation of movement behaviours as a way to mitigate it when necessary. Ultimately, this thesis sought to build a more complete picture of neuroinflammation in mTBI, from detection to intervention, advancing both scientific understanding and clinical potential.

7.10 Clinical Implications

7.10.1 *Individualising Treatment for Mild Traumatic Brain Injury*

Identifying regions with increased T2 relaxation times and potential neuroinflammation offers valuable insights into the brain abnormalities that may be present acutely following mTBI. These findings could have important clinical implications by enabling more individualised treatment approaches. Basing treatment decisions on a patient's specific neurobiological profile - for instance, using T2 relaxometry to stratify patients by the severity of possible inflammation - could allow clinicians to better tailor recovery plans. For example, patients displaying more pronounced abnormalities on T2 scans might benefit from an extended stand-down period before

returning to competitive sports or benefit from more conservative physical and cognitive activity plans during early recovery. This would reduce the risk of an overly lenient approach to rest and rehabilitation. It is important to note that the intention is not to suggest that research-grade MRI scans are a routine or universally accessible diagnostic tool for all mTBI cases. However, for individuals with a high symptom burden, complex clinical presentation, or a history of prolonged recovery, advanced imaging may already be under consideration. In such cases, incorporating quantitative T2 relaxometry as an adjunct to standard MRI protocols could add diagnostic value and aid in decision-making. Consideration would need to be given to optimising scan time, reducing associated costs and standardising acquisition parameters as well as processing pipelines to ensure the feasibility of clinical implementation.

Moreover, the detection of inflammation-related abnormalities may prompt the inclusion of targeted anti-inflammatory strategies in the patient's treatment plan - interventions that might not otherwise have been considered. For instance, the potential role of pharmacological agents to mitigate inflammation in the acute phase of mTBI warrants further investigation. Alternatively, behavioural strategies such as tailored PA could offer a non-pharmacological means of modulating inflammation, especially given the well-established relationship between PA and inflammatory processes (da Luz Scheffer & Latini, 2020; Godinho et al., 2021; Kreber & Griesbach, 2016; Mee-Inta et al., 2019). This clinical application reinforces the connection between the MRI findings discussed in Studies 1 and 2 and the PA-focused analysis in Study 3. If T2 relaxometry can be used to detect and quantify possible neuroinflammation, PA may serve as a practical, personalised intervention to modulate this response and support optimal recovery. Ultimately, the goal is to move toward a model of care that recognises inter-individual variability in inflammatory responses and enables treatments to be adapted accordingly, contributing to safer, more efficient return to play or work.

7.10.2 Creating Time-use Budgets

With the detection of possible neuroinflammation and the need to mitigate it to support effective recovery, it is important to provide patients with clear, specific guidance on which types of PA may be most beneficial. A key clinical implication of this research is the potential to introduce “time-use budgets” as a collaborative tool between clinicians and patients. These plans can help structure a balanced daily routine by allocating proportions of time to various movement behaviours. Although further validation with larger samples is necessary, CoDA offers a promising

method for determining the optimal distribution of movement behaviours to support recovery. This information could then inform personalised clinical recommendations. Current clinical guidelines, such as the Consensus Statement on Concussion in Sport, or the Sport Concussion in New Zealand National Guidelines, provide useful frameworks but do not account for the interdependent nature of movement behaviours across a 24-hour period. It is essential to consider PA types not as isolated or fixed quantities, but as interconnected proportions within a whole. This way, we can not only recommend what type of movement behaviour would be beneficial to increase but can specifically suggest what movement behaviour(s) to proportionally decrease.

The analyses presented in Study 3 offer valuable insights in this regard and could support the development of practical time-use budgets in clinical settings. These plans would outline recommended allocations of sedentary behaviour, light PA, moderate-to-vigorous PA, and sleep, tailored to enhance the likelihood of a successful recovery. With further research, CoDA-derived “ideal” PA ratios could underpin more precise and effective PA prescriptions, enabling patients to implement evidence-informed movement patterns into their daily routines.

7.10.3 Monitoring Recovery and Identifying At-Risk Groups

In addition to informing acute treatment plans, this research contributes to the critical need for ongoing recovery monitoring and the identification of patients at risk of poor outcomes. While accurate diagnosis and effective early rehabilitation are vital, there remains a pressing need for objective tools to track recovery progress and evidence-based strategies to improve long-term outcomes, particularly in complex cases. In some instances, neuroimaging such as MRI may not be deemed necessary during the acute phase (e.g., when patients report minimal symptoms and show unremarkable scores on objective assessments). However, imaging may become more valuable in the subacute or chronic phases to support recovery monitoring. For patients showing signs of delayed or complicated recovery, quantitative T2 relaxometry could provide a more detailed picture of brain health. If elevated neuroinflammation is detected, treatment plans could be revised accordingly, for example, by intensifying anti-inflammatory strategies, adjusting PA prescriptions, or modifying return-to-play/work/education protocols. To implement this approach effectively, further longitudinal research is required to establish normative T2 relaxation values across different stages of recovery. These baselines would enable meaningful comparisons, facilitating the identification of abnormal or concerning patterns in complex cases.

Given the well-established links between brain trauma, neuroinflammation, and the increased risk of long-term psychological and neurological conditions, serial T2 relaxometry scanning may offer a valuable tool for long-term monitoring (Boulton & Al-Rubaie, 2025; Calderone et al., 2024; Delmonico et al., 2022; Dodd et al., 2022; Elder et al., 2019; Freire et al., 2023; Gardner & Yaffe, 2015; Hossain et al., 2022; Howlett et al., 2022; Kim et al., 2023; Pasternak et al., 2016; Risbrough et al., 2022; Simon et al., 2017; Tagge et al., 2018). For example, Ayerra et al. (2025) demonstrated a mechanistic link between T cells, peripheral immune cells recruited by proinflammatory cytokines and chemokines, and neurodegeneration. Using wild-type mice and a controlled cortical impact model of TBI, they assessed behavioural, histological, and immune responses. Notably, in the absence of T cells, neurodegeneration was attenuated and neurological outcomes improved. Objective imaging markers such as quantitative T2 relaxometry could help identify chronic inflammatory responses and individuals at increased risk of neurodegenerative outcomes. This may facilitate earlier interventions aimed at reducing chronic neuroinflammation and mitigating preventable, long-term damage.

7.10.4 Objectivity to Complement Subjectivity

A key clinical contribution of this research is the advancement of objective measurement tools to complement existing subjective symptom reports. Currently, diagnostic and prognostic decisions for mTBI are heavily reliant on patient self-reporting. While patient-reported symptoms are an important aspect of clinical care, they are vulnerable to both intentional and unintentional inaccuracies. For instance, social desirability bias may lead patients to over- or under-report symptoms based on perceived expectations from teammates, family, or clinicians (Van de Mortel, 2008). In sports settings, where mandatory stand-downs and structured return-to-play protocols exist, athletes may deliberately minimise symptom severity to expedite return to competition (Hainline et al., 2013; Torres et al., 2013). Additionally, self-reports may be unintentionally inaccurate due to poor memory recall or unconscious bias, further limiting their reliability. Given the complex and often "invisible" nature of mTBI, there is a critical need for objective tools that can validate or supplement subjective accounts. Quantitative T2 relaxometry is one such method, offering a potentially sensitive and non-invasive marker of neuroinflammation. With further validation, particularly against established biomarkers such as blood-based indicators of inflammation or histology, T2 relaxometry could enhance diagnosis, monitor recovery, and inform clinical decisions. This would address the limitations of relying solely on subjective data.

There is also a known disconnect between subjective symptom reports and standard clinical imaging, which often fails to detect abnormalities in patients with ongoing post-concussive symptoms (Mayer et al., 2015). More nuanced imaging modalities that can detect subtle or diffuse brain abnormalities post-mTBI would enhance clinicians' ability to validate patient experiences and justify continued treatment. Objective tools could also help determine whether a patient's brain has fully recovered before resuming pre-injury activity levels - an important consideration in preventing further injury, neurodegeneration, or second impact syndrome during a vulnerable period post-injury (Engelhardt et al., 2021; Risbrough et al., 2022; Vagnozzi et al., 2007). Establishing robust, objective biomarkers is especially important given the subtle, non-specific nature of mTBI symptoms and the limited sensitivity of conventional diagnostics (Leddy, 2025).

Another challenge in managing mTBI is its heterogeneous recovery trajectory. While some individuals recover quickly with minimal intervention, others experience prolonged symptoms and lasting functional impairments (Danielli et al., 2023; Hossain et al., 2022; Kara et al., 2020; McInnes et al., 2017; Neumann et al., 2023; Polinder et al., 2018; Verboon et al., 2021; Visser et al., 2022). Identifying those at risk of delayed recovery is therefore essential for providing timely and individualised care. Although FDA-approved blood biomarkers, such as ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP), show promise for acute-phase diagnosis, there remains a lack of objective biomarkers for patients presenting one to two weeks post-injury, when many seek clinical evaluation (Diaz-Arrastia et al., 2014; Kobeissy et al., 2024). A deeper understanding of post-mTBI neurological changes, facilitated by objective imaging, could help identify individuals with a heightened risk of poor outcomes. In particular, an objective biomarker of neuroinflammation could inform clinical timing for anti-inflammatory interventions, potentially mitigating secondary injury cascades and long-term neurodegenerative processes (Pasternak et al., 2012).

7.10.5 Catalysing Future Possibilities: Targeted Treatment for Neuroinflammation

Looking ahead, there is considerable potential for targeted therapies if neuroinflammation can be reliably tracked post-injury. While T2 relaxometry already holds clinical relevance, its *future* applications may be transformative, especially if further validation supports its use as a non-invasive, longitudinal biomarker of neuroinflammation. Chronic inflammation is known to play a pivotal role in the development of persistent symptoms following mTBI and is implicated in a wide range of adverse health outcomes and neurodegenerative processes (Ayerra et al., 2025;

Calderone et al., 2024; Clarke et al., 2024; Corps et al., 2015; da Luz Scheffer & Latini, 2020; Kim et al., 2023; Markovic et al., 2021; Mee-Inta et al., 2019; Pasternak et al., 2016; Shi & Yong, 2025; Simon et al., 2017). As such, developing reliable methods for monitoring neuroinflammation may be instrumental in preventing long-term deterioration following mTBI by facilitating targeted treatment.

Despite its significance, neuroinflammation remains an underexplored therapeutic target in the context of mTBI (Simon et al., 2017). However, several relevant promising avenues are emerging. Microglia, the central nervous system's resident immune cells (discussed in detail in Chapter 1), play a central role in the inflammatory cascade following injury. Microglial replacement therapies are being explored as a strategy to reduce inflammation and promote neural repair (Bolte & Lukens, 2021). Pharmacological approaches are also showing promise. For instance, minocycline has been demonstrated to inhibit microglial activation, reduce interleukin-1 β expression, limit cerebral oedema, and preserve BBB integrity (Thapa et al., 2021). More recently, Bano et al. (2025) investigated a microglia-targeted intervention focused on NADPH oxidase 2 (NOX2), an enzyme in microglia responsible for producing reactive oxygen species and contributing to neuroinflammation and neurodegeneration. Their findings identify NOX2 as a critical driver of the secondary injury cascade and a compelling therapeutic target for attenuating neuroinflammation.

Similarly, Hu et al. (2022) examined the use of hydroxychloroquine (HCQ) in a mouse model of TBI to inhibit inflammation via the TLR4/NF- κ B signalling pathway. HCQ administration significantly reduced neuroinflammatory responses, including microglial activation, immune cell infiltration, BBB disruption and brain oedema, ultimately improving neurological outcomes. Izzy et al. (2025) explored a novel immunomodulatory approach involving intranasal delivery of an anti-CD3 monoclonal antibody. This treatment enhanced the migration of regulatory T cells to the brain, promoting interleukin-10 and the beneficial phagocytic function of microglia while reducing microglia-induced inflammation.

Kim et al. (2023) have also demonstrated the efficacy of early anti-inflammatory treatment using cyclosporine A, dexamethasone, or cholecalciferol in a mouse model of TBI. These treatments led to significantly lower peak expression of pro-inflammatory cytokines TNF- α , interleukin-1 β , and interleukin-6, and were associated with reduced inflammatory damage compared to untreated controls. Finally, oestrogen has been identified as a potentially

neuroprotective agent, with evidence suggesting it may act through the inhibition of neurotoxic astrocyte pathways and the attenuation of neuroinflammation (Boulton & Al-Rubaie, 2025; Wang et al., 2021).

Together, these findings underscore the importance of investigating diverse and targeted treatment modalities tailored to individual inflammatory profiles. To achieve this, future research must work toward identifying distinct inflammatory phenotypes among individuals with mTBI. These phenotypes should account for multiple modulating factors, including age, sex, genetic predisposition, secondary insults, and biomarker availability (e.g., serum- or imaging-derived), to inform precision treatment strategies (Simon et al., 2017). Despite inflammation's central role in the pathophysiology and long-term consequences of mTBI, no effective treatments currently exist to mitigate neuroinflammation and promote central nervous system recovery. With the advent of objective tools for detecting, quantifying, and monitoring inflammation, emerging interventions, such as those highlighted above, could offer a path forward. Effective therapies for neuroinflammation require a precise understanding of the cellular mechanisms involved, as well as an understanding of the temporal and topographical properties of neuroinflammation. Targeted treatments may ultimately provide a means of preserving brain structure and function post-injury. Advancing our understanding of mTBI-related neuroinflammation will be essential to the development of effective, individualised therapies in the future.

7.11 Research Strengths

7.11.1 Novel Contributions

A key strength of this work lies in its original contribution to the field of brain trauma through the integration of underutilised methods into novel clinical contexts. I address a significant gap in the neuroimaging literature by evaluating the use of quantitative T2 relaxometry to detect subtle brain abnormalities following mTBI - a context in which this method has not previously been studied. While quantitative T2 relaxometry is well established in clinical applications such as epilepsy, subjective cognitive decline, and multiple sclerosis (Adel et al., 2023; Misbah et al., 2024; Rivas-Fernández et al., 2025; Sarkar et al., 2023), its application to brain trauma remains limited, with only one known case study to date (Pedersen et al., 2020). Applying this technique to an mTBI population represents a novel and important step toward identifying biomarkers of injury that are not captured by standard imaging protocols. This broadens the clinical utility of T2

relaxometry and offers new insights into the pathophysiology of this prevalent but poorly understood condition. Moreover, this research also addresses a gap in the PA literature by applying CoDA to investigate time-use behaviours in individuals with acute mTBI, an approach that, to the best of my knowledge, has not been previously undertaken. Although exploratory, this work advances the field by shifting the focus from isolated PA metrics to a more ecologically valid, holistic analysis of how individuals allocate their time post-injury. As with T2 relaxometry, CoDA is a validated analytical method, but its novel application in the context of mTBI represents a meaningful methodological advancement.

The distinct originality of this research is grounded in its methodological innovations. Quantitative T2 relaxometry offers two major advantages: first, it may detect subtle neuroinflammation that escapes standard clinical imaging; and second, it quantifies tissue changes, reducing the subjectivity inherent in qualitative MRI interpretation and enabling more precise intra- and inter-individual comparisons. Similarly, the application of CoDA provides a nuanced understanding of time-use behaviours by capturing relative, compositional patterns rather than absolute measures - an important shift in how PA and sedentary behaviour are conceptualised in recovery contexts. Together, these innovations represent a significant contribution to both neuroimaging and PA research in mTBI. Each chapter of this thesis reflects a strong emphasis on advancing the field through novel methods, filling critical gaps in the literature, and ultimately laying the groundwork for more personalised and evidence-based approaches to diagnosis, monitoring, and rehabilitation following mTBI.

7.11.2 Carr-Purcell-Meiboom-Gill Sequence

The MRI sequence used to estimate T2 relaxation values, called the Carr-Purcell-Meiboom-Gill (CPMG) sequence (Carr & Purcell, 1954; Meiboom & Gill, 1958), offers several advantages that strengthen the methodological rigour of Studies 1 and 2. CPMG enables precise and reproducible T2 relaxation time estimates by employing a series of 180-degree refocusing pulses, which effectively reduce the impact of magnetic field inhomogeneities and better isolate T2 decay from other confounding effects, such as susceptibility artefacts, compared to conventional spin-echo sequences (McIntosh, 2013; Yamada et al., 1989). An additional strength of CPMG is that it acquires multiple echoes within a single repetition time (TR), which improves both the signal-to-noise ratio (SNR) and acquisition efficiency (St-Onge, 2024). This efficiency, reflected in shorter

scan durations, is particularly valuable when scanning clinical participants who may be fatigued or otherwise symptomatic due to their injury.

Additionally, the original Carr-Purcell method, that involved a 90-degree excitation pulse followed by a chain of 180-degree refocusing pulses all along the same axis (e.g., the x-axis) was sensitive to imperfections in the refocusing pulses, such as when the flip angle is slightly less than 180-degrees (Deoni, 2010; St-Onge, 2024). Ideal 180-degree pulses generate true spin echoes, but imperfect pulses can lead to the formation of stimulated echoes (Cheng et al., 2012). This occurs when a portion of the transverse magnetisation is not completely refocused and is temporarily stored as longitudinal magnetisation, which is then recalled by subsequent RF pulses (Deoni, 2010). These stimulated echoes occur at non-standard echo times and can distort the expected signal decay curve, leading to inaccurate T2 estimation. However, the Meiboom-Gill improvement on the original method addressed this issue by applying the initial 90-degree pulse along one axis (e.g., the x-axis) and then applying the series of 180-degree refocusing pulses along a perpendicular axis (e.g., the y-axis). This phase cycling distributes any errors so that they are averaged across time, increasing the accuracy of the echo train (Brown et al., 2014; St-Onge, 2024). Therefore, the use of this improved sequence represents another methodological strength of the MRI analyses presented in this thesis.

7.11.3 Recovery Re-scans and Sample Size

A notable strength of Study 1 is the inclusion of a small subset of participants who underwent repeat MRI scans following clinical recovery. Although the number of re-scanned participants was limited, the longitudinal data generated is highly valuable in advancing our understanding of mTBI. Specifically, it offers insight not only into the brain's acute response to injury but also into the trajectory of neurological recovery over time. This longitudinal component allows for an initial exploration of whether clinical recovery is paralleled by neurobiological recovery. In particular, the partial or full reduction in T2 relaxation times observed in regions that were significantly elevated during the acute phase offers preliminary support for the hypothesis that brain tissue is undergoing physiological recovery in tandem with clinical improvement. Moreover, the resolution of these elevated values reinforces the interpretation that increased T2 relaxation times in the acute scans were related to injury-specific pathology rather than incidental variation.

However, while these findings represent an important first step in mapping longitudinal recovery processes, the small sample size limits their reliability and generalisability. Further research with larger longitudinal cohorts is essential to validate and expand upon these preliminary observations. In contrast, a key strength of Study 2 is the sample size. With 40 participants in both the mTBI and healthy control groups, the study achieves a substantial cohort for an MRI investigation, particularly given the financial cost and participant burden associated with neuroimaging research. This relatively large sample allows for more robust statistical analyses, extending the findings of the first study and increasing the generalisability of the findings.

7.11.4 Physical Activity Recording Devices

A key strength of Study 3 is the use of an objective, accelerometer-based device to capture movement behaviours. This approach enabled precise quantification of PA, improving data reliability while minimising recall bias and the limitations associated with subjective reporting. Furthermore, the low participant burden associated with passive monitoring via wearable devices represents a practical advantage over traditional self-reported activity logs, which are often time-consuming and prone to inaccuracies. Although objective activity monitors have been utilised in prior research (e.g., Neely et al., 2022; Petit et al., 2022; Seehusen et al., 2021), much of the existing literature on daily PA and mTBI recovery continues to rely on subjective measures (e.g., Boigontier et al., 2020; Buckley et al., 2022; Coslick et al., 2020; Grool et al., 2016; Howell et al., 2016; Krainin et al., 2021; Remigio-Baker et al., 2020; Wilson et al., 2020). Another major strength lies in the extended wear time of the activity tracking devices, with participants wearing the sensors for an average of 11.5 days. This prolonged monitoring period yielded a robust dataset for calculating daily averages, thereby enhancing the internal validity of the findings. This wear time also supports the tolerability of the Axivity AX3 devices as an objective measurement method.

7.11.5 Real World Impact

In addition to advancing our scientific understanding of mTBI, this research offers tangible clinical benefits. While the specific clinical implications have been outlined in the preceding section, it is worth reiterating that the potential real-world impact of this work represents a key strength. With further validation, such as comparison with established blood-based markers of inflammation, or replication in larger, more diverse samples, both quantitative T2 relaxometry and CoDA hold promise for clinical application. These methodologies could ultimately support more

accurate diagnosis, personalised recovery monitoring, and improved rehabilitation strategies, thereby contributing to better outcomes for individuals recovering from mTBI. Therefore, while contributing to theoretical concepts and general understanding is important, this research also has tangible benefits and real-world applications.

7.12 Research Limitations

Careful consideration of relevant limitations to each of the three studies of this thesis have been included in their respective chapters (Chapters 4, 5 and 6). To avoid repetition, the current section acknowledges only additional limitations that can be commonly applied to multiple chapters.

7.12.1 Making Causal Inferences

A key limitation of this research, and quantitative MRI in general, lies in the difficulty of inferring underlying biological processes, such as neuroinflammation, using neuroimaging alone. Although advanced techniques like quantitative T2 relaxometry are sensitive to microstructural alterations in brain tissue, they do not directly measure cellular or molecular processes (e.g., compared to taking a biopsy). For instance, elevated T2 relaxation times may reflect increased extracellular free water, which may be interpreted as indicative of neuroinflammation. However, this method is inherently indirect and non-specific because each millimetre-scale voxel encompasses thousands of neurons (Braitenberg & Schüz, 1998). Therefore, elevated T2 relaxation times could also result from mixed pathological processes, such as haemorrhage, cellular atrophy or gliosis, although this is unlikely in a sample of *mild* TBI. Without corroborating evidence from histological, biochemical, or molecular imaging studies, it is not possible to definitively attribute observed changes in T2 signal to inflammatory processes alone. Although Studies 1 and 2 together support the finding of increased T2 relaxation times in mTBI, they remain primarily hypothesis-generating regarding the interpretation that this increase reflects underlying neuroinflammation. As such, the interpretations presented in these studies regarding the biological mechanisms underlying mTBI must remain cautious.

To strengthen the hypothesis that elevated T2 relaxation times reflect brain inflammation, future studies should incorporate additional, complementary imaging modalities. For example, diffusion imaging techniques, such as free water imaging, can provide information about the magnitude and directionality of water diffusivity in white matter tracts. These measures may be

sensitive to key components of the inflammatory response, including glial activation and proliferation, immune cell infiltration, and increases in extracellular water (Neumann et al., 2023; Pasternak et al., 2012; Sun et al., 2024). Integrating T2 relaxometry with such approaches would help contextualise findings within a broader biological framework, although alternative neuroimaging modalities have their own unique limitations to consider too. Ultimately, this limitation of T2 relaxometry highlights the need for multimodal imaging strategies and underscores the importance of combining quantitative MRI with biological markers to more confidently interpret the presence and role of neuroinflammation in mTBI.

7.12.2 The Sample

One notable limitation of this work is the inclusion of only male participants, which reduces the external validity and generalisability of findings to the broader mTBI population. This decision aimed to maximise the feasibility of collecting high-quality MRI data. Including both sexes would have necessitated stratified analyses to account for potential sex-based differences in mTBI presentation, differences that may be influenced by hormonal fluctuations or anatomical factors such as neck musculature (Koerte et al., 2020; Merritt et al., 2019; Solomito et al., 2019; Tabor et al., 2022). For instance, Di Battista et al. (2020) reported a divergent relationship between inflammation and symptom burden in males and females: in males, interferon-gamma (IFN- γ ; a cytokine and modulator of the immune response) was positively correlated with symptoms, whereas in females, symptom burden negatively correlated with IFN- γ , TNF- α , and myeloperoxidase (an enzyme found in neutrophils and monocytes that has a role in the immune response) (Di Battista et al., 2020). Therefore, sex-based differences should be considered when looking at the pathophysiology and recovery trajectory of mTBI, including a possible sexually dimorphic inflammatory response (Tabor et al., 2022). Additionally, the menstrual cycle introduces variability in circulating hormones such as oestrogen and progesterone, which may influence both central and peripheral inflammatory processes. Oestrogen and progesterone have been shown to suppress proinflammatory cytokines (e.g., interleukin-1 β , interleukin-6, TNF- α), enhance anti-inflammatory cytokines (e.g., interleukin-10 and transforming growth factor beta [TGF- β]), and reduce cerebral oedema (Tabor et al., 2022). The selection of only males for this research therefore allowed for a substantial sample size to be collected for group comparison of mTBI versus controls to test the feasibility of T2 relaxometry to be used in this context without introducing confounding factors due to sex-based differences in pathomorphology.

Additionally, all three studies included in this thesis involved participants who sustained an mTBI exclusively in sports settings - that is, each case was classified as a sports-related mTBI occurring during training or competition. While this recruitment strategy offers advantages in terms of sample homogeneity and the reduction of certain confounding variables (e.g., general fitness or cardiovascular health), it also limits the generalisability of the findings. As sports-related mTBI account for only ~20% of all mTBI, the applicability of the results of all three studies is uncertain (Safinia et al., 2016; Theadom et al., 2020). In addition, several potentially influential confounding variables were not systematically accounted for. These include genetic predispositions, the biomechanical characteristics of the current injury, and the use of medications such as anti-inflammatories. Such factors could influence levels of fluid accumulation and, consequently, the T2 relaxometry results reported in Studies 1 and 2. For instance, it is possible that a genetic susceptibility to exaggerated inflammatory responses may underlie the elevated T2 relaxation times observed in certain participants, yet this remains unexplored. To enhance interpretability and clinical relevance, future research should aim to collect more comprehensive background information for all participants. This could include standardised neuropsychological assessments conducted at the same time as neuroimaging, as well as detailed data on medication use, comorbid medical conditions, and prior injuries. These additions would allow for a more nuanced analysis of the relationship between individual characteristics and neuroimaging findings and help identify potential moderating factors influencing recovery trajectories post-mTBI.

7.12.3 Timing

Other methodological constraints also warrant consideration. Timely access to participants in the acute post-injury phase was challenging - either due to individuals not seeking immediate care or facing delays in appointment availability. To try and mitigate this, I worked closely with the lead sports physician at the primary recruitment site to accelerate participant contact. All MRI scans and wearable device fittings were completed within 14 days post-injury, but with a mean first-visit time of 10.7 days. This means that truly acute data were not captured and therefore the quantification of the inflammatory response may be incomplete. For example, the initial cytokine, chemokine and microglia response may peak within the first week (Alam et al., 2020) and this timeframe would not have been captured for most of the participant MRI scans. While logistically very challenging, earlier data collection post-injury would offer valuable insights into the

immediate pathophysiological changes and early behavioural responses during a critical period of recovery.

Additionally, the majority of the mTBI participants (87.5%) were recruited from a single specialised clinic, Axis Sports Concussion Clinic in Auckland, NZ. This may introduce sampling bias, as individuals who seek specialised care may differ systematically from those who do not seek care or who are managed by general practitioners or physiotherapists. These differences might relate to symptom severity, access to resources, or motivation for recovery. For example, it may be that patients with more severe mTBI are generally the ones to seek care at a specialised clinic - limiting the generalisability of the findings to those with milder forms of mTBI. While the direction and magnitude of this potential bias are unclear, future research should strive to recruit more diverse samples across multiple care settings to enhance external validity.

7.12.4 Recovery

A considerable limitation not only of this research but the mTBI field in general, lies in how recovery was operationalised. For most participants, recovery status was determined by their treating physician and documented in their electronic medical records. In each case, this was a careful consideration of their symptom burden as well as more objective assessment measures (full clinical processes detailed as per previous publications; Kara et al., 2020; McGeown et al., 2020). This clinical decision-making process offers a standardised and clinically relevant benchmark. However, it is still vulnerable to limitations. For example, it may be that their subjective symptom reports indicated recovery while their underlying brain damage was not “recovered” to baseline levels. Or their subjective reports or assessment outcomes may be intentionally or unintentionally inaccurately represented due to a desire to return to play as quickly as possible. Moreover, recovery may hold different meanings for different individuals, raising the broader question of how best to define and measure it. Ultimately, the question of what *recovery* really means and how we can meaningfully quantify it is still open for investigation.

Lastly, as clinical recovery for most of the mTBI group was calculated based on the participants’ discharge date from the concussion clinic that they were recruited from, appointment delays may have introduced inaccuracies in this measure. For example, participants may have been clinically recovered shortly after an appointment but needed to wait until their following appointment before being formally discharged. This means that many of the recovery times recorded for participants may be overestimating their true clinical recovery. Moreover, there could

also be delays present for the subset of participants that were not recruited through a concussion clinic and had their recovery time calculated based on follow up BIST questionnaires. As the follow up BISTs were sent weekly to these participants, it may be that they were recovered shortly after one BIST, but it was not until the following BIST was completed that a low enough score was obtained that a recovery time was calculated by the research team. More research into the way we conceptualise and quantify recovery is crucial in this field.

7.13 Future Directions

7.13.1 Longitudinal Data

The findings from this research not only advance our understanding of the pathophysiology of mTBI and its assessment via neuroimaging and PA measures but also open several important avenues for future research. These directions logically extend from the current studies and address the key limitations and unanswered questions that have emerged. Firstly, a critical extension of this research is the development of longitudinal designs to track the temporal course of recovery. Due to resource constraints, only a small subset of participants in Study 1 underwent follow-up MRI scans. However, longitudinal data were invaluable in revealing potential changes in T2 relaxation times over time. A fully powered longitudinal study that captures imaging and PA data at multiple recovery stages - baseline (pre-injury, if possible), acute, subacute, and recovery - would provide a richer understanding of the temporal dynamics of neuroinflammation and recovery.

This type of future research could explore the dynamic and complex relationship between inflammation and recovery from injury more comprehensively. In particular, the exploratory negative correlation found between T2 relaxation times and recovery in Study 2 only touches the surface of a very important avenue for research. Further research is needed to validate this relationship and clarify the mechanistic pathways that might link acute inflammatory processes, as reflected in T2 relaxation times, to recovery trajectories following mTBI. For example, are there specific aspects of this inflammatory response that are most beneficial for recovery and do these factors differ systematically between patients? Investigating the specific link between acute inflammation and recovery trajectories further may help to delineate the diverse and largely unpredictable outcomes post-mTBI. Using a measure of neuroinflammation, such as T2 relaxometry, at multiple time points during recovery could help us understand at what point the

brain's inflammatory response moves from being beneficial to detrimental. That is to say, is there a certain time point where the negative correlation found here between T2 relaxation times and recovery flips to a positive association - indicating that the inflammatory response has now become deleterious and associated with poor recovery outcomes. If research can pinpoint a critical time where inflammation is no longer beneficial for brain repair and healing, then intervention could be focused during this pivotal time. Ultimately, this future research could ask at what point during recovery does neuroinflammation become harmful and what can we do to mitigate this?

Longitudinal data could also explore the interplay between PA and neuroinflammation more comprehensively. While Study 3 investigated associations between PA patterns and recovery outcomes, longitudinal studies are needed to assess whether and how specific PA behaviours can influence T2 relaxation over time. While I acknowledge that this type of design presents financial and logistical challenges, particularly to obtain baseline and very acute measures immediately after injury, it would allow for analysis of how early movement patterns relate to subsequent brain changes and recovery outcomes. This type of research would directly inform practical guidelines and recommendations that clinicians could incorporate into their treatment plans. Doing so could help to further validate the use of T2 relaxometry as a *measure* of neuroinflammation and PA as a behavioural method to *modify* neuroinflammation.

7.13.2 Advancements in MRI Acquisition Techniques

The long acquisition times required to obtain T2 relaxation estimates (~12 minutes in the current studies) can be clinically prohibitive (Gruenebach et al., 2023; Hilbert et al., 2018). However, recent advancements in MRI acquisition sequences offer promising opportunities to build on current findings while enhancing clinical utility. Techniques such as parallel imaging, simultaneous multi-slice acquisition, and AI-accelerated sequences have substantially reduced scan times (Feinberg & Setsompop, 2013; Larkman & Nunes, 2007; Nonninger et al., 2025; Wang et al., 2021). For example, AI-assisted reconstruction methods can generate high-resolution images from fewer measurements by leveraging large datasets and learned signal models (Wang et al., 2021).

One particularly promising technique is GRAPPATINI, an accelerated T2 mapping sequence that may reduce scan times, lower participant burden, and increase clinical applicability (Gruenebach et al., 2023; Hilbert et al., 2018). GRAPPATINI integrates two approaches: parallel imaging (GRAPPA) and a model-based rapid acquisition method (MARTINI) (Hilbert et al.,

2018). This sequence not only provides quantitative T2 relaxation values but also produces synthetic T2-weighted images with multiple echo times, all without increasing acquisition time. In a study involving 14 healthy participants, Hilbert et al. (2018) demonstrated that GRAPPATINI enabled highly reproducible, whole-brain T2 mapping at a tenfold acceleration, achieving an acquisition time of just 1:44 minutes.

Gruenebach et al. (2023) also evaluated the clinical feasibility and reliability of GRAPPATINI for brain imaging in a sample of 62 healthy volunteers scanned three times across two days. Their findings showed reproducible T2 relaxation values suggesting the method is robust at both intra- and inter-subject levels. While some limitations remain, such as increased noise in the T2 maps due to the parallel imaging component and a potential reduction in image quality, further research is warranted to refine its application in clinical brain imaging. Nonetheless, GRAPPATINI represents a significant step forward, enabling high-resolution, whole-brain T2 mapping in under two minutes (Gruenebach et al., 2023; Hilbert et al., 2018). These advancements may help make quantitative T2 MRI protocols more accessible in clinical environments where time and cost are critical constraints.

7.13.3 The Sample

Additionally, in relation to the sample, a primary future direction is focusing more specifically on female participants. There is evidence that females have more complicated and prolonged recovery trajectories than males and this warrants further investigation (Levin et al., 2021; Mikolić et al., 2021). A larger study could stratify analyses by sex, allowing exploration of the impact of circulating hormones, sex-specific inflammatory responses, neuroimaging profiles, and recovery patterns. Including female participants in future research, and examining hormone levels at the time of injury, will be essential for enhancing the generalisability of findings and elucidating sex-specific mechanisms of injury and recovery. Future studies should also aim to enhance the sampling strategy. For the PA analyses in particular, a larger and more diverse cohort is necessary to increase statistical power and behavioural variability. Moreover, matching control participants more closely to the mTBI group would strengthen internal validity. For instance, recruiting control participants who are also athletes - with careful consideration of which sports may be appropriate and which ones may leave the sample vulnerable to confounding factors (e.g., some sports may have a higher incidence of head impacts and therefore not truly represent a healthy population).

7.13.4 Extending the Physical Activity Analysis

The exploratory analyses in Chapter 6 revealed the potential of CoDA to investigate the role of PA in mTBI recovery. These findings, while preliminary, suggest that CoDA may be a valuable tool for identifying how different proportions of movement behaviours relate to recovery. However, further research is needed to clarify optimal activity patterns and to confirm whether PA is both safe and beneficial in the acute post-injury phase. Future studies should replicate the mTBI-control group comparisons with a substantially larger and more diverse sample to determine whether the absence of significant differences in PA was due to insufficient power or reflects genuine equivalence in activity tolerance. If the latter is confirmed, this could provide stronger evidence that PA is safe and tolerable in the early stages post-injury. Additionally, larger samples would allow for more robust CoDA modelling to determine the ideal composition of movement behaviours (e.g., sedentary time, light PA and moderate-to-vigorous PA) that best support recovery. This line of research could ultimately inform evidence-based PA guidelines tailored to mTBI recovery, addressing a critical gap in clinical practice.

7.13.5 T2 Relaxometry Validation

One of the most promising, though still tentative, findings of this research is the potential utility of quantitative T2 relaxometry as a biomarker of neuroinflammation following mTBI. Increased T2 relaxation times were observed in both the case series and group-level analyses; however, the underlying biological mechanisms remain uncertain. I have hypothesised that these increases may reflect subtle neuroinflammatory changes, potentially resulting from BBB disruption and glial cell activation as part of the secondary injury cascade. Nonetheless, this interpretation remains speculative, and further validation is essential. A key direction for future research, therefore, is to establish whether T2 relaxometry reliably reflects neuroinflammation by aligning it with established markers. This could include biomarkers such as pro- and anti-inflammatory cytokines (e.g., interleukin-10, which modulates microglial recovery), or histological validation in preclinical models, examining the presence of inflammatory cells such as neutrophils, lymphocytes and macrophages. Triangulating T2 relaxometry data with these markers would be an important step toward confirming its diagnostic and prognostic value.

A promising direction for future research would be to complement quantitative T2 relaxometry with blood-based biomarkers in the acute phase following mTBI. With ongoing advances in our understanding of mTBI pathophysiology and the growing feasibility of rapid blood

sampling and analysis, this represents not simply a viable extension of the current work but a critical next step. Effective diagnostic and prognostic decision-making depend on fast, accurate, and non-invasive measures. While T2 relaxometry offers a sophisticated imaging option, particularly in complex cases, blood-based biomarkers could enhance accessibility and clinical feasibility. In addition to aiding in the validation of T2 relaxometry as a marker of neuroinflammation, they would allow for the examination of a broader panel of biological indicators associated with injury and inflammation (e.g., interleukin-6, CRP, and TNF- α).

Moreover, incorporating blood-based biomarkers would enable the assessment of circulating hormones, such as follicle-stimulating hormone (FSH), oestrogen, luteinising hormone (LH), and progesterone, particularly important for addressing sex-related differences in injury response. This would help to address a key limitation of the current research and contribute valuable, objective data to inform both clinical decision-making and policy development. Overall, integrating neuroimaging with blood-based biomarkers could provide a more comprehensive and actionable understanding of mTBI recovery and risk.

7.14 Conclusions

Despite major advances in neuroscience, much of the human brain remains a mystery, and significant gaps persist in how brain injuries are assessed and treated. Neuroinflammation is a defining feature of the secondary injury cascade following brain injury, yet our understanding of its role in recovery, inter-individual variability, and effective interventions remains limited. This thesis sought to address both sides of that challenge - by exploring potential ways to measure and modify the brain's inflammatory response to injury.

The first two studies focused on the novel application of quantitative T2 relaxometry, a specialised MRI technique sensitive to microstructural abnormalities reflected in tissue water content. The individual-level case series in Study 1 and the group-level analysis in Study 2 both revealed significantly elevated T2 relaxation times in individuals with mTBI compared to healthy controls. While the case series enabled a nuanced exploration of clinical heterogeneity and methodological utility, the group-level analysis provided essential validation and improved generalisability. Given T2 relaxometry's established sensitivity to fluid shifts, and the plausible connection between elevated extracellular water and hallmarks of neuroinflammation, such as via

blood-brain barrier disruption and glial cell activation, I hypothesise that these increases in T2 relaxation times reflects neuroinflammatory processes post-mTBI.

Shifting from measurement to intervention, the third study examined a promising approach to supporting recovery: physical activity. Study 3 employed compositional data analysis to explore movement behaviours during acute mTBI recovery. Physical activity was selected based on growing empirical support for its role in promoting neurological health and modulating inflammation. This study provided preliminary evidence for the safety and feasibility of early engagement in physical activity and demonstrated the utility of compositional data analysis in generating ecologically valid, clinically actionable recommendations.

Together, these findings support the use of quantitative T2 relaxometry as a sensitive, non-invasive method for detecting subtle brain changes that may reflect neuroinflammation after mTBI. They also highlight the potential of compositional data analysis to inform personalised physical activity plans aimed at improving recovery by modulating neuroinflammation. By offering a means to objectively validate subjective symptoms and monitor neurobiological change over time, as well as an accessible intervention strategy, this work contributes to more informed, individualised, and effective approaches to mTBI management. With several limitations to consider, including sample homogeneity and the non-specificity of T2 relaxometry as a marker of inflammation, there are multiple avenues for future research. These include validating the current findings using multimodal methods, incorporating longitudinal designs to track the temporal course of recovery, as well as utilising advanced MRI acquisition techniques, blood-based biomarkers, and more diverse participant populations.

mTBI remains a pervasive yet frequently misunderstood condition, its subtle and often invisible injury evolution contributing to under-recognition, limited investigation, and suboptimal care. Like an iceberg, the brain hides its complexity and vulnerability beneath the surface, so the true burden of mTBI may be concealed by an unremarkable exterior. This thesis seeks to reveal that hidden story, by advancing our understanding of how mTBI alters the brain and how recovery might be supported in ways that are biologically informed and meaningfully personalised. In doing so, it offers a step forward in making the invisible impacts of mTBI visible and, ultimately, more treatable. As a result, this work moves us closer to a future where mTBI is not just recognised but truly understood.

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Appendices

Appendix 1: Ethics Approval Letters

Ethics reference: 2022 EXP 11078

18 February 2022

Dr Mangor Pedersen

90 Akoranga Drive
Northcote
Auckland
0627
New Zealand

Tēnā koe Dr Pedersen

APPROVAL OF APPLICATION

Study title: Predicting recovery from mild traumatic brain injury using advanced brain imaging, saliva and physical activity data

I am pleased to advise that your application was **approved** by the Southern Health and Disability Ethics Committee (the Committee) **with non-standard conditions**. This decision was made through the EXP pathway.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study's sponsor, to ensure that these conditions are met. No further review by the Southern Health and Disability Ethics Committee is required.

Standard conditions:

- Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.
- Before the study commences at *each given* locality in New Zealand, it must be authorised by that locality in Ethics RM. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

Non-standard conditions:

Advertisements

1. Please note ensure that all advertising material must be approved by HDEC as an amendment prior to use.

Data and Tissue Management Plan

1. Please provide further information regarding the activity watch, such as how data will be uploaded/downloaded and who will have access to the generated data (particularly whether the device company retains ownership rights to the data). This information should also be included in lay terms in the PISCF.

Participant Information Sheet

1. Please clarify why the saliva samples will be labelled with the ID code only; state how long samples will be retained for; include a Māori tissue statement (exemplar available in the HDEC PISCF template); and advise that karakia will be not available at the time of sample donation / destruction.
2. Please address the risk of confidentiality breach, as this is a possibility in all clinical studies. Please include a 'compensation in event of injury' ACC statement.
3. Please state whether the activity watch data is uploaded to a cloud or requires uploading / downloading manually, who has access to watch data. Please ensure all statements in the consent form are explained in the PIS (e.g. explain who may have access to identified data and why).

Consent Form

1. Please include health provider notification in the event of an abnormal finding of clinical significance as this is a mandatory component of study participation. Please delete the optional YES/NO tickbox.

Non-standard conditions must be completed before commencing your study, however, they do not need to be submitted to or reviewed by HDECs.

If you would like an acknowledgement of completion of your non-standard conditions you may submit a post approval form amendment through the [Ethics Review Manager](#). Please clearly identify in the amendment form that the changes relate to non-standard conditions and ensure that supporting documents (if requested) are tracked/highlighted with changes.

For information on non-standard conditions please see paragraphs 125 and 126 of the [Standard Operating Procedures for Health and Disability Ethics Committees \(SOPs\)](#).

After HDEC review

Please refer to the [SOPs](#) for HDEC requirements relating to amendments and other post-approval processes.

Your next progress report is due by 17th February 2023.

Further information and assistance

Please contact the HDECs Secretariat at hdec@health.govt.nz or visit our website at www.ethics.health.govt.nz for more information, as well as our [General FAQ](#) and [Ethics RM FAQ](#).

Nāku noa, nā



Mr Anthony Fallon

Chair

Southern Health and Disability Ethics Committee

Encl: Appendix A: documents submitted

Appendix A: Documents submitted

Document Type	File Name	Date	Version
Protocol	Protocol		
PIS/CF	Consent Form		
PIS/CF	Participant Information Sheet		
Scientific Peer Review	Evidence of Peer Review - HRC Funding Approval Letter		
Surveys/questionnaires	Brain Injury Screening Tool (BIST)		
Surveys/questionnaires	Rivermead Post Concussion Symptoms Questionnaire (RPCSQ)		
CV for Coordinating Investigator	CV_Mangor_Pedersen_2021		
Data and Tissue Management Plan	Tissue & Data Management Plan		

<http://www.ethics.health.govt.nz>

Auckland University of Technology Ethics Committee (AUTEC)

Auckland University of Technology
D-88, Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

18 February 2022

Mangor Pedersen
Faculty of Health and Environmental Sciences

Dear Mangor

Re Ethics Application: **22/12 Predicting outcome of mild Traumatic Brain Injury with advanced brain imaging, saliva and physical activity data**

Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC).

Your ethics application has been approved for three years until 18 February 2025.

Please note this approval is for the main study, the student component will be reviewed separately.

Non-Standard Conditions of Approval

1. Insert in the "How the study works" section of the Information Sheet a statement such as: If you have transport difficulties due to your concussion please be assured that we will reimburse any travel costs that you incur. We also encourage you to bring a support person and any parking costs will also be covered.'

Non-standard conditions must be completed before commencing your study. Non-standard conditions do not need to be submitted to or reviewed by AUTEC before commencing your study.

Standard Conditions of Approval

1. The research is to be undertaken in accordance with the [Auckland University of Technology Code of Conduct for Research](#) and as approved by AUTEC in this application.
2. A progress report is due annually on the anniversary of the approval date, using the EA2 form.
3. A final report is due at the expiration of the approval period, or, upon completion of project, using the EA3 form.
4. Any amendments to the project must be approved by AUTEC prior to being implemented. Amendments can be requested using the EA2 form.
5. Any serious or unexpected adverse events must be reported to AUTEC Secretariat as a matter of priority.
6. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the AUTEC Secretariat as a matter of priority.
7. It is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard and that all the dates on the documents are updated.
8. AUTEC grants ethical approval only. You are responsible for obtaining management approval for access for your research from any institution or organisation at which your research is being conducted and you need to meet all ethical, legal, public health, and locality obligations or requirements for the jurisdictions in which the research is being undertaken.

Please quote the application number and title on all future correspondence related to this project.

For any enquiries please contact ethics@aut.ac.nz. The forms mentioned above are available online through <http://www.aut.ac.nz/research/researchethics>

(This is a computer-generated letter for which no signature is required)

The AUTEC Secretariat
Auckland University of Technology Ethics Committee

Cc: , alice.theadom@aut.ac.nz; tkaai@aut.ac.nz; scott.duncan@aut.ac.nz; Tom Stewart; mayan.bedgood@aut.ac.nz

Appendix 2: Participant Information Sheet

Acute Sports-Related Concussion Study

Participant Information Sheet

Kia ora, Talofa lava, Bula vinaka and warm greetings to you all,

You are invited to take part in our study investigating sports-related concussions. This information sheet will provide you with more information about the study and your participation.

Please take the time to read through the information enclosed. Once you do, you will be able to sign a Consent Form to join the study. Participation in this research is voluntary and you can withdraw at any time. You are more than welcome to discuss this study with friends, whānau, or healthcare providers before agreeing to take part.

1. Study Details

Title: Predicting Outcome of Mild Traumatic Brain Injury in Males with Advanced Brain Imaging, Saliva and Physical Activity Data

Lead researcher: Dr Mangor Pedersen

Research Team: Prof. Alice Theadom, Prof. Sir Richard Faull, Dr Samantha Holdsworth, Ms Mayan Bedggood, Ms Christi Essex

Contact: Mayan Bedggood (mayan.bedggood@aut.ac.nz) or Christi Essex (christi.essex@autuni.ac.nz)

Ethics: This study has been approved by the Health and Disability Ethics Committee (HDEC; Ref: 2022 EXP 11078)

Funder: The Health Research Council New Zealand is the primary funder of this study

2. Research Aims

Concussions are common in New Zealand. They occur when a force to the head causes the brain to move within the skull leading to symptoms such as dizziness, fatigue, and confusion which could take weeks to years to recover from. There are currently no measures to accurately predict how well someone will recover from a concussion.

We aim to recruit 40 sports players with concussions and 50 controls to address the study aims. These are:

- (1) Look at differences between sports players with concussion and injury free controls using data from MRI scans, saliva and physical activity patterns.
- (2) Find out whether there are markers in the brain, saliva and physical activity patterns that could predict how an individual will recover from a concussion.

Our research findings will be provided to participants that are interested and shared with research and clinical communities through scientific publications. Some of the data will be used by two student researchers for PhD qualifications.

3. Eligibility

You are eligible to participate in this study if you are:

- A male residing in Auckland or surrounding regions, aged 16-35 years old
- Sustained a concussion during a sports game or training in the last 14 days

You are ineligible to participate in this study if:

- You sustained a severe injury or have existing neurological conditions e.g., a brain tumor
- You are unable to be scanned in an MRI machine due to cultural or medical reasons e.g., you have magnetic metal implants in your body.

4. Participation

Below is an outline of what your participation in the study will involve:

Step 1: Read study information and sign consent form.

Step 2: Book in for a brain MRI to take place within 14 days of your concussion.

Step 3: Attend MRI session at the Centre for Advanced Magnetic Resonance Imaging (CAMRI), located at the University of Auckland Grafton Campus, where free onsite parking is available. Complete an MRI Safety form and a brief intake questionnaire prior to the scan. Provide a small saliva sample and receive a physical activity watch (similar to a *Fitbit*) to wear for two weeks. Please allow approximately 1.5 hours altogether for this session.

Step 4: Study team to collect physical activity watch at a place convenient for you (e.g. from your letterbox) after two weeks of wear time.

Step 5: Study team to record date of recovery from your concussion. This can be determined either by your doctor (e.g. at Axis Sports Medicine Clinic) or by completion of a brief symptom questionnaire that can be emailed to you each week.

4.1 Magnetic Resonance Imaging (MRI)

MRI is routinely used for clinical purposes and has no known harmful effects on the human body. It is used to take images of the brain structure and how it functions. Your MRI session will take place at the Centre for Advanced MRI (CAMRI), located at the University of Auckland's Faculty of Medical and Health Sciences, Park Road, Grafton. Parking here is free, and we will compensate you for travel with a petrol voucher. If you have transport difficulties, we can arrange a for taxi for you. You are most welcome to bring a support person with you.

The MRI scan itself is approximately 45 minutes long. All metallic objects/jewelry will need to be removed and a hospital gown will be worn for the scan. You will lie horizontally on a bed in the scanner for the duration of the scan and asked to remain as still as possible. A lightweight brace will be placed around your head to help you. You can contact the MRI operator at any time and are able to be removed from the scanner at any time.

4.2 Saliva Sampling

Two small saliva samples will be taken while you are at CAMRI for your MRI session. The test involves placing a small cotton swab under the tongue for 2 minutes. Samples will be processed for concussion and inflammation-related biomarkers at an AUT affiliated laboratory. No DNA samples and no genetic information that can identify you, your family, or ancestry will be extracted from the samples.

We want to acknowledge beliefs around sacredness and the shared value of tissue samples removed. We encourage you to discuss the storing and removal of your tissue with your whānau as appropriate.

4.3 Physical Activity Watch – Axivity AX3

This is a physical activity tracking device worn on the wrist for 2 weeks following your appointment. The device is like a “Fitbit” and is safe to be worn in water and while sleeping. It is used to collect information about the timing, duration, and intensity of your physical activity as you recover.

You do not need to alter your activity while wearing the watch and we urge you to follow your rehabilitation advice from your doctors and physios. After 2 weeks the study team will arrange collection of your watch. Data will be loaded confidentially on to a secure drive upon return.



If the device is damaged or lost, please contact the research team for a replacement.

5. Confidentiality

All efforts will be made to maintain confidentiality of your data. Your name will only appear on the Consent Form to allow us to contact you if any clinically abnormal findings arise so that further medical action can be sought. All questionnaires, saliva samples, physical activity data, and MRI scans will be labelled by a participant ID number to keep your identity confidential. You can withdraw your consent for the collection of your information at any time, by informing the lead researcher. If you withdraw your consent, your study participation will end, and the study team will stop collecting information from you. If you agree, information and data collected up until your withdrawal from the study will still be included in the study.

Saliva samples will be retained for up to six months after data collection before being destroyed or returned to you (upon request). A karakia will not be available at the time of the saliva sample donation or destruction. Your MRI data will be stored indefinitely on a password-protected database, to allow for publication and future re-analysis. All listed co-investigators will have access to the data. You have the right to request access to your information and request correction of any information you disagree with. You will be asked if you would like to receive the results of the study in your consent form.

Should you agree, the research team will obtain any data relevant to the study (e.g., your injury diagnosis; treatment plan etc.) from your clinical notes stored in the Axis Sports Medicine patient portal if you are attending this clinic. This data will be securely transferred and stored.

6. Benefits and Risks

6.1 Study Benefits

There are no direct benefits of this study to participants. The benefits of this study are indirect and will help us understand concussion recovery and guiding treatment and diagnosis of concussions in the future. Individualised treatment plans will improve return-to-play guidelines with benefits to players, clinical staff, and the New Zealand health system.

6.2 Compensation

There will be no costs to you to take part in this study. You will receive a \$20 voucher at the end of your MRI session and a \$50 voucher once the watch has been collected and we have your recovery date recorded (\$70 total). If transport is an issue, we can also provide a taxi voucher.

6.3 Possible Study Risk

There are no known side effects or risks associated with MRI scanning or saliva sampling. MRI scanning is noninvasive, this means it is painless and involves no radiation exposure, needles, or injections. MRI is unsafe for people who have magnetic metal implants in their body (e.g. pacemaker, hearing aid, screws/plates from an operation, etc.). You will be asked to fill out an MRI screening form to confirm the procedure will be safe for you. People who are prone to claustrophobia can find MRI scanning difficult and we do not recommend that they participate.

There is a possibility of a confidentiality breach with clinical studies. The study team will work hard to ensure that your confidentiality is respected and upheld so this does not occur.

6.4 Detection of Abnormalities or Injury

It is possible (although unlikely) that we may incidentally find an abnormality in your brain that is clinically significant. In this event, your GP must be informed. Depending on the nature of the abnormality this may affect your ability to obtain insurance or your ability to work in certain professions. If you would not want to know, you should not participate. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

If you are injured in this study, you are eligible to apply for compensation from ACC. If your claim is accepted, you will receive funding to assist in your recovery.

7. Further Research

Data sharing encourages transparency in science and allows other researchers to make use of collected data. Other researchers may request the use of the data from this study. You can give us permission on the Consent Form for your confidential data to be shared in accordance with the Privacy Act 2000. De-identified data may be included in secondary research (by the researchers on this study, or by different researchers).

8. Contacts

Please keep this Information Sheet and a copy of the Consent Form for your future reference. If you have any questions, concerns or complaints, you can contact:

Dr. Mangor Pedersen (AUT); Lead Researcher

Phone: 021 464 422 or Email: mangor.pedersen@aut.ac.nz

For Māori health support please contact Prof. Tania Ka'ai (AUT) at tania.kaai@aut.ac.nz

Health and disability ethics committee (HDEC): 0800 4 ETHICS or hdec@moh.govt.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

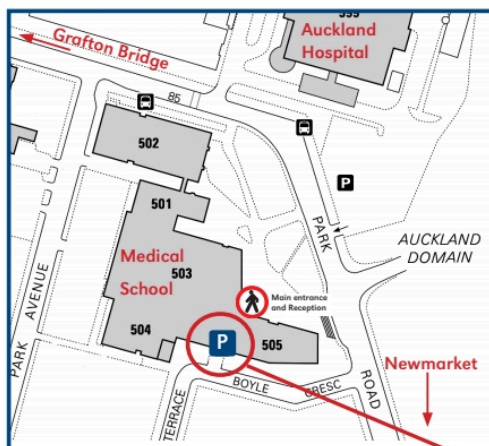
Phone: 0800 555 050

Fax: 0800 2 SUPPORT (0800 2787 7678)

Email: advocacy@hdc.org.nz

Centre for Advanced MRI

Map and Directions



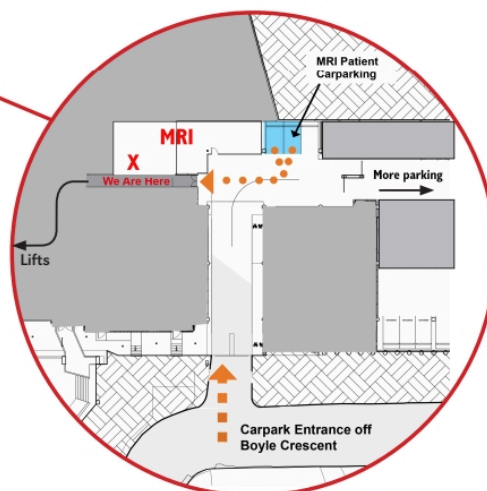
Where are we?

The Centre for Advanced MRI is located in the basement of Building 505
85 Park Road
Grafton, Auckland



If you are driving we have parking spaces in our underground carpark, accessed from Boyle Crescent.

Go down the drive and you will see our parking spaces ahead. If these are full there are further car parks available. Please continue through to barriers, press the button to talk to reception and they will let you through.



For patients who are not driving you can enter via the main entrance of the Faculty of Medical and Health Sciences and reception staff will assist with directions to the Centre.

Contact us

MRI Reception desk (09) 303 5966

Appendix 3: Consent Form

Consent Form

Project Title: Predicting Outcome of Mild Traumatic Brain Injury in Males with Advanced Brain Imaging, Saliva and Physical Activity Data

Project

Supervisor: Dr. Mangor Pedersen

Please tick to indicate you consent to the following

☐ I have read and understood the Participant Information Sheet.

☐ I have had an opportunity to ask questions and to have them answered

☐ I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.

☐ I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without being disadvantaged in any way.

☐ I understand that if I withdraw from the study then I will be offered the choice between having any data or tissue that is identifiable as belonging to me removed or allowing it to continue to be used. However, once the findings have been produced, removal of my data may not be possible.

☐ I am not suffering from any neurological diseases or conditions that might impair my participation in this study nor do I have any metal implants or contraindications for MRI scanning

☐ I consent to the research team collecting and processing my data and saliva samples

If I decide to withdraw from the study, I agree that the data collected up to that point can be used for analysis.

☐ Yes ☐ No

☐ I consent to my GP or current provider being notified about my participation in the study and about my results in the unlikely event of any findings that may need clinical follow-up.

After completion of the study, I would like to have my saliva samples returned to me.

☐ Yes ☐ No

☐ If I **do not** want my saliva samples returned to me, I am aware that my saliva samples will be disposed of using established guidelines for discarding biohazard waste.

☐ I agree to an approved auditor appointed by the New Zealand Health and Disability Ethics Committees, or any relevant regulatory authority or their approved representative reviewing my relevant information (e.g., records) for the sole purpose of checking the accuracy of the information recorded for the study.

☐ I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.

☐ I know who to contact if I have any questions about the study.

☐ I understand my responsibilities as a study participant.

☐ I agree to take part in this research.

I wish to receive a summary of the results from the study.

☐ Yes ☐ No

Future Research:

I consent to the sharing of relevant clinical notes from my consultations at Axis Sports Medicine to be shared with the research team

☐ Yes☐ No

I consent to the possibility of that my research data can be used for other research projects in the future.

☐ Yes☐ No**Participant's name:**

.....

Participant's Contact Details:

Email:.....

Phone:.....

.....

Participant's signature:

.....

Date:

.....

Approved by the Health and Disability Ethics Committee (2022 EXP 11078) and the Auckland University of Technology Ethics Committee (22/12) on 18/2/22

Appendix 4: Brain Injury Screening Tool (BIST)



Brain Injury Screening Tool (BIST)

A guide to traumatic brain injury assessment

The BIST was developed to be a brief tool for use on initial presentation after injury to guide health care pathway decision making and to monitor symptoms and recovery over time. Its purpose is to help guide the clinical assessment conversation by operationalising current international best practice guidelines.¹

The BIST has been developed for health professionals working across primary and secondary health care and for sports and other contexts where traumatic brain injuries (TBI) can occur.

The BIST can facilitate clinical decision making through identification of people who are at low, medium or high risk of longer-term difficulties.

This tool should be used in addition to clinical judgment and other assessments such as the Vestibular/Oculomotor Motor Screening (VOMS), King-Devick or the Romberg's test. Additional questioning to add to the clinical picture is encouraged.

The first 9 questions in the BIST are designed to assist if there are clinical indicators that the person is at high risk of complications or poor recovery and requires hospital evaluation. The 15-item symptom scale is designed to assist in identifying patients at moderate risk of poor recovery who may benefit from early specialist treatment and low risk patients who are likely to recover well, supported within primary care.

Date of Injury:

Time of Injury:

Date of Consultation:

Age¹:

Gender/Sex:

1. If over 65 years, socially isolated or living alone, consider referral to the Emergency Department.

Ethnicity:

If your answer is OTHER please specify:

1. Please tell me about what happened² (Observe for high risk indicators such as suspicion of skull fracture, focal neurological deficit, high speed, focal blunt trauma or fall from height (e.g. >5 stairs)

2. If high risk indicators present, consider referral to Emergency Department.

2. Did anyone with you at the time of the injury say anything else about what happened?

3. Have you been sick/vomited?³

Yes No a. If yes, how many times

3. If >1 vomiting episode, consider referral to Emergency Department.

4. Were you knocked out (or did you lose consciousness)?⁴

Yes No Unknown a. If yes, how long hrs mins

4. If loss of consciousness >brief, consider referral to Emergency Department.

5. Did you have a fit or seizure straight afterwards? E.g. go stiff or shake violently?⁵

Yes No Unknown

5. If yes, consider referral to Emergency Department.

6. Are you feeling better, worse or about the same since the injury?⁶

Better Worse About the same

6. If symptoms have worsened, consider referral to Emergency Department.

7. Have you hit your head or had a concussion/brain injury before ?⁷

Yes No a. If yes, how many times
b. when was the last injury?

7. If recent or unrecovered previous injury, consider referral to Emergency Department.

If recent injury but recovered the person may be moderate risk of poor recovery and early specialist input may be required.
Consider referral to concussion service.

8. Are you currently taking any medications that thin the blood e.g. anti-coagulants? Yes⁸ No

8. If yes, consider referral to emergency department.

9. Have you ever experienced any difficulties with your mental health?

Yes⁹ No

9. If yes, the person may be at moderate risk of poor recovery and early specialist input may be required. Consider referral to concussion service.

Please ask the patient the following question.

Compared with before the accident, please rate how much you experience the following right now (at this point in time);

												
		Not at all	Mild (a little)			Moderate (quite bad)				Severe (very bad)		
		0	1	2	3	4	5	6	7	8	9	10
Physical	Headache (my head hurts) ¹⁰											
	My neck hurts											
	I don't like bright lights											
	I don't like loud noises											
Total physical score (out of 40)												
Vestibular-ocular	I feel dizzy or like I could be sick											
	If I close my eyes, I feel like I am at sea											
	I have trouble with my eyesight (vision)											
	I feel clumsy											
Total vestibular score (out of 40)												
Cognitive	It takes me longer to think											
	I forget things											
	I get confused easily											
	I have trouble concentrating											
Total cognitive score (out of 40)												
If more than 24 hours post-injury, please also rate these physical symptoms												
	I get angry or irritated easily											
	I feel restless											
	I feel tired during the day											
	I need to sleep a lot more or find it hard to sleep at night											

¹⁰. If severe headache, consider referral to Emergency Department.

Total symptom severity score within 24 hours (out of 120 ¹¹)		Total symptom severity score >24 hours (out of 160 ¹²)	
Number of symptoms endorsed within 24 hours (out of 12)		Number of symptoms endorsed >24 hours (out of 16)	
What is the dominant symptom cluster? (High proportion or most severe symptoms reported (e.g. physical, vestibular or cognitive?))			

11. If 50 or more consider referral to specialist concussion clinic, as this person is likely to be at moderate risk of poor recovery.
If <50 this person is at low risk, monitor and follow up in 7-10 days.

12. If 66 or more consider referral to specialist concussion clinic, as this person is likely to be at moderate risk of poor recovery.
If <66 this person is at low risk, monitor and follow up in 7-10 days. If minimal improvement in scores since previous visit, consider referral to concussion clinic.

Injuries to the brain can affect how a person feels, behaves, thinks and how able they are to do everyday tasks.

On a scale of 0 to 100, where 0 means that you do not feel the injury has had any impact on you at all and 100 means you feel that injury stops you from doing anything, how much do you feel your injury is impacting on you at this point in time?



Acknowledgements

This tool has been developed by the ACC Concussion Clinical Expert Group: Alice Theadom, Natalie Hardaker, Penelope Day, Kris Fernando, Katherine Forch, Kevin Henshall, Doug King, Mark Fulcher, Renata Gottgroy, Sam Jewell, Stephen Kara, Patria Hume.

Reference

Silverberg ND, et al on behalf of the American Congress of Rehabilitation Medicine Brain Injury Interdisciplinary Special Interest Group Mild TBI Task Force. Management of Concussion and Mild Traumatic Brain Injury: A Synthesis of Practice Guidelines. Archives of Physical Medicine and Rehabilitation, 2020, 101; 382-393

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**AUT TRAUMATIC BRAIN
INJURY NETWORK**

Appendix 5: Centre for Advanced MRI (CAMRI) Screening Form

MRI Safety Screening Form

Name:

DOB:

NHI/Study ID:

Height:

Weight:

Scan #:

	YES	NO
Have you had a previous MRI scan?		
Do you have or have you EVER had a cardiac pacemaker or ICD (<i>Implanted Cardioverter Defibrillator?</i>)		
Have you EVER had an eye injury involving a metallic fragment? <i>If yes, was it removed?</i>		
Have you ever had any brain/head, inner ear or eye surgery? <i>i.e. Aneurysm clip, ventricular shunt, cochlea implant, ocular implant</i> <i>Please list:</i>		
Have you ever had heart surgery or vascular procedures? <i>i.e. heart valve, vascular stent or graft</i> <i>Please list:</i>		
Have you ever had any other surgery/operations? <i>Please list surgery and date:</i>		
Do you have any metallic, electronic, magnetic or other implants / devices? <i>i.e. Joint replacement, drug infusion device, neurostimulator, shrapnel / bullets?</i> <i>Please list:</i>		

Do you have any of the following?	Yes	NO
Tattoos, permanent cosmetics or permanent make up		
Medicated skin patches – <i>Nicotine, hormone or silver dressings</i>		
Body piercings or acupuncture needles, pellets / seeds		
Hearing aids		
Dentures or partial plate		
<i>Female Patients</i> Is there any possibility you might be pregnant or breastfeeding?		

Consent for MRI

To the best of my knowledge the answers above are accurate and true, and I give my consent to proceed with my MRI scan. By signing this form, you are confirming that we may collect, store and use your information in the manner set out in our [Privacy Policy \(https://camri.auckland.ac.nz/\)](https://camri.auckland.ac.nz/)

Signature:

Date:

MRT's Initials:

If you answer YES or are uncertain regarding any of the above, please contact us on (09) 303 5966 prior to your appointment.

Please Turn Over

Use of your Images

As a University, it may be useful to use your images (without your name or other identifying details) for all or some of the following purposes -

Education and training by Centre for Advanced MRI staff

Scientific publications, reports and presentations

University teaching

Publicity material for the Centre for Advanced MRI

The Centre for Advanced MRI website and websites of organisations we collaborate with (e.g. Siemens the manufacturer of the machine)

Publicity materials for non-profit organisations

Television documentaries or other public interest media

Databases that may be published on the internet

I give consent for my images to be used for the above purposes provided that all details that could allow me to be identified have been removed

YES

NO

Signature:

Appendix 6: Study Intake Questionnaire

Intake Questionnaire

Acute Concussion in Sports Players

Thank you for participating in our study! Please complete the below questions by either circling the appropriate answer or writing the information in the space provided. This information will be helpful for our data analysis.

Participant ID # _____

Age _____

1. What ethnic group do you belong to?

- ☐ European,
- ☐ Māori
- ☐ Pacific peoples
- ☐ Asian
- ☐ Middle Eastern
- ☐ Latin American
- ☐ African
- ☐ Other _____

2. Have you had COVID-19? Yes / No

If yes, when did you experience it? Year _____ Month _____

Do you experience any lingering symptoms from having COVID-19? Yes / No

If yes, what are the symptoms? _____

3. Please rate your mood today on the below scale

1. Very happy
2. Somewhat happy
3. Neutral
4. Somewhat sad
5. Very sad

4. Please rate your level of physical activity, on average, in the last month

1. At least once a day
2. Most days
3. Several times a week
4. About once a week
5. Less than once a week

5. When did you last exercise? Date _____, in the morning / afternoon

Appendix 7: First Publication



Individual-level analysis of MRI T2 relaxometry in mild traumatic brain injury: Possible indications of brain inflammation

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ABSTRACT

Mild traumatic brain injury (mTBI), often called concussion, is a prevalent condition that can have significant implications for people's health, functioning and well-being. Current clinical practice relies on self-reported symptoms to guide decision-making regarding return to sport, employment, and education. Unfortunately, reliance on subjective evaluations may fail to accurately reflect the resolution of neuropathology, exposing individuals with mTBI to an increased risk of further head trauma. No objective technique currently exists to assess the microstructural alterations to brain tissue which characterise mTBI. MRI-based T2 relaxation is a quantitative imaging technique that is susceptible to detecting fluid properties in the brain and is hypothesised to indicate neuroinflammation. This study aimed to investigate the potential of individual-level T2 relaxometry to evaluate cellular damage from mTBI. 20 male participants with acute sports-related mTBI (within 14 days post-injury) and 44 healthy controls were recruited for this study. Each mTBI participant's voxel-wise T2 relaxometry map was analysed against healthy control averages using a voxel-wise z-test with false discovery rate correction. Five participants were re-scanned after clinical recovery and results were compared to their acute T2 relaxometry maps to assess reduction in potential neuroinflammation. T2 relaxation times were significantly increased in 19/20 (95 %) mTBI participants compared to healthy controls, in regions including the hippocampus, frontal cortex, parietal cortex, insula, cingulate cortex and cerebellum. Results suggest the presence of increased cerebral fluid in individuals with mTBI. Longitudinal results indicated a reduction in T2 relaxation for all five participants, indicating a possible resolution over time. This research highlights the potential of individual-level T2 relaxometry MRI as a non-invasive method for assessing subtle brain pathology in mTBI. Identifying and monitoring changes in the fluid content in the brain could aid in predicting recovery and developing individualised treatment plans for individuals with mTBI. Future research should validate this measure with other markers of inflammation (e.g. from blood biomarkers) to test whether T2-relaxometry is related to subtle brain inflammation in mTBI. In addition, future research should utilise larger control groups to establish normative ranges and compute robust z-score analyses.

1. Introduction

Approximately 69 million people worldwide experience a mild traumatic brain injury (mTBI) each year (Oris et al., 2023). Whilst in many cases, people recover well, others can experience chronic, disabling impacts that affect their daily functioning (McInnes et al., 2017; Verboon et al., 2021). mTBI occurs when a person experiences a strong force on the head that causes the brain to move within the skull.

The predominant mechanism of injury is a sudden impact, rotational force or rapid deceleration or acceleration of the brain. The primary injury in mTBI is from the immediate mechanical damage to the brain, resulting in focal and diffuse damage (Alam et al., 2020; Verboon et al., 2021). Following this primary injury, a cascade of secondary injuries can occur. These include inflammation, excitotoxicity, metabolic disturbances, vascular damage, and blood-brain barrier disruption (Kim et al., 2023; Slavoaca et al., 2020; Soltani et al., 2020).

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The term 'mild TBI' may not correspond to the personal experience of many people, as many of those with an mTBI experience long-lasting symptoms that persist beyond the two to four weeks 'standard' recovery time (Kara et al., 2020). The symptoms that accompany the secondary injuries can, if left untreated, last for weeks, months or even years (Slavoaca et al., 2020). Common symptoms of mTBI include headaches, difficulty concentrating, sleep difficulties, a foggy feeling, vestibular disorders, confusion, slowed reaction times, nausea, changes in vision, sensitivity to light, and irritability (Di Battista et al., 2020; Markovic et al., 2021; Verboon et al., 2021). In the short term, these symptoms can have severe negative impacts on the lives of patients'. In the longer term, mTBI has been associated with reduced work productivity and increased risk of psychiatric and neurodegenerative diseases (Theadom et al., 2017; Wang et al., 2021).

Neuroinflammation is one of the primary drivers behind the secondary injuries associated with brain injuries (Markovic et al., 2021; Piao et al., 2013). The initial tissue damage triggers the activation and recruitment of immune cells by facilitating the production of cytokines and chemokines (Kim et al., 2023). The effect of this inflammatory response is to limit the spread of injury in the brain and to restore homeostasis. Microglia play a key role in responding to inflammatory events by identifying structural abnormalities and working to isolate damaged regions of the brain to prevent the spread of injury. Shortly after the injury, microglia release proinflammatory cytokines, a vital and adaptive part of neuronal preservation (Alam et al., 2020). Neuroinflammation can be beneficial in the acute phase following brain injury, promoting repair of the damaged tissue, possibly inducing neurogenesis and reducing the risk of infection (Monsour et al., 2022). However, when this inflammation occurs in excess, it can contribute to the loss of neurons and death of brain tissue, resulting in a secondary injury cascade (Corps et al., 2015; da Luz Scheffer & Latini, 2020; Kim et al., 2023; Markovic et al., 2021; Mee-Inta et al., 2019).

T2 relaxometry is a novel MRI method that is used to assess microstructural tissue alterations that can accompany different neurological diseases and conditions. This type of MRI provides an indicator of intracellular and extracellular injury (Pell et al., 2004), such as in epilepsy (Adel et al., 2023; Winston et al., 2017). The most important property to consider that impacts T2 relaxation time is the water content of the tissue. This water can consist of free water molecules, which are smaller and have a faster spin frequency and a longer T2 relaxation time. Or, the water content can be bound with larger macromolecules with a spin frequency comparable to the Larmor frequency with shorter T2 relaxation times. In regular, healthy tissue, these two types of water exist in equilibrium, but in many pathological conditions (e.g. inflammation), the bound water is released and the free water increases. This creates an inefficient medium for T2 relaxation; therefore, T2 relaxation time increases as tissue water content increases and can indicate pathology (Cheng et al., 2012; Ghugre et al., 2011; Liu et al., 2018).

In mTBI patients, brain regions with higher T2 relaxometry signals could reflect accumulated fluid caused by the secondary damage to the brain. Previous research has applied quantitative T2 MRI in other brain disorders, such as epilepsy; however, few studies have used this technique with mTBI. Pedersen et al. (2020) identified possible brain inflammation in a professional Australian Rules football player who had incurred multiple mTBIs, demonstrating the potential promise of this technique. This study found that abnormally elevated T2 relaxometry trended toward baseline at each additional MRI throughout the recovery period, but had not yet resolved at the final follow-up. Furthermore, T2 relaxometry is a marker of TBI in animal studies and mouse models of mTBI indicate that T2 relaxometry can be a valuable tool for identifying acute neurostructural perturbations post-mTBI (Yang et al., 2015).

Standard clinical neuroimaging post-mTBI is often negative, with no clinically significant findings (Mayer et al., 2015). This can perpetuate the notion that the injury did not result in neuronal pathology despite the patient presenting as symptomatic. Ultimately, there is a need for an advanced method of quantitative MRI that can detect subtle changes in

the brain acutely after mTBI. Advanced T2 MRI methods may uncover individual abnormalities that are hypothesised to be indicative of possible neuroinflammation despite clinically normal radiology findings. In this context, T2 relaxometry could indicate areas of fluid accumulation, and possibly transient neuroinflammation, post-mTBI and validate subjective symptom reports or indicate pathology despite a lack of subjective symptoms. Acute T2 relaxometry measures could be utilised to detect injury and predict recovery outcomes from mTBI based on the quantified fluid in the brain upon acute presentation.

The current study comprises a series of 20 acute mTBI cases individually compared to a control group. This technique will enable a detailed investigation of potential brain abnormalities on an individual level, enabling any findings to be considered in the context of the patient's clinical presentation. Deepening our understanding of the underlying pathology of mTBI could contribute to individualised treatment plans and improved patient recovery outcomes.

2. Methods

2.1. Participants and procedure

This study consists of 20 male sports players ($M = 21.6$ years old [$16-32$], $SD = 4.76$) with acute (≤ 14 days) sports-related mTBI. Injuries were sustained from participation in rugby union ($n = 13$), football ($n = 2$), hockey ($n = 1$), futsal ($n = 1$), gymnastics ($n = 1$), surfing ($n = 1$), and jiu-jitsu ($n = 1$). The population template for comparison was derived from 44 male controls that had not suffered an mTBI in the last 12 months and had no lingering symptoms from an mTBI ($M = 23.3$ years old [$16-30$], $SD = 4.38$). The age of individual mTBI participants and the average age of controls may vary slightly between the 20 individual statistical tests, as our hypothesis is to conduct individual-specific analyses rather than estimate between-group differences. The difference between the mean age of mTBI and control groups was not statistically significantly ($p = 0.14$). See Table 1 for a summary of participant demographics and injury details. Participants in the mTBI cohort were recruited through Axis Sports Concussion Clinics in Auckland, New Zealand and via community pathways (e.g. physiotherapists, word-of-mouth, digital and print advertisements). The control group were recruited through print and social media advertisements, and word-of-mouth. Brain Injury Screening Tool (BIST) questionnaires were completed to determine symptom severity and clinical recovery (Theadom et al., 2021). Five mTBI participants were re-scanned after clinical recovery. All research was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the Health and Disability Ethics Committee (HDEC – 2022 EXP 11078), New Zealand and all participants provided written informed consent prior to data collection.

2.2. Magnetic resonance imaging

All magnetic resonance images were acquired using a 3 T Siemens MAGNETOM Vida fit scanner (Siemens Healthcare, Erlangen, Germany) located at the Centre for Advanced Magnetic Resonance Imaging (CAMRI) at The University of Auckland, New Zealand, using a 20-channel head coil. A T2 mapping sequence was used to investigate the anatomical T2 relaxometry. T2 maps were acquired using an 8 echo Carr-Purcell-Meiboom-Gill (CPMG) sequence ($TEs = 28.9, 57.8, 86.7, 115.6, 144.5, 173.4, 202.3$ and 231.2 ms; $TR = 6$ s; slice thickness = 2.0 mm; voxel size = $2.0 \times 2.0 \times 2.0$ mm; matrix size = $112 \times 128 \times 63$; flip angle (FA) = 180° ; base resolution = 128; phase resolution = 100 %; phase field of view (FOV) = 87.5 %). Total T2 mapping acquisition time was ~ 12:02 min. Note that accelerate mapping methods, e.g., GRAP-PATINI (Hilbert et al., 2018), can greatly reduce acquisition time which makes T2 mapping more clinically feasible. See Supplementary Materials 1, for mean and coefficient of variation for the T2-maps across all subjects. T1-weighted anatomical images were collected for quality

Table 1
Participant demographic and injury details.

Case	Post-injury MRI (days)	Prior mTBI's	Recovery (days)	Symptom Reports post-injury	BIST (/160)	Injury details	Health issues
1	5	1	20	Headaches, tiredness, emotional, feeling like he was "in a dream"	140	Rugby – knee to head	None
2	12	1	31	Headaches, nausea, fatigue	12	Hockey – ball to face (left eye)	Unknown
3	13	0	27	None reported	78	Football – in goal, slipped and fell backwards hitting head on ground	Unknown
4	13	1	26	Visual disturbances (seeing "stars"), unsteady, headaches, sensitivity to light	18	Rugby – head collision	Unknown
5	10	1	56	Impaired balance, disoriented, feeling "not well", visual disturbances	61	Gymnastics – fell off bar and onto back, two days later fell again and hit top of head	ADHD, anxiety, depression
6	5	0	26	Vomited, ringing in ears, dizziness, headaches, neck pain, light sensitivity, difficulty focusing	42	Rugby – lifted and dumped onto his neck in a tackle causing cervical hyperflexion	None
7	6	0	47	Impaired balance, dizziness, headaches, sensitivity to light and noise, difficulty concentrating, irritable	13	Rugby – kicked in the back of the head	Unknown
8	10	2	27	None reported	6	Rugby – knee to the head	Unknown
9	13	?	18	Double vision, fogginess, slowed thinking, indecisiveness	56	Rugby – head hit ground	Unknown
10	11	10	?	None reported	54	Surfing – hit head on board	Unknown
11	13	4	24	Dizziness, dazed, headaches, neck pain, sensitivity to light, fogginess, mild cognitive symptoms	52	Rugby – head-to-head collision	Unknown
12	12	0	23	Loss of consciousness, "zoning out", headaches/pressure in the head, difficulty concentrating	13	Rugby – left side of head hit ground and right side of head hit player's knee/elbow	Unknown
13	13	?	17	Dazed, pressure in head, neck pain, fogginess, reduced cognitive sharpness	79	Rugby – head to knee and then elbow to face	None
14	13	1	20	None reported	2	Football – ball kicked into face and fell to ground	None
15	6	?	18	Ataxia, confusion	22	Rugby – struck on right side of face with elbow	Unknown
16	12	4	117	Impaired balance, blurry vision, "pins and needles" in hands, dizziness, headaches	117	Rugby – knee to back of head	History of migraines
17	5	2	66	None reported	0	Rugby – shoulder hit head	None
18	13	0	26	None reported	34	Rugby – knee to head	Unknown
19	8	0	32	None reported	28	Futsal – elbow to face	Unknown
20	13	2	31	None reported	69	Jiu-jitsu – knee to right side of head	None

control purposes. The T1 weighted images were acquired using a magnetisation-prepared rapid gradient echo (MPRAGE) sequence (TR = 1.9 s; TE = 2.5 ms; TI = 979 ms; FA = 9°; slice thickness = 0.9 mm; voxel size = 0.4 x 0.4 x 0.9 mm; matrix size = 192 x 512 x 512; phase FOV = 100 %). Total T1-weighted acquisition time was ~ 4:31 min.

A radiologist reviewed clinically relevant MRI images from each participant to check for clinically significant abnormalities that might require further attention.

2.3. Data processing and statistical analysis

All MRI images were received in DICOM format, converted to NIfTI format, and arranged according to the *Brain Imaging Data Structure (BIDS)* (Gorgolewski et al., 2016). Image quality assurance checking was conducted in the MR View toolbox of MRtrix3 (Tournier et al., 2019) by two investigators in the study (MJB, MP) using the participants' T1 weighted image as the underlay and their T2 map as the overlay to check for artifacts or abnormalities caused by scanning or processing. T2 maps were skull stripped using the *bet* function in FSL (Smith, 2002) before normalising each image to the MNI standard space by registering them to a MNI152 2.0 x 2.0 x 2.0 mm template image using FSL FLIRT (Jenkinson et al., 2002). For each subject, the third T2 echo volume (86.7 ms) was extracted to generate a group average brain image and binary grey matter, white matter, and cerebrospinal fluid masks. Lastly, we removed the first volume, using the offset as a fitting parameter to the T2 relaxation data (Milford et al., 2015) and a monoexponential function at each voxel was fitted across all eight echo-times using qMRLab (Karakuzu et al., 2020) in Matlab R2022 to calculate the T2 relaxation time

for each participant.

Z-tests were used to quantify differences between individual mTBI subjects and controls. Before statistical analysis, each image was smoothed using a 6 mm full-width-half-maximum (FWHM) kernel. All voxels residing within the grey matter mask were considered for final analysis. Given that the main statistical assumption of a z-test is that the underlying data distribution is Gaussian with a mean of 0 and standard deviation of 1, we used a Rank-Based Inverse Normal Transformation (Blom, 1954) to normalise the data. All T2-relaxometry voxels for each image were ranked and transformed into a Gaussian shape with a distribution mean of 0 and a standard deviation of 1. Z-score maps were obtained by subtracting voxel values between individual mTBI maps and the mean of controls divided by the standard deviation of the controls. This is a similar individual-based statistical approach to previous studies (Jolly et al., 2021; Mito et al., 2023; Pedersen et al., 2020).

We conducted a one-tailed z-test, interpreting positive values only, as the biology of increased T2 relaxometry is well understood, i.e., increased water properties in tissue (Cheng et al., 2012; Ghugre et al., 2011; Liu et al., 2018). In contrast, the interpretation of decreased T2 relaxometry is less well understood. False Discovery Rate (FDR – Benjamini & Hochberg, 1995) was used to correct for multiple comparisons in the z-score maps using a threshold of $q < 0.05$. This method obtained z-values and relaxometry times (in ms) for each FDR-based significant cluster, individually for each mTBI participant. Lastly, to determine if the significant T2 relaxometry clusters had resolved with clinical recovery, we subtracted the acute voxel-wise z-maps of the five participants with recovery MRI re-scans from the voxel-wise z-maps of their recovery MRI scans. See Fig. 1 for a schematic overview of our

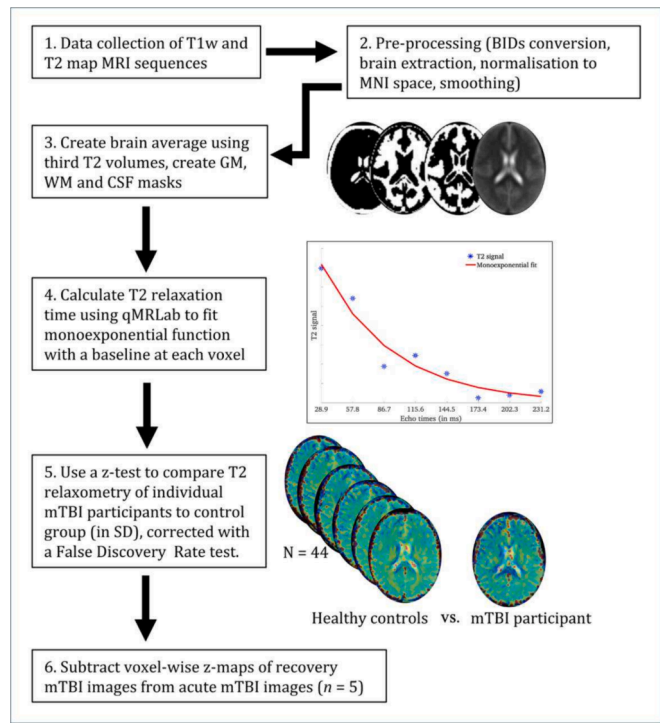


Fig. 1. Methodology for MRI data processing and analysis.

processing and analysis pipeline.

3. Results

3.1. Summary of acute scan findings

The quantitative T2 analysis indicated regions with significantly higher T2 relaxometry times in 19/20 mTBI participants (95 %), detailed in Table 2. While several significant voxel clusters, such as the cingulate cortex, superior parietal cortex and insula, were shared across multiple participants (see Fig. 2), most of the findings were individual to each case study. A radiologist analysed each participant’s MRI scans, and no clinically significant findings were reported.

3.2. Case series of recovery re-scan findings

Recovery re-scans indicated either a full reduction (i.e. in all significant acute regions) or a partial reduction (i.e. for some areas but not others) in T2 relaxometry for all five re-scanned participants. The remainder of the Results section will provide comprehensive details about the five case studies that had recovery re-scans, with information regarding their injury, symptoms and specific T2 relaxometry results for specific areas of their brains. A detailed description of individual acute scan results for the remaining participants can be found in the Supplementary Materials 2.

3.2.1. Case 1

Case study one suffered an mTBI as a result of a knee to the head during rugby. He experienced headaches, tiredness, abnormal emotional expression and feeling like he was in a dream. These symptoms largely settled at the clinical assessment four days post-injury, with only mild headaches and tiredness being experienced. Brain Injury Screening Tool (BIST) scores were low, with no individual statements obtaining abnormally high scores and an initial total score of 12/160. This patient has experienced one other mTBI in their life, during primary school. Recovery time for the current mTBI is recorded as 20 days. Four significant voxel clusters are apparent when assessing the T2 relaxometry

Table 2
Individual results showing voxel clusters in mTBI with significantly higher T2 relaxometry times compared to controls.

Case	Region(s)	Raw T2 Relaxometry (ms)	Z-score compared to controls (SD)
1	L superior parietal	146.50	8.40
	L lateral superior frontal	2.69e + 06*	4.08
	L medial superior frontal	74.18	4.38
		79.78	6.50
	L orbitofrontal cortex		
2	L superior parietal	63.67	9.39
	L anterior insula	63.72	18.65
	R superior frontal	72.10	6.91
3	R somatosensory cortex	76.10	8.66
	R intraparietal sulcus	51.54	15.69
4	L anterior insula	68.26	12.12
	L posterior cerebellum	66.95	7.04
5	R anterior parietal	55.86	12.83
6	L hippocampus	95.22	5.00
	L lateral occipital	71.83	9.33
7	L superior parietal	73.15e + 04*	7.26
	R intraparietal sulcus	72.34	14.39
	R temporoparietal junction	65.49	3.40
		89.35	8.72
	R superior cerebellum		
8	Cingulate cortex	73.47	8.27
	L inferior supramarginal gyrus	76.10	16.31
9	L superior parietal	65.66	8.81
	R posterior insula	70.28	5.31
10	L superior parietal	54.89	15.92
	R inferior parietal	65.95	14.48
	R superior parietal	70.83	8.46
11	L parahippocampal cortex	76.46	10.37
		6.50	4.83
	L orbitofrontal cortex	79.23	10.22
	R anterior occipital	74.74	4.34
	R orbitofrontal cortex		
12	R superior cerebellum	79.46	13.15
	R superior temporal sulcus	69.54	10.23
13	L anterior temporal	125.00	4.70
14	L inferior supramarginal gyrus	70.15	25.44
		57.68	13.83
	L anterior occipital	274.06	8.38
	L hippocampus	87.64	19.60
	R premotor cortex		
15	R inferior parietal	70.64	12.33
	R posterior parietal	66.73	19.85
	R superior cerebellum	104.69	5.78
	R medial prefrontal cortex	83.92	8.13
16	R sensorimotor cortex	74.02	14.86
17	Cingulate cortex	99.04	11.08
	L superior frontal	259.39	6.05
	L posterior cerebellum	1.61e + 08*	5.37
18	L superior frontal	303.65	5.28
19	None	N/A	N/A
20	L anterior cingulate cortex	66.32	17.51
		121.10	5.68
	L medial frontal cortex	79.65	4.57
	L sensorimotor cortex	38.98	5.49
	L precuneus	100.25	5.60
	L temporoparietal junction	73.53	15.48
		22.05	4.89
	R anterior cingulate cortex		
	R superior parietal		

*As these peak relaxometry values are very high, they could be coming from voxels outside the brain, in the cerebrospinal fluid. However, parts of the clusters appear to be situated within the brain, so they have been included in the analyses.

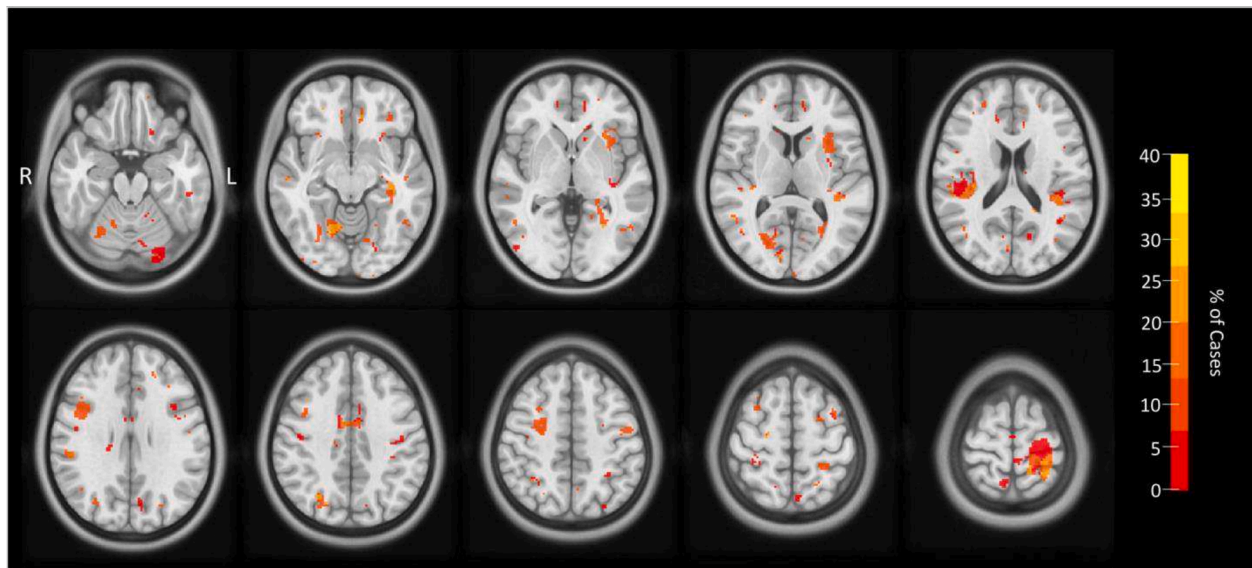


Fig. 2. Common regions of significant T2 relaxometry.

MR images (see Fig. 3). There is a significant cluster in the left superior parietal region, with relaxometry times up to 8.40 SD higher than the controls (peak relaxometry value = 146.5 ms). Two significant clusters are found in the left superior frontal region, the first more laterally with relaxometry times up to 4.08 SD higher than controls (peak relaxometry value = $2.7e + 06$ ms). As the peak relaxometry value is very high, it could indicate that this peak value is coming from a voxel situated outside the brain, in the cerebrospinal fluid. However, some parts of the cluster appear to be located within the superior frontal region of the brain. The second left superior frontal region is more medial, with relaxometry times up to 4.38 SD higher than controls (peak relaxometry value = 74.2 ms). Lastly, there is a significant cluster in the left orbitofrontal cortex, with relaxometry times up to 6.50 SD higher than controls (relaxometry value = 79.8 ms). After recovery, re-scans indicated that T2 relaxometry was reduced by 14.09 SD in the left superior parietal region, 2.01 SD in the left lateral superior frontal region, and 4.52 SD in the left orbitofrontal cortex. No significant reduction was found for the left medial superior frontal region cluster.

3.2.2. Case 2

Case study two suffered an mTBI when a ball hit his left eye during a hockey game. He experienced developing headaches and nausea after the match and reported mild headaches and fatigue at his clinical assessment nine days post-injury. The patient's BIST scores were low, with no symptom domains or individual statements obtaining abnormally high scores and an initial total score of 6/160. Recovery time for this injury is recorded as 31 days. Furthermore, he suffered one previous mTBI in 2022. Three significant voxel clusters were identified when analysing the T2 relaxometry images (see Fig. 3). The first is in the left superior parietal region, with relaxometry times up to 9.39 SD higher than controls (peak relaxometry value = 63.7 ms). There are also significant clusters in the left anterior insula, with relaxometry times up to 18.65 SD higher than controls (peak relaxometry value = 63.7 ms) and in the right superior frontal region, with relaxometry times up to 6.91 SD higher than controls (peak relaxometry value = 72.1 ms). After clinical recovery, re-scans indicated that T2-relaxometry was reduced by 8.66 SD in the left superior parietal region, 40.88 SD in the left anterior insula, and 6.15 SD in the right superior frontal region.

3.2.3. Case 3

Case study three suffered an mTBI when he collided with another player during a football game. The patient did not report any specific

symptoms during his clinical assessment 11 days post-injury. The patient's BIST scores were low with no symptom domains or individual statements obtaining abnormally high scores and an initial total score of 13/160. The patient reported no previous mTBIs and the recovery time for the current mTBI was recorded as 27 days. Two significant voxel clusters are identified when analysing the T2 relaxometry images (see Fig. 3). The first is in the right somatosensory cortex in the parietal lobe, with relaxometry times up to 8.66 SD above controls (peak relaxometry value = 76.1 ms) and the second is in the right intraparietal sulcus, with relaxometry times up to 15.69 SD higher than controls (peak relaxometry value = 51.5 ms). After clinical recovery, re-scans indicated that T2-relaxometry was reduced by 1.54 SD in the right somatosensory cortex and by 0.06 SD in the right intraparietal sulcus.

3.2.4. Case 4

Case study four had a head-to-head collision with a teammate during a rugby game and suffered an mTBI as a result. At the time of injury, the patient reports "seeing stars" and being unsteady, followed by headaches and sensitivity to light. Symptoms resolved within a few days and were exacerbated approximately nine days post-injury during Jujitsu training. At his clinical assessment, 12 days post-injury, the patient reports headaches and fatigue. BIST scores were low, with no symptom domains or individual statements obtaining abnormally high scores and an initial total score of 22/160. The patient has reported one previous mTBI, in 2021. Recovery time for the current mTBI is recorded as 26 days. When analysing T2 relaxometry MRI data for this patient, two significant clusters of voxels were discovered (see Fig. 3). The first is in the left anterior insula, with relaxometry times up to 12.12 SD higher than controls (peak relaxometry value = 68.3 ms) and the second is in the left posterior cerebellum, with relaxometry times up to 7.04 SD above controls (peak relaxometry value = 67.0 ms). After clinical recovery, re-scans indicated that T2-relaxometry was reduced by 11.22 SD in the left anterior insula, but no reduction was found in the left posterior cerebellum.

3.2.5. Case 5

Case study five sustained an mTBI during gymnastics training when he fell off a high bar. The patient reports stumbling when returning to his feet but not experiencing any other symptoms at the time of injury. The following day, he reports feeling disoriented and unwell. Two days after the first injury, the patient again falls on his head during gymnastics training. This time, the patient reports seeing flashes of colour and

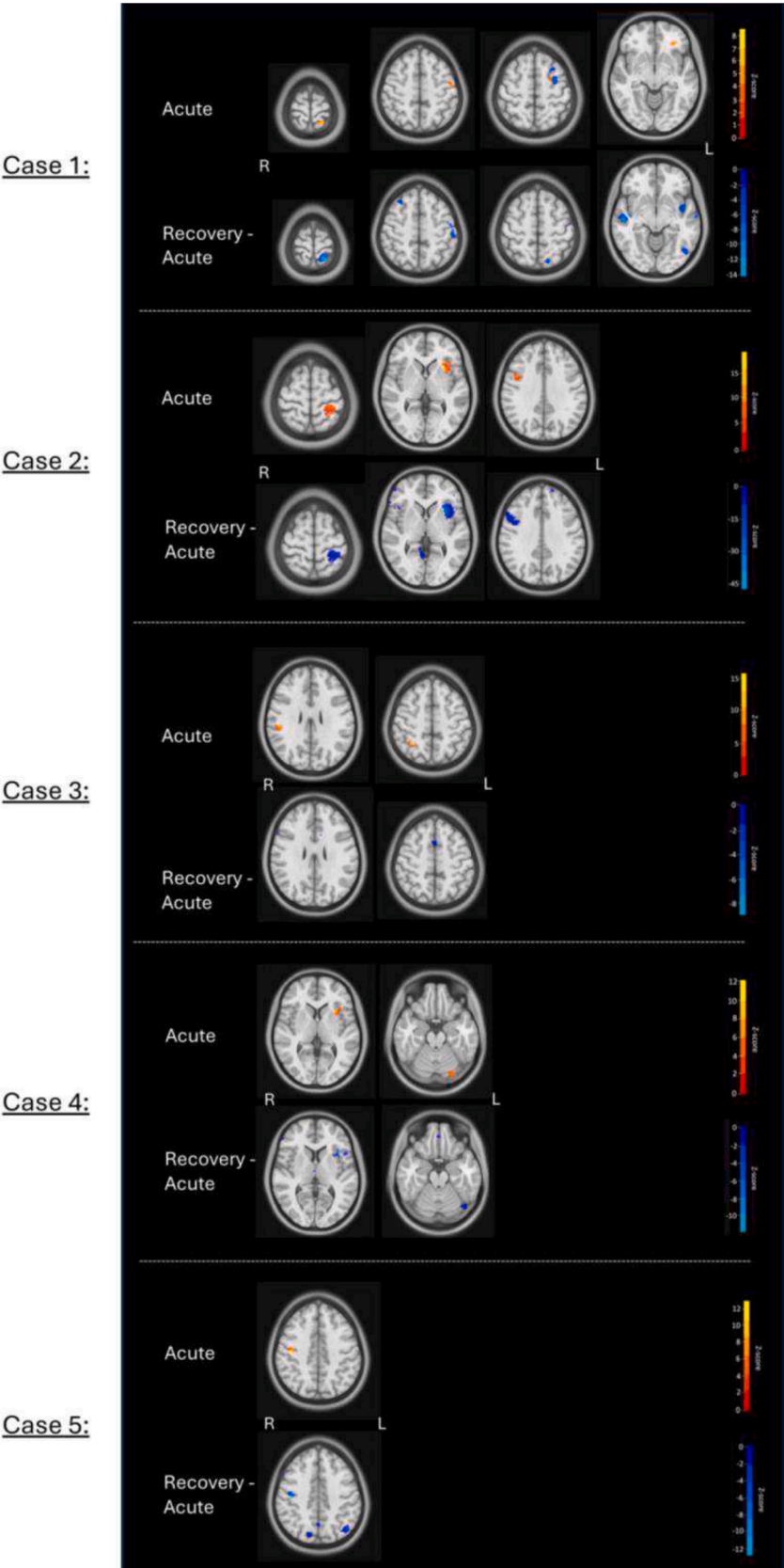


Fig. 3. T2 Relaxometry acutely following mTBI (top) and at recovery (bottom) (in SD) for cases 1–5.

blurred vision. No additional symptoms are reported during his clinical assessment seven days post-injury. BIST scores were low, with no symptom domains or individual statements obtaining abnormally high scores and an initial total score of 34/160. Recovery time for this injury is recorded as 56 days, and this patient has suffered one previous mTBI in approximately 2017/2018. When analysing the T2 relaxometry images, one significant cluster of voxels was found in the right anterior parietal lobe (see Fig. 3), with relaxometry times of up to 12.83 SD above controls (peak relaxometry value = 55.9 ms). After clinical recovery, re-scans indicated that T2-relaxometry was reduced by 12.68 SD in this region.

3. Discussion

3.1. Individual-level brain abnormalities in acute mTBI

Group-level statistical analyses dominate clinical neuroscience, and while they have utility in enabling reliable comparisons between groups, they may not detect brain abnormalities unique to individuals. Our study compared each mTBI patient to the average of controls, enabling a comprehensive analysis of significant voxel clusters for specific individuals. We found that 19/20 mTBI patients had significantly higher T2 relaxometry times than the control group (see Fig. 3). Regions with significantly higher T2 relaxometry are summarised in Table 2 and include the left hippocampus, left superior parietal cortex, left superior frontal cortex, left orbitofrontal cortex, left supramarginal gyrus, left anterior insula, left posterior cerebellum, right temporoparietal junction, right superior cerebellum, right medial prefrontal cortex, right somatosensory cortex, and the cingulate cortex. Given T2 relaxometry's sensitivity to quantify water properties, we hypothesise that our findings could indicate signs of subtle neuroinflammation during acute stages of mTBI. These findings are corroborated by our recent T2-relaxometry group analysis (Bedggood et al., 2024). Here, we compared 40 mTBI and controls, and the results indicated that whole-brain average T2-relaxometry was significantly increased in the mTBI group compared to controls – which further validates our current finding that 95 % of participants in this case series had increased T2-relaxometry compared to controls. However, the group analysis results indicated that increased T2-relaxometry were widespread, particularly in superior cortical regions of the brain, which highlights the potential differences between individual and group imaging markers in clinical populations.

A radiologist reviewed MRI scans from all participants, and none were deemed to have any findings that would warrant clinical follow-up. This indicates that the patients in this study may have potentially pathological brain abnormalities despite no findings on hospital-based MRI protocols. Of note, the radiologist's report for case 18 did indicate a structural brain change in the left superior frontal gyrus (see Supplementary Materials 2). This region was not deemed clinically significant by the radiologist and likely unrelated to the current brain injury. Still, this region spatially aligned with our findings of a significant T2 relaxometry voxel cluster in the left superior frontal lobe and further supports our hypothesis that T2 relaxometry can identify structural brain abnormalities. This further demonstrates the utility of T2 relaxometry for uncovering subtle abnormalities.

3.2. Common regions of increased T2 relaxometry across mTBI individuals

As well as individual variation in T2 relaxometry times, we observed a range of significant voxel clusters that multiple participants had in common, affecting up to 40 % of mTBI cases (Fig. 2). These regions include the cingulate cortex, anterior insula, cerebellum and superior parietal cortex. Regions with increased T2 relaxometry times across multiple participants could indicate that specific brain regions are more susceptible to acute brain changes following mTBI. If there were regions that appear more vulnerable, these regions could serve as potential

biomarkers for injury and predictive indicators for recovery from mTBI for future players. For example, fluid accumulation in specific brain regions acutely following injury may be linked to poorer recovery. Therefore, early identification of this pathology could facilitate individualising treatment plans (e.g., a more conservative return to sport) and improve recovery outcomes.

3.3. Recovered mTBI participants show reduced T2 relaxometry

For all five participants with longitudinal data available, MRI recovery re-scans suggest that increased T2 relaxometry present in the acute scans is reduced, at least partially, once they are clinically recovered (see Fig. 3). These recovery re-scans provide valuable evidence to support the idea that the fluid accumulation found on acute scans was linked to the mTBI, as it seems to resolve as the participant recovers. This evidence aligns with a previous case report suggesting that brain-specific T2 relaxometry reduces after clinical recovery (Pedersen et al., 2020). This finding raises the question of whether mTBI is an acute or chronic injury with regard to brain pathology. Conducting recovery re-scans with a larger sample size would enable conclusions regarding whether this pattern is generalisable to the mTBI population. If our findings are replicated at a larger scale, they could be utilised as an objective measure of recovery from mTBI.

3.4. Clinical implications of increased T2-relaxometry

Conventional MRI images are generally qualitative. Without a quantitative metric to interpret the signal intensities (independent of scanner hardware and sequences), comparing MRI images longitudinally or across subjects is challenging. While the conventional method provides good tissue contrast, the signal intensity can only be interpreted qualitatively. Consequently, interpreting the resulting images relies on selecting an appropriate sequence and a sound understanding of the signal contrast relative to the pathophysiology. By not depending on this subjective process and to obtain quantitative information, the contributions of different contrast mechanisms need to be extracted (Cheng et al., 2012). Quantitative measures can isolate the contributions of individual MR contrast mechanisms (i.e. T1, T2 and T2*). The relaxation time is sensitive to water content, iron levels and tissue structure. It measures the biophysical parameters by decoupling the contrast mechanisms contributing to the signal.

Uncovering regions with increased T2-relaxometry and possible acute inflammation following mTBI could affect the individual's recovery and return to play. For example, gaining a deeper understanding of brain abnormalities post-injury could help clinicians individualise treatment plans instead of basing the plan on group averages, self-reports, or generic guidelines for recovery. To base treatment decisions on personal data means tailoring the plan for what would benefit the individual – for example, increasing or decreasing the recommended stand-down period before returning to play. Therefore, the chance of being too lenient in the approach to rest and recovery is reduced. Furthermore, knowing whether someone's brain was showing signs of pathology could instigate a need for altering the recommended physical activity, as it has been linked to inflammation (da Luz Scheffer & Latini, 2020; Godinho et al., 2021; Kreber & Griesbach, 2016; Mee-Inta et al., 2019), or it could entail incorporating other methods for reducing inflammation (e.g. anti-inflammatory medications – Bergold, 2016) that would not have otherwise been suggested. Overall, understanding brain pathology on an individual level and subsequently customising treatment plans could result in a more efficient and safer return to play for athletes with an mTBI.

3.5. Limitations and future directions

The current study has several limitations to consider when discussing the results. Firstly, while all MRI scans were conducted during a 14-day

window in the 'acute' stage following mTBI, there was inter-participant variability in the exact timing and injury severity. Minor timing and severity differences could be a potential explanatory variable to consider for differences in neuroinflammation. Furthermore, the current study only included male participants which could reduce transferability to wider mTBI populations. If both sexes were to be included, separating them into different groups and comparing them would be sensible. This would require a larger sample size and reduce the feasibility of the study. With the selection of only males, it maintains homogeneity and allows for a substantial sample size to be collected for individual analysis. Larger future studies could include females too and look at group differences. Although our simulations suggest that 44 controls are sufficient for a reliable z-test (see [Supplementary Materials 3](#)), future research would benefit from utilising larger control groups in order to establish normative ranges, or predictive machine learning approaches, in mTBI. However, we can envisage challenges conducting this type of single-subject analysis in patients with gross brain abnormalities due to lack of an equivalent control brain and potential image distortions during MNI normalisation process. Lastly, while the BIST was utilised to measure injury and clinical recovery, our future research aims to include additional clinical and behavioural data as well as more standardised clinical and functional measures to encapsulate a more comprehensive picture of participants' clinical presentation.

Although longitudinal research is challenging (especially as MRI studies are a large commitment for the participants), it would be beneficial for future research to re-scan more mTBI participants after recovery. This way, T2 relaxometry times, and therefore sites of possible neuroinflammation, could be compared in the 'injured' and the 'recovered' brains of participants to see if significant clusters in the acute scans normalise with recovery. The possibility that increased T2-relaxometry indicates subtle inflammation in the brain is, at this stage, still uncertain and requires further validation. Future research should validate this measure with other markers of inflammation, for example IL-10, a pro-inflammatory marker that also promotes microglial recovery in rat models of mild TBI injury ([Maiti et al., 2019](#)).

4. Conclusion

We observed that nearly all mTBI participants had evidence of elevated brain T2 relaxometry after an mTBI. We hypothesise that these findings could indicate possible neuroinflammation and enable a deeper understanding of their injuries' pathology. However, this remains uncertain and needs to be validated with further research. Furthermore, comparing the recovery MRI scans of five participants to their acute scans indicated that T2 relaxometry reduces at recovery. This suggests a possible transient nature to the brain pathophysiology and provides a possible objective imaging technique for reliably judging recovery following mTBI. Quantitative T2 relaxometry methods provide individual, detailed maps of potential brain abnormalities and may offer new insights into a patient's clinical presentation. Understanding the role that this increase in T2-relaxometry, and possible inflammation, plays acutely post-mTBI could have implications for individualising treatment approaches and, therefore, improving recovery outcomes for mTBI patients.

CRedit authorship contribution statement

Mayan J. Bedggood: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Christi A. Essex:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation. **Alice Theadom:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Samantha J. Holdsworth:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Richard L.M. Faull:** Writing – review &

editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Manor Pedersen:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

De-identified data will be made available upon reasonable request.

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Appendix A. Supplementary data

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Appendix 8: Second Publication

RESEARCH ARTICLE OPEN ACCESS

MRI-T2 Relaxometry is Increased in Mild Traumatic Brain Injury: Indications of Acute Brain Abnormalities After Injury

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ABSTRACT

Mild traumatic brain injury (mTBI) is a common condition, particularly pervasive in contact sports environments. A range of symptoms can accompany this type of injury and negatively impact people's lives. As mTBI diagnosis and recovery largely rely on subjective reports, more objective injury markers are needed. The current study compared structural brain MRI-T2 relaxometry between a group of 40 male athletes with mTBI within 14 days of injury and 40 age-matched male controls. Voxel-averaged T2 relaxometry within the gray matter was increased for the mTBI group compared to controls ($p < 0.001$), with statistically significant increased T2 relaxometry particularly in superior cortical regions. Our findings indicate subtle brain abnormalities can be identified in acute mTBI using MRI-T2 relaxometry. These brain abnormalities may reflect inflammation present in the brain and could constitute an objective injury marker to supplement current subjective methods that dominate clinical decisions regarding diagnosis and prognosis. Future research should validate this potential marker with other data types, such as blood biomarkers or histological samples.

1 | Introduction

Mild traumatic brain injury (mTBI) is a common and disabling brain injury that occurs due to a force to the head caused by a sudden impact, rotational force, rapid deceleration or acceleration (Danielli et al. 2023; McAllister 2011; Oris et al. 2023; Verboon et al. 2021). This force leads to brain movement within the skull and subsequent focal and diffuse damage (Alam et al. 2020; Verboon et al. 2021). Common symptoms of mTBIs include headaches, difficulty concentrating, sleep difficulties, disturbed balance, confusion, slowed reaction times, nausea and sensitivity to light or noise (Danielli et al. 2023; Markovic et al. 2021; Verboon et al. 2021). Therefore, mTBI can impact patients' lives

in diverse ways and can be associated with reduced work productivity and increased risk of psychiatric and neurodegenerative diseases (Theadom et al. 2017; Wang et al. 2021). Referring to an mTBI as 'mild' may not correspond to the personal experience of many people, as many suffer enduring symptoms that persist beyond the expected recovery time and can burden the individual for weeks, months or even years (Danielli et al. 2023; Kara et al. 2020; Rosen 2024; Slavoaca et al. 2020).

The primary injury in mTBI is from the immediate mechanical damage to the brain that can result in a combination of focal coup and contrecoup damage as well as diffuse damage (Alam et al. 2020; Toma and Nguyen 2020). Following this, a cascade

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Summary

- Current understandings of brain pathology underlying mild traumatic brain injury (mTBI) have many gaps, and recovery is variable and largely based on subjective reports.
- Objective markers of injury are required to enhance diagnostic and prognostic capabilities and improve recovery trajectories.
- Our findings suggest that quantitative MRI-T2 relaxometry times are increased acutely following mTBI compared to controls, possibly indicative of neuroinflammatory processes post-injury.
- MRI-T2 relaxometry could represent an objective injury marker acutely following mTBI and be utilized to supplement clinical decision making.
- Insight into mTBI neuropathology could lead to safer, more efficient return to sport, work, or education.

of secondary injuries can occur, in which inflammation is a key component (Markovic et al. 2021; Piao et al. 2013; Rosen 2024). Neuroinflammation is a dynamic response of the brain's immune system to harmful stimuli or events and is initiated by the activation and recruitment of immune cells by facilitating the production of cytokines and chemokines (Pasternak et al. 2012, 2016). Microglia play a crucial role in responding to inflammatory events as they survey the brain, phagocytose pathogens and cellular debris, and release inflammatory mediators to aid in the clearance of necrotic tissue to prevent further spread of the injury (Alam et al. 2020; Pasternak et al. 2012; Simon et al. 2017; Strogulski et al. 2023; Yu et al. 2022). Neuroinflammation can be beneficial in the acute phase following brain injury, promoting repair of damaged tissue, possibly inducing neurogenesis and reducing the risk of infection (Monsour et al. 2022). However, when inflammation occurs in excess, it can contribute to loss of neurons and death of brain tissue, which, in some cases, represents a preventable secondary injury cascade (Corps et al. 2015; da Luz Scheffer and Latini 2020; Kim et al. 2023; Markovic et al. 2021; Mee-Inta et al. 2019; Pasternak et al. 2016).

In the brain, free water is found within the ventricles as cerebrospinal fluid (CSF) and surrounding the brain parenchyma. However, free water can also accumulate in the extracellular space of the parenchyma due to brain trauma or hemorrhage, for example, that rupture the blood–brain barrier (Pasternak et al. 2009). As a result of the inflammatory response following mTBI, a higher amount of water can accumulate in the extracellular space, increasing the free water to bound water ratio. This accumulated fluid, or free water, reflects the fractional volume of unrestricted water and is hypothesized to indicate extracellular changes driven by underlying pathologies (Lyall et al. 2018). This can be a result of multiple different aspects of the inflammatory response, such as inflammatory edema or microglia and other immunoreactive cells (e.g., astrocytes) that induce excessive osmosis of water into the extracellular space from the blood–brain barrier (Albrecht et al. 2016; Lyall et al. 2018; Pasternak et al. 2012).

MRI-T2 relaxometry is a measure of the loss of spin coherence of excited water molecules and subsequently represents the dynamic nature of water and its interaction with macromolecules in tissue (Albrecht et al. 2016; Deoni 2010). Water bound with larger macromolecules has a spin frequency comparable to the Larmor frequency and is linked with shorter T2 relaxation times. In contrast, free water molecules are smaller, with a faster spin frequency and a longer T2 relaxation time (Cheng et al. 2012; Ghugre et al. 2011; Liu et al. 2018). In healthy tissue, these types of water exist in equilibrium. However, bound water is released in some pathological conditions, increasing the free-water molecule ratio. This creates a medium inefficient for T2 relaxation, subsequently increasing T2 relaxation time as the free water content increases (Cheng et al. 2012; Ghugre et al. 2011; Liu et al. 2018). As T2 relaxometry assesses microstructural tissue alterations, primarily based on water content, it is possible that it may provide a marker of cellular injury and related outcomes of inflammatory processes (Adel et al. 2023; Cheng et al. 2012; Ghugre et al. 2011; Gracien et al. 2016; Liu et al. 2018; Maillard et al. 2004; Pell et al. 2004; Winston et al. 2017; Yang et al., 2015). For mTBI patients, increased T2 relaxometry times may reflect extracellular fluid accumulation in the brain, indicative of neuroinflammatory edema due to inflammatory processes characteristic of the secondary injury cascades associated with mTBI.

To the author's knowledge, only two previous case series have used this technique in mTBI. Pedersen et al. (2020) used MRI-T2 relaxometry and identified potential markers of brain inflammation in a professional Australian Rules football player who had incurred multiple mTBIs. The abnormally elevated T2 relaxometry persisted throughout each symptomatic MRI scan and normalized as the patient recovered. However, T2 relaxation times remained elevated compared to baseline on the last 'recovery' scan, suggesting that there may also have been a chronic increase of T2 relaxometry after repetitive mTBIs. In addition, our previous case series analysis (Bedggood et al. 2024) compared T2 relaxometry for 20 individual mTBI participants with the average T2 relaxometry for 44 healthy controls. T2 relaxometry was increased in 19/20 (95%) mTBI participants in at least one cluster of voxels. In five mTBI participants, the areas of increased T2 relaxometry were, at least, partially resolved on recovery re-scans. The aforementioned research demonstrates the potential utility of this MRI method in deepening our understanding of brain pathology following acute mTBI, while highlighting a need for larger group analyses.

Objective markers of brain injury are required to improve mTBI diagnosis and aid in recovery predictions. Given that hospital-based neuroimaging post-mTBI often shows no findings (Mayer et al. 2015), objective measures such as T2 relaxometry may enable clinical decision support with additional objective evidence, complementing subjective self-reporting and clinical symptomatology. Our previous case series (Bedggood et al. 2024) assessed the potential for MRI-T2 relaxometry to identify and quantify subtle brain abnormalities on an individual level. Our current study extends this research by conducting statistical analysis on a group level with a substantially larger mTBI cohort. With this, we increase the power and external validity of the findings and contribute to a significant gap in existing research with regard to MRI-T2 relaxometry and brain

trauma. For the current study, we hypothesized that the mTBI group would have significantly increased brain T2 relaxometry compared to the control group, potentially indicating acute neuroinflammation following mTBI.

2 | Materials and Methods

Ethics approval was obtained from the Health and Disability Ethics Committee, New Zealand (HDEC—2022 EXP 11078). Institutional approval was also obtained (AUTEC reference 22/12).

2.1 | Participants

We recruited two groups between 16 and 35 years of age. The first group consisted of 40 males with a mean age of 21.4 years (± 5.0 years) with acute sports-related mTBI (≤ 14 days post-injury). Participants for this group were included if their injury occurred in a sports game or training and was diagnosed by a doctor. Diagnosis was based on a combination of (1) clinical history with a plausible mechanism, (2) sport concussion assessment tool (SCAT-5) or brain injury screening tool (BIST) symptom scores, (3) clinical examination to exclude any neurological or intracranial abnormalities, (4) review of video if available, and (5) eye-witness accounts if available. The second group consisted of 40 healthy male controls (athletes and non-athletes) with a mean age of 22.1 years (± 3.8 years) who had not suffered an mTBI in the last 12 months, had not suffered more than five total mTBIs in their lifetime, and did not have lingering symptoms from a previous mTBI (to minimize potential confounding effects of cumulative damage and/or chronic inflammation). Participants for either group were excluded if they had an existing significant neurological condition or were contraindicated for an MRI scan (e.g., certain metal implants, or braces). An independent-sample t-test showed no significant age difference between the groups, $t(78) = 0.71$, $p = 0.48$.

mTBI participants were recruited at the Axis Sports Concussion Clinics in Auckland, New Zealand, and via community links (e.g., physiotherapists, word of mouth, digital and print advertisements). Participants in the mTBI group comprised 27 rugby players, five football players, two hockey players, two martial artists, one futsal player, one gymnast, one surfer, and one swimmer. Participants were scanned, on average, 10.7 ± 2.9 days following their injury. Control participants were recruited via print advertisements at the Auckland University of Technology and The University of Auckland and social media advertisements. All participants were provided with study information prior to providing informed consent. See Table S1 in the Supporting Information S1 for additional information on mTBI participants.

2.2 | Magnetic Resonance Imaging Procedure

All magnetic resonance images were acquired using a 3T Siemens MAGNETOM Vida fit scanner (Siemens Healthcare, Erlangen, Germany) located at the Centre for Advanced

Magnetic Resonance Imaging (CAMRI) at The University of Auckland, New Zealand, using a 20-channel head coil. A T2 mapping sequence was collected to investigate anatomical T2 relaxometry. T2 maps were acquired using an eight echo Carr-Purcell-Meiboom-Gill (CPMG) sequence (TEs = 28.9, 57.8, 86.7, 115.6, 144.5, 173.4, 202.3, and 231.2 ms; TR = 6 s; slice thickness = 2.0 mm; voxel size = $2.0 \times 2.0 \times 2.0$ mm; matrix size = $112 \times 128 \times 63$; flip angle (FA) = 180° ; base resolution = 128; phase resolution = 100%; phase field of view (FOV) = 87.5%). Total T2 mapping acquisition time was 12:02 min. T1-weighted anatomical images were collected for quality control purposes. T1-weighted images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR = 1.9 s; TE = 2.5 ms; TI = 979 ms; FA = 9° ; slice thickness = 0.9 mm; voxel size = $0.4 \times 0.4 \times 0.9$ mm; matrix size = $192 \times 512 \times 512$; phase FOV = 100%). Total T1-weighted acquisition time was 4:31 min. A radiologist reviewed clinically relevant MRI images from each participant to check for clinically significant abnormalities that might require further attention.

2.3 | Data Processing and Statistical Analysis

All MRI images were received in DICOM format, converted to NIfTI format using *dcm2nii* (Li et al. 2016) and then arranged according to the *Brain Imaging Data Structure (BIDS)* (Boré et al. 2023). Image quality assurance checking was conducted in the *MR View* toolbox of *MRtrix3* (Tournier et al. 2019) by two investigators in the study (MJB, MP) using the participants' T1 weighted image as the underlay and their T2 map as the overlay to check for artifacts or abnormalities caused by scanning or processing. Then, preprocessing was conducted on the T2 maps using *PyCharm* version 2022.2.3. This preprocessing step included brain extraction (skull stripping) using the *bet* function in FSL (Smith 2002) before normalizing each image to the MNI standard space by registering them to a MNI152 $2.0 \times 2.0 \times 2.0$ mm template image using *FSL FLIRT* (Jenkinson et al. 2002). The third T2 echo volume (86.7 ms) was extracted for each participant to generate a group average brain image and binary gray matter (GM), white matter (WM), and CSF masks. Lastly, we removed the first volume, using the offset as a fitting parameter to the T2 relaxation data (Milford et al. 2015) and a monoexponential function at each voxel was fitted across all eight echo-times using *qMRLab* (Karakuzu et al. 2020) in *Matlab R2022B* to calculate the T2 relaxation time for each participant. Note, MRI acquisition and processing details up until this point are the same as specified in our previous case series (Bedgood et al. 2024).

An in-house script in Matlab was then used to convert files back to NIfTI format and apply a smoothing of 6 mm FWHM. Each participant's average brain T2 relaxation was then calculated by removing T2-relaxometry voxels with > 160 ms (i.e., artifactual relaxation times) and applying a gray matter mask to all voxels. Using the *DPABI Statistics Tool* (Yan et al. 2016), a two-sample t-test was conducted with a two-tailed hypothesis. Voxel-wise permutation testing with threshold free cluster enhancement (TFCE) was conducted with 20,000 permutations to reduce the type 1 error rate and because it is relatively insensitive to varying smoothing parameters (Smith and

Nichols 2009). A second gray matter mask was included at this stage to combat partial volume effects of GM, WM, and CSF and ensure that any voxels smoothed beyond the gray matter were excluded from the final statistical analysis. In addition, an independent-sample *t*-test was conducted in *Jamovi* version 2.3.19.0 (The Jamovi Project 2024) to quantify whole-brain averaged differences in T2 relaxometry between mTBI and controls.

3 | Results

3.1 | Analysis 1: Average Whole-Brain T2 Relaxometry Between mTBI and Controls

A two-tailed independent *t*-test was conducted to determine if there was a difference in mean total gray matter T2 relaxometry between the mTBI and control groups. The mTBI group (70.3 ± 1.55 ms) had significantly higher average total brain T2 relaxometry compared to the control group (69.1 ± 1.48 ms), $t(78) = 3.56$, $p < 0.001$ (see Figure 1). To ensure that total intracranial volume (TIV) did not have an impact on group differences in T2 relaxometry, we also conducted an independent-sample *t*-test on TIV between mTBI and controls, which was not significant, $t(78) = 1.25$, $p = 0.216$.

3.2 | Analysis 2: Significant Voxels Compared Between mTBI and Controls

There were significant differences found between mTBI and controls using a TFCE permutation test, correcting for multiple comparisons. These differences were driven by elevated T2 relaxometry in dorsal cortical brain regions of mTBI participants, with slightly fewer statistical differences observed in the inferior regions. Elevated T2 relaxation times in the mTBI group were

observed in multiple anatomical regions, including the superior and middle frontal gyri, paracentral lobule, pre- and postcentral gyri, superior and inferior parietal lobules, anterior cingulate cortex, hypothalamus, anterior and middle temporal lobules, and the cuneus of the occipital lobe. See Table 1 for specific T2 relaxometry values that represent the difference between mTBI and controls for example brain regions, as well as Figure 2 for an illustration of these regions.

The commonly used Yeo 7 network parcellation mask (Yeo et al. 2011) was also used to quantify the proportion of TFCE voxels within each of the 7 networks in the brain (see Figure 3) that were significantly different between mTBI and controls. The highest proportion of voxels that were significantly increased for mTBI compared to controls was significant in cortical networks, including the somatomotor network (11% of voxels), dorsal attention network (9% of voxels), and ventral attention areas (7% of voxels). Less significant voxels were seen in the fronto-parietal network (4% of voxels), visual network (2% of voxels), default mode network (1% of voxels), and limbic network (0.5% of voxels).

TABLE 1 | Example brain regions with significant group differences in T2 relaxometry times (ms).

Region	T2 relaxometry (ms)
L superior frontal gyrus	5.523
L middle frontal gyrus	4.474
L paracentral lobule	3.203
L precentral gyrus	4.311
L post central gyrus	5.815
L postcentral gyrus	3.215
L anterior cingulate	4.034
L anterior cingulate	3.817
L hypothalamus	3.938
L medial temporal lobule	3.440
L inferior parietal lobule	4.322
L cuneus	5.257
R middle frontal gyrus	4.528
R inferior frontal gyrus	4.058
R precentral gyrus	3.674
R postcentral gyrus	4.572
R superior parietal lobule	4.486
R inferior parietal lobule	5.006
R anterior temporal lobule	4.595

Note: Each MRI-T2 relaxometry time indicates the difference between the two groups in ms, calculated by subtracting the control group values from the mTBI group values. Therefore, positive values indicate regions where the T2 relaxometry times were higher for the mTBI group compared to controls. These are examples of regions with a statistically significant difference in relaxometry times and do not represent an all-encompassing list of brain-wide differences.

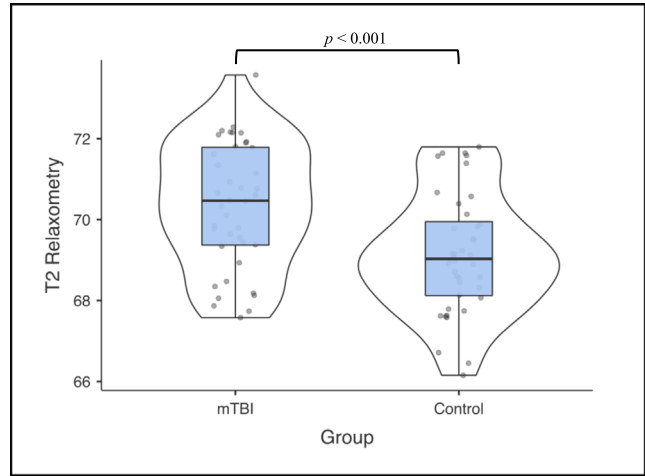


FIGURE 1 | Violin plot depicting statistically significant group difference in average whole-brain T2 relaxometry for mTBI versus controls. An independent-sample *t*-test was used to calculate the difference between groups (using *Jamovi*), with a significance threshold of $p < 0.05$. Average T2 relaxation time is indicated by the y-axis and measured in milliseconds (ms). The median is indicated by a solid center line for each group.

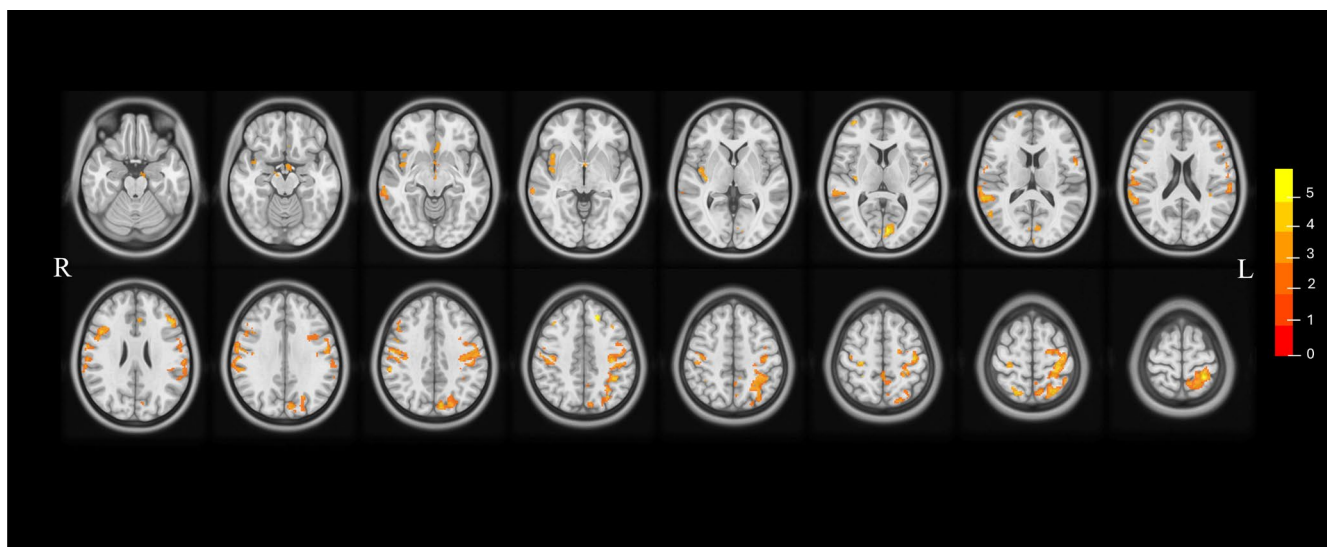


FIGURE 2 | The above figure illustrates group differences in average T2 relaxometry across the whole brain, measured in t-values. This finding indicates significantly increased T2 relaxometry in the mTBI group compared to the control group.

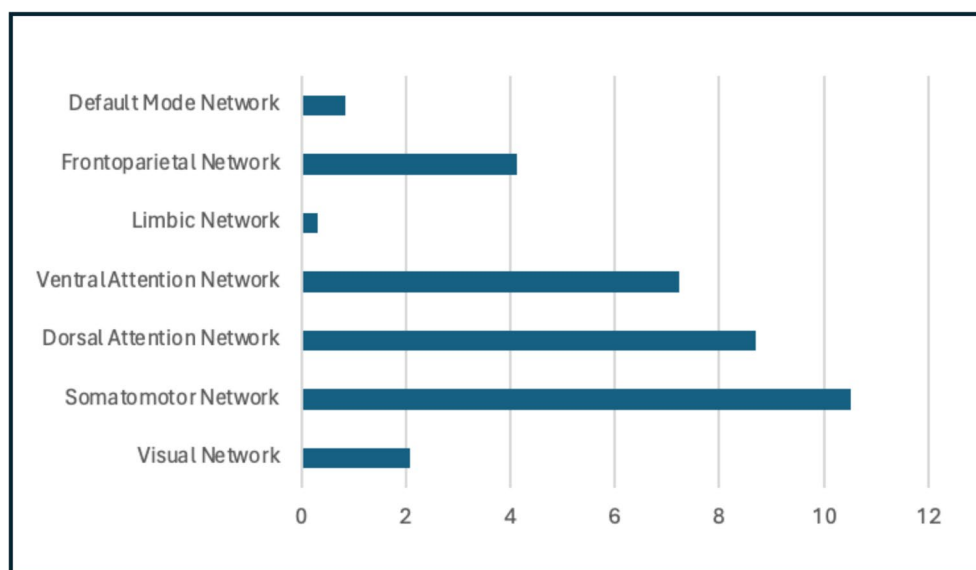


FIGURE 3 | Proportion of voxels within brain networks that are significantly increased for mTBI compared to controls (%).

4 | Discussion

The current study aimed to investigate the potential of quantitative MRI-T2 relaxometry to be used as an objective marker of injury. We found that brain MRI-T2 relaxometry was increased acutely following sports-related mTBI compared to healthy controls (Figure 1), which supports our study's hypothesis. T2 relaxation times are influenced by the water content of tissue, with longer relaxation times observed in tissue with a higher ratio of free water molecules compared to bound water molecules. This ratio of water molecules can be observed in conditions including disease and trauma and may be reflective of the brain's inflammatory response. Inflammation encapsulates many processes and can lead to increases in extracellular free water (Albrecht et al. 2016; Lyall et al. 2018; Pasternak et al. 2012). While we do not know if our findings represent increased intracellular and/or extracellular fluid accumulation,

as we cannot directly test this with MRI-T2 methods, we hypothesize that our results are indicative of inflammatory processes acutely post-mTBI. This finding may be due to the inflammatory response that is a part of the secondary injury cascade following mTBI, which aligns with our study time-frame (within 14 days post-injury).

There is existing support for the notion that excessive fluid accumulation could have utility as a biomarker of neuroinflammation (Pasternak et al. 2012). For example, a significant relationship has been found (Lesh et al. 2021) between a known inflammation-related metabolite, glutathione (GSH), and free water, supporting the idea that free water indicates an inflammatory response in the brain. Increased free water has been found in WM; Sun et al. (2024) associated with small vessel disease (SVD), which is suggested to indicate neuroinflammation (Duering et al. 2018; Sun et al. 2024). Furthermore, free water

has been correlated with elevated levels of brain interferon-gamma, a cytokine that has a crucial role in an array of immune responses, solidifying the sensitivity of free water as a marker of neuroinflammation (Febo et al. 2020; Sun et al. 2024). Finally, further support for the hypothesis that increased water volume represents neuroinflammation comes from schizophrenia research, where abnormalities in the immune response play a key role in the pathophysiology (Lyll et al. 2018; Pasternak et al. 2016). The link between free water and neuroinflammation needs to be validated further, given that free water may be influenced by multiple factors, including neuronal degeneration, hemorrhage, or edema. Validation could be done by assessing correlations with more established measures of immune function, such as those using histological samples.

It is important to note, however, that the prior research mentioned above, supporting the link between increased water and inflammatory processes, is dominated by a type of diffusion MRI method. While both diffusion and T2 relaxometry are sensitive to extracellular water changes, they are measuring different properties (Pasternak et al. 2012). Diffusion techniques may be able to show free water increases during an inflammatory response as inflammation can lead to a breakdown in cellular barriers and subsequently increase the amount of freely diffusing water in the extracellular space, which is detected by free water diffusion MRI (Duering et al. 2018; Dumont et al. 2019; Febo et al. 2020; Pasternak et al. 2012; Sun et al. 2024). While diffusion techniques more directly measure the mobility of water molecules, T2 relaxometry revolves around water-protein interactions and the tissue microenvironment (Albrecht et al. 2016; Cheng et al. 2012; Deoni 2010; Duering et al. 2018; Pasternak et al. 2016). Therefore, while it is useful and relevant to consider research using free water diffusion methods when assessing a potential link to neuroinflammation, caution should be taken with direct comparisons to the potential link between T2 relaxometry and neuroinflammation. Future research could endeavor to utilize both methods and analyze correlations between them.

MRI-T2 relaxometry has previously been utilized in various clinical research settings, including hippocampal sclerosis research (e.g., Adel et al. 2023; Bartlett et al. 2007; Jackson et al. 1993; Winston et al. 2017), juvenile dermatomyositis (e.g., Maillard et al. 2004), multiple sclerosis (e.g., Gracien et al. 2016) and in a rodent model of mTBI (e.g., Yang et al. 2015). However, to the author's knowledge, only two previous studies have looked at MRI-T2 relaxometry in human mTBI (Bedgood et al. 2024; Pedersen et al. 2020) and the current study is the first research looking at its use, on a group level, in a cohort of mTBI. Our results were consistent with a previous case study that found increased T2 relaxometry in a sports player with an acute mTBI (Pedersen et al. 2020) and our case series (Bedgood et al. 2024) that also demonstrated increased T2 relaxometry in individuals with acute mTBI compared to controls. It is possible that increased T2 relaxometry reflects other processes, such as hemorrhage, changes in iron, molecular changes in the tissue composition, or tissue necrosis (Pasternak et al. 2016). However, we did not see evidence of hemorrhage; tissue necrosis would be unlikely in a mild injury like mTBI, and our previous research, while limited, has suggested that T2 relaxometry times may normalize as the patient recovers (Bedgood et al. 2024; Pedersen et al. 2020),

which is consistent with a transient inflammatory process post-injury, as opposed to a more permanent loss of neuronal tissue. Therefore, we believe the increased T2 relaxometry in the mTBI group is more likely to be indicative of subtle brain inflammation post-mTBI. However, further research is needed to eliminate other possible causes of increased T2 relaxometry.

We observed that increased T2 relaxometry was widespread but particularly prominent in superior dorsal regions of the frontal and parietal lobes. Specific anatomical regions with elevated T2 relaxation times included areas such as the superior, middle, and inferior frontal gyri, the cingulate gyrus, the DLPFC, anterior cingulate cortex, precentral and postcentral gyri, the insula, middle and superior temporal gyri, the TPJ, and cuneus (see Figure 2). Cortical networks with elevated T2 relaxation times included the somatomotor, dorsal attention, and ventral attention networks. The dorsal cortical location of increased T2 relaxometry could represent areas of increased vulnerability following mTBI. This could be due to where coup and contrecoup damage commonly occur or where there is likely to be more concentration of force in cortical sulci, for example (Drew and Drew 2004; Kornguth et al. 2017; Toma and Nguyen 2020). Our findings overlap with existing research indicating a predictable profile of brain regions that are vulnerable in mTBI, including the frontal and temporal lobes in general and, more specifically, the dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, temporal polar cortex, amygdala, hippocampi, cerebellum, and brainstem (Bigler 2023; McAllister 2011). Although previous research has shown that T2 relaxometry decreased after clinical recovery, it remains unknown what the longer-term implications are, especially as cortical regions are known to be an early marker for cumulative damage and chronic injury, including neurodegenerative disease (Bieniek et al. 2021; Ghajari et al. 2017; McKee et al. 2016, 2018).

One of the multi-faceted challenges that accompany mTBI is that while some people recover quickly with no intervention, many experience chronic symptoms and functional deficits. Therefore, there is a need to identify those at risk of slowed recovery so clinicians can provide individualized treatment where necessary. Although FDA-approved blood biomarkers (ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein) are promising from an acute clinical perspective, there are currently no reliable biomarkers of mTBI that could be utilized a week or two after injury, when many patients present to clinics (Diaz-Arrastia et al. 2014; Kobeissy et al. 2024). Furthermore, the process of recovery relies on subjective symptom reporting. Enhancing our understanding of neurological changes that take place post-mTBI may identify those at a greater risk of poor recovery trajectories. A reliable biomarker of inflammation is important as it may provide a time window for anti-inflammatory treatment in the acute stages post-mTBI, which could minimize secondary injury cascades relating to neurodegenerative processes (Pasternak et al. 2012). Ultimately, having an objective marker of injury and/or recovery from mTBI has the potential to contribute to a safer and more efficient return to play, education, or employment.

The current study has limitations that should be considered when evaluating the findings. Firstly, we only included male participants, which will reduce external validity and transferability

to wider mTBI populations. If both sexes were to be included, separating them into distinct groups and comparing them would be most sensible, as there may be sex differences in presentation following mTBI (e.g., due to differences in hormones at the time of injury or neck musculature). Creating this between-group comparison would require a larger sample size and reduce the feasibility of the study. The selection of only males allows for a substantial sample size to be collected for group comparison of mTBI versus controls to test the feasibility of imaging markers in a homogenous sample. For future studies, we aim to include females too and look at group differences (e.g., looking at the influence of estrogen and progesterone hormones for females during the acute phase of injury), increasing the generalizability and clinical utility of results. Furthermore, while injury history and clinical information are available for most of the mTBI group, the same was not collected for the control group in the current study. In addition, various assessments were conducted on the mTBI participants at the discretion of their doctors and specific clinic guidelines, including the SCAT-5, BIST, Cognigram, and buffalo concussion treadmill test (BCTT); however, we did not collect data from any full neuropsychological assessments as a consistent measure for analysis in the current study. We acknowledge these as limitations and aim to collect more comprehensive background information for both groups in future research, including standardized neuropsychological testing at the same time point as the brain scans, to assess potential correlations between these measures.

While we made efforts to recruit participants as soon after their injury as possible, the MRI scans varied within a 14-day time frame. Future research should endeavor to scan participants within a shorter time frame to increase the homogeneity between injury and scan, reducing possible timing confounds. In addition, it is important to consider the relative strengths and limitations of conducting cross-sectional versus longitudinal research. Longitudinal designs offer increased internal validity, information about the prognostic utility of objective markers, potential correlations between objective markers and subjective self-reports, and how these may change throughout recovery, and they can add to our knowledge about the transient versus chronic nature of potential inflammatory responses post-mTBI. However, longitudinal research is more expensive and, therefore, less feasible to conduct with large sample sizes. In addition, there is a higher commitment and participant burden, which can increase attrition and subsequently reduce external validity. Lastly, accessibility to ongoing assessments can also be an issue, which may introduce sampling bias and further limit generalizability. Conversely, while cross-sectional designs are less expensive and require a lower participant burden with subsequent higher feasibility and ease of analysis, they offer less information regarding the time course of the injury or participant recovery. This means there is limited potential to assess the objective marker's utility in predicting recovery from mTBI, for example. Therefore, conducting a longitudinal study and re-scanning all participants upon clinical recovery to see if elevated T2 relaxometry resolves with symptom resolution and whether it could be used to predict recovery would be beneficial. Doing so could strengthen the link between this objective marker and subjective reports and help decipher the transient versus chronic nature of the inflammatory response instigated by an mTBI.

Further research is needed to support the potential of T2 relaxometry as an imaging marker of mTBI injury. As the increase in extracellular volume within a voxel could be caused by a multitude of processes, we cannot be certain that the increased T2 relaxometry that we found is indeed indicative of inflammation. Validating the MRI-T2 relaxometry findings with blood biomarkers or histological measures of inflammation would be beneficial in strengthening the clinical utility of this potential injury marker. Lastly, future research could supplement the current approach by utilizing free water imaging methods too. While T2 relaxometry can identify changes in water content via molecular interactions, free water imaging can identify extracellular volume more directly. It is possible that this is more specific to neuroinflammation and therefore could strengthen current T2 relaxometry findings (Pasternak et al. 2016).

5 | Conclusions

MRI-T2 relaxometry was increased in athletes with mTBI compared to healthy controls. Increased T2 relaxometry was widespread but particularly prominent in the dorsal cortices of the brain. Our results suggest possible brain inflammation acutely following mTBI and could represent an objective injury marker for diagnostic and prognostic purposes. Future research should replicate this finding and validate whether advanced MRI methods, alongside other biomarkers, have clinical utility.

Author Contributions

Mayan J. Bedggood: conceptualization, methodology, project administration, investigation, validation, resources, data curation, software, formal analysis, visualization, writing – original draft, writing – review and editing. **Christi A. Essex:** writing – review and editing, project administration, investigation. **Alice Theadom:** funding acquisition, conceptualization, methodology, writing – review and editing, supervision. **Helen Murray:** writing – review and editing. **Patria Hume:** writing – review and editing. **Samantha J. Holdsworth:** writing – review and editing. **Richard L. M. Faull:** writing – review and editing. **Mangor Pedersen:** funding acquisition, conceptualization, methodology, project administration, validation, resources, data curation, software, formal analysis, visualization, writing – review and editing, supervision.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix 9: Third Publication

Moving for Recovery: Using time-use compositions to Explore Physical Activity and Sleep in Sports-Related Concussion

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Abstract

Sports-related concussions are a prevalent and often misunderstood form of traumatic brain injury worldwide. While earlier clinical guidelines advocated for strict physical and cognitive rest until full symptom resolution, a growing body of evidence now supports the inclusion of physical activity (PA) as a critical component of effective concussion recovery. To date, much of the research has examined the role of PA in isolation, without accounting for the inherently interdependent nature of daily movement behaviours. Time-use composition frameworks address this limitation by analysing how time is proportionally distributed across various activities and how reallocating time among these behaviours can influence health outcomes. To the author's knowledge, this is the first study to employ Compositional Data Analysis (CoDA) to assess the relative contributions of four key movement behaviours - sedentary behaviour, light PA, moderate-to-vigorous PA, and sleep - on concussion recovery. Using a homogeneous sample of 35 male athletes with acute sports-related concussion and 45 matched healthy controls, the study explored group differences in time-use composition, optimal behavioural distributions for recovery, and the impact of reallocating time among behaviours. While no statistically significant differences or associations were observed across most movement behaviours, sleep emerged as a positive predictor of recovery time in the unadjusted model. Additionally, although not statistically significant, the compositional isotemporal substitution analysis suggested that reallocating 60 minutes per day to either light or moderate-to-vigorous PA could theoretically shorten recovery duration by approximately four days. These findings demonstrate the potential of CoDA to provide nuanced insights into how the relative distribution of daily activities and sleep may influence concussion recovery. Future research with larger and more diverse samples is warranted to enhance clinical applicability and guide evidence-based treatment recommendations.

Key words: Physical activity, movement, exercise, concussion, mTBI, TBI, brain injury, recovery, CoDA, compositional data analysis, time-use epidemiology

Introduction

Concussion and Physical Activity

Sports-related concussion (SRC) is a type of traumatic brain injury resulting from direct or indirect biomechanical forces to the head, neck or body during sports or exercise (Alam et al., 2020; Patricios et al., 2023; Verboon et al., 2021). These forces - such as rapid acceleration, deceleration, or rotational movement - can be transmitted to the brain, leading to cellular disruption, potential axonal injury, altered cerebral blood flow, and inflammation (Patricios et al., 2023). SRC can be seen as an “invisible injury” with no external signs of damage, yet they can result in a wide variety of symptoms. These include headaches, difficulty concentrating, sleep disturbances, balance problems, nausea, and heightened sensitivity to light or noise (Alam et al., 2020; Di Battista et al., 2020; Markovic et al., 2021; Verboon et al., 2021). While a variable number of individuals recover within 14 days, approximately 10–30% experience persistent symptoms that can severely affect daily life (Kara et al., 2020; McInnes et al., 2017; Verboon et al., 2021). The variability in recovery trajectories remains poorly understood, presenting challenges for clinicians in managing a patient’s return to everyday activities (McGeown et al., 2020). This underscores the urgent need for further research into whether specific interventions or activity modifications during the acute phase can positively influence recovery outcomes.

Since the first International Conference on Concussion in Sport in 2001, the standard recommendation for managing sports-related concussion has been physical and cognitive rest until full symptom resolution (Howell et al., 2019; Leddy et al., 2019; Markovic et al., 2021; Micay et al., 2018; Willer et al., 2019). However, recent research has questioned the effectiveness of prolonged rest and has even identified potential risks associated with it (Dobney et al., 2017; Lawrence et al., 2018; Leddy, 2025; Leddy et al., 2019). Evidence now suggests that resting for more than three days offers minimal benefit for adult recovery (Leddy et al., 2016; Silverberg & Iverson, 2013). For example, Thomas et al. (2015) found that individuals prescribed five days of strict rest reported more symptoms and slower recovery. Similarly, Schneider et al. (2017) concluded that an initial rest period of 24–48 hours followed by gradual re-engagement in activity yields better outcomes. Reflecting this evolving evidence base, instead of advocating strict rest until all symptoms resolve, the 2022 Concussion Consensus Statement now supports a brief period (24–48 hours) of relative rest - including basic daily activities and limited screen exposure - followed by a gradual return to light physical activity, such as walking, as long as it is well tolerated. Activity intensity can then be progressively increased, provided any symptom exacerbation is mild and short-lived.

These updated recommendations are supported by a growing body of research indicating that PA plays a significant role in recovery from SRC. Numerous studies have shown that PA can shorten recovery time and reduce post-concussion symptoms (Buckley et al., 2022; Chizuk et al., 2022; Coslick et al., 2020; Grool et al., 2016; Leddy, 2025; Leddy et al., 2021; Seehusen et al., 2021). The approach to measuring the impact of PA varies across studies. Some have focused on structured aerobic exercise programs (e.g., Leddy et al., 2021), while others have examined naturalistic, daily-life activity levels (e.g., Grool et al., 2016; Seehusen et al., 2021). Research has also explored the role of different intensity levels - ranging from mild-to-moderate PA (e.g., Buckley et al., 2022) to moderate-to-vigorous PA (e.g., Coslick et al., 2020) - as well as the importance of adherence to PA regimens in promoting recovery (e.g., Chizuk et al., 2022). Importantly, no adverse events have been reported as a result of initiating PA, even when started within days of injury and in highly symptomatic individuals as young as 13 years old (Chizuk et al., 2022; Leddy et al., 2021). This highlights not only the efficacy but also the safety of early, appropriately dosed PA following SRC. Recent systematic reviews further support the positive effects of PA on

concussion recovery (Art et al., 2023; Leddy et al., 2023; Reid et al., 2022), reinforcing its role as a valuable component of post-concussion care.

A significant limitation in the current literature on PA and concussion recovery lies in the methods used to assess PA. Many studies have relied on subjective self-report measures (Boisgontier et al., 2020; Buckley et al., 2022; Coslick et al., 2020; Grool et al., 2016; Howell et al., 2016; Krainin et al., 2021; Majerske et al., 2008; Remigio-Baker et al., 2019, 2020; Wilson et al., 2020). Self-reported data are prone to various inaccuracies, including social desirability bias, where participants may overestimate their activity levels to align with perceived expectations (Van de Mortel, 2008). In the absence of objective validation, PA levels may also be unintentionally under- or over-reported. Moreover, self-report measures often lack precision in capturing the timing, duration, and intensity of activity, and they can impose a significant burden on participants (Buckley et al., 2021; Lawrence et al., 2018; Lishchynsky et al., 2019; Remigio-Baker et al., 2020; Seehusen et al., 2021; Wilson et al., 2020). Given these limitations, there is a clear need for future research to prioritise the use of objective PA tracking technologies. Doing so will enhance the accuracy, consistency, and interpretability of findings related to PA and SRC recovery.

A New Way to Look at Physical Activity: Compositional Data Analysis

Most existing research has examined PA outputs in isolation, typically exploring whether higher or lower levels of PA correlate with specific outcomes. Some studies have gone further by categorising daily behaviours into light PA, moderate-to-vigorous PA, sedentary behaviour, and sleep, in order to evaluate their individual effects on health-related outcomes (Grgic et al., 2018). However, because each day consists of a fixed 24-hour period, these behaviours are inherently interdependent - an increase in one necessarily results in a corresponding decrease in at least one of the others (Pedisic, 2017). Given this interdependence, changes in activity behaviours should be considered within the context of the entire 24-hour day. For example, increasing light PA could unintentionally reduce sleep or increase sedentary time, potentially diminishing the intended health benefits. As such, evaluating PA, sedentary behaviour, and sleep as *proportions* of a whole offers a more comprehensive framework for understanding their combined influence on health and recovery (Dumuid et al., 2021).

To address this complexity, Dumuid et al. (2018) introduced a novel statistical approach for predicting changes in continuous outcome variables based on **relative**, rather than **absolute**, changes in behaviour compositions. Compositional Data Analysis (CoDA) was developed specifically to analyse data constrained within a constant-sum structure (such as time-use data), which traditional statistical models are not well equipped to handle (Dumuid et al., 2020). CoDA uses log-ratio transformations to convert data from a constrained simplex space into an unconstrained real space, enabling the use of conventional statistical techniques while preserving the interdependent relationships among behaviours (Dumuid et al., 2018; Dumuid et al., 2020; Liangruenrom et al., 2023; Mellow et al., 2023).

Time-use epidemiology investigates how time is distributed across various daily activities, its influence on health outcomes, and how optimising this allocation can enhance overall well-being. Time-use is considered one of the most relevant and modifiable behavioural risk factors in many health-related contexts (Pedisic, 2017). The primary components of time-use research - PA, sleep, and sedentary behaviour - are collectively referred to as *movement behaviours* (Dumuid et al., 2020). Emerging evidence suggests that health outcomes are influenced not merely by changes in individual behaviours, but by the reallocation of time among them. For instance, substituting sedentary time with light or moderate-to-vigorous PA has been associated with improved cardiometabolic biomarkers (Grgic et al., 2018). Traditional analytical approaches that evaluate these behaviours

independently fail to account for their compositional nature, since time spent on one activity inherently affects time available for others (Pedisic, 2017). CoDA offers a more robust framework for addressing this issue by examining the relative distribution of time across behaviours. It allows researchers to identify optimal time-use patterns tailored to specific populations and to generate evidence-based, actionable recommendations for improving health (Dumuid et al., 2021; Grgic et al., 2018).

Recent research on PA has emphasised the significance of how the *relative* contributions of various movement behaviours influence overall health within a fixed timeframe, typically a 24-hour day (Dumuid et al., 2021; Hedayatrad et al., 2022). These studies underscore the interconnected nature of movement behaviours and highlight the importance of tailoring time-use recommendations to specific health goals, rather than relying on a uniform, one-size-fits-all approach. Although time-use epidemiology and CoDA techniques have been applied in a limited number of studies involving other neurological populations, such as individuals recovering from stroke (Ezeugwu & Manns, 2024; Hooker et al., 2022; Orme et al., 2020), to the author's knowledge, this is the first study to employ CoDA to examine recovery following SRC. The present study aims to objectively compare movement behaviour patterns between individuals with acute SRC and healthy controls using CoDA methodology. Specifically, it seeks to: (1) determine whether the 24-hour time-use composition of movement behaviours differs between the two groups; and (2) explore the relationship between time-use composition and the number of days to concussion recovery.

Methods

Participants

We recruited two groups between 16 and 35 years of age. The first group consisted of 35 male sports players ($M = 21.71$ years, $SD = 5.10$) in the acute (≤ 14 days) phase post-SRC. Participants for this group were included if their injury occurred in a sports game or training and was diagnosed by a physician. Diagnosis was based on a combination of (1) clinical history with plausible mechanism, (2) Sport Concussion Assessment Tool (SCAT-5) or Brain Injury Screening Tool (BIST) symptoms scores, (3) clinical examination to exclude any neurological or intracranial abnormalities, (4) review of video if available, and (5) eye-witness accounts if available. The second group consisted of 45 healthy male controls ($M = 23.13$ years, $SD = 4.34$). These were a mix of athletes and non-athletes who had not suffered a concussion in the last 12 months, had not suffered more than five total concussions in their lifetime and did not have lingering symptoms from a previous concussion (to minimise potential confounding effects of cumulative damage and/or chronic inflammation). Participants for either group were excluded if they had an existing significant neurological condition or were contraindicated for an MRI scan (e.g., certain metal implants, or braces).

The concussion participants were recruited at their initial consultations at Axis Sports Concussion Clinics in Auckland, New Zealand and via community links (e.g. physiotherapists, word of mouth, digital and print advertisements). The control group were recruited via convenience sampling from the general population through print advertisements at the Auckland University of Technology and The University of Auckland, as well as social media advertisements. Participant data collected for this study has been de-identified to protect participant confidentiality. All participants were provided with a participant information sheet and consent form and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Ethics approval was obtained from the Health and Disability Ethics Committee (HDEC – 2022 EXP 11078), New Zealand.

Materials and Procedure

All participants were fitted with an Axivity AX3 physical activity tracking device immediately following recruitment (within 14 days following their concussion for the concussion group) to wear on either of their wrists (see Figure 1). The device is a data logger and features MEMS 3-axis accelerometer and flash based on-board memory. It is designed to be worn at all times, which enabled the collection of continuous 24/7 movement behaviour data. Using the Open Movement Software (OMGUI, version 1.0.0.43, Open Movement, Newcastle University, UK), each device was initialised to record for 15 days (to enable 14 full days of data to be extracted after allowing for the participants to be fitted with the devices at varying times of the day) at 50 Hz sampling frequency, with a range of $\pm 8g$.

Participants were not asked by researchers to alter their physical activity in any way. The concussion participants recruited through Axis Sports Concussion Clinics underwent extensive clinical examination by a Sport and Exercise Physician. They received verbal and written education regarding physical loading to address their symptoms and were scheduled for a follow up consultation approximately 14 days post-injury (Kara et al., 2020; McGeown et al., 2020). Following the 15-day wear-time, researchers collected the devices from participants at a location convenient to them. If the participant was recruited from Axis Sports Concussion Clinics, then clinical recovery was determined by their physician (as per previous publications; Kara et al., 2020; McGeown et al., 2020) and their date of discharge was used to calculate clinical recovery time (in days). For those participants recruited through the community, their clinical recovery time was calculated using the date that their follow up BIST scores were ≤ 20 .

Figure 1

Axivity AX3 Wrist-Worn Device



Measurements

Time-Use Behaviours

Time-use behaviours were extracted from the Axivity AX3 accelerometer devices. Firstly, raw data from each device was downloaded via the *OMGUI* software in the form of .cwa files and then the *GGIR* package in R (Migueles et al., 2019) was used to determine device wear time and extract time use behaviour variables. The variables of interest were daily time spent in sedentary behaviour, light intensity PA, moderate intensity PA, vigorous intensity PA, and sleep (recorded in minutes). The gravity-based acceleration unit (*g*) thresholds used to determine these intensities were 40g for light PA, 100g for moderate PA and 400g for vigorous PA (Hildebrand et al., 2014; Hildebrand et al., 2016). The minutes of moderate and vigorous intensity PA were combined into moderate-vigorous PA. Additionally, the sleep duration was calculated based on accumulated nocturnal sustained inactivity within a sleep period window that is identified using a Heuristic Algorithm looking at Change of Z-angle (HDCZA) (van Hees et al., 2018). All participants with at least three days of 24-hour wear time were included in the analyses, and minutes in each behaviour of

interest were averaged across valid days. The derivation of time use variables was performed in R software (version 4.2.2).

Covariates

Age (years) and initial symptom burden (total BIST scores) were included as covariates to rule out the possibility of them confounding the primary association of interest for the second analysis.

Statistical Analyses

Time-use behaviours were treated as compositional data (i.e., all behaviours sum to 24 hours) and analysed using the *compositions* (Van den Boogaart & Tolosana-Delgado, 2008) and *deltacomp* (github.com/tystan/deltacomp) R packages. No zero imputation was required as there were no missing values in the dataset. All statistical analyses were performed in R and the code can be found in the Supplementary Materials.

Analysis One: Group Comparison Concussions versus Controls

The average time spent in each movement behaviour were reported as geometric means, which were normalised to 1440 minutes (i.e., minutes in 24 hours) in order to calculate compositional means. Compositions were created for each of the four movement behaviour variables (minutes of sedentary behaviour, light PA, moderate-vigorous PA, sleep) using the *comp* function in the *compositions* package in R. The movement behaviour compositions were then expressed as isometric log-ratio coordinates, which allows compositional data to be analysed using traditional statistical methods (Dumuid et al., 2018; Dumuid et al., 2020; Liangruenrom et al., 2023). To compare the time-use-composition of the concussion group to healthy controls, a compositional multivariate analysis of variance (MANOVA) was conducted with group as the independent variable with two levels (concussion, control) and the movement behaviour isometric log ratios as the dependent variables (Martín Fernández et al., 2015). Partial eta squared (η_p^2) was calculated as an indication of effect size for the model.

Analysis Two: Time-Use-Composition Association with Recovery

To estimate the ideal time-use-composition for optimising clinical recovery time following concussion, a compositional isotemporal substitution analysis was performed (Grgic et al., 2018). This process consists of creating a specific set of isometric log ratio coordinates from the time-use behaviour composition and fitting a series of linear regression models. Firstly, sequential binary partition (SBP) matrices were created for the sedentary behaviour, light PA, moderate-vigorous PA and sleep variables (see Table 1) which are used as a series of instructions for constructing isometric log ratios (ilr).

Table 1*Sequential Binary Partition Matrices for all Movement Behaviours***(A) SBP for Sedentary Behaviour**

	<i>sed</i>	<i>lpa</i>	<i>mvpa</i>	<i>sleep</i>
<i>ilr1</i>	+1	-1	-1	-1
<i>ilr2</i>	0	+1	-1	-1
<i>ilr3</i>	0	0	1	-1

(B) SBP for Light PA

	<i>sed</i>	<i>lpa</i>	<i>mvpa</i>	<i>sleep</i>
<i>ilr1</i>	-1	+1	-1	-1
<i>ilr2</i>	-1	0	+1	-1
<i>ilr3</i>	-1	0	0	+1

(C) SBP for Moderate-Vigorous PA

	<i>sed</i>	<i>lpa</i>	<i>mvpa</i>	<i>sleep</i>
<i>ilr1</i>	-1	-1	+1	-1
<i>ilr2</i>	-1	-1	0	+1
<i>ilr3</i>	+1	-1	0	0

(D) SBP for Sleep

	<i>sed</i>	<i>lpa</i>	<i>mvpa</i>	<i>sleep</i>
<i>ilr1</i>	-1	-1	-1	+1
<i>ilr2</i>	-1	-1	+1	0
<i>ilr3</i>	-1	+1	0	0

For each of the movement behaviours, only the first *ilr* (*ilr1*) is interpreted, which expresses the ratio of the behaviour of interest, relative to the others. In the SBP for sedentary behaviour, *ilr1* represents the time spent in sedentary behaviour relative to all other behaviours; for light PA, *ilr1* represents the time spent in light PA relative to all other behaviours, and so on. A series of compositional multiple regression models were fitted to each set of *ilrs*. The *ilr1* variables for each movement behaviour were included as independent variables, while recovery time (in days) was specified as the dependent variable. Four models were fit in total, each time using a different SBP, such that each behaviour of interest was represented as *ilr1*. From these models, the coefficient for *ilr1* was extracted. Following this, adjusted models were repeated with the inclusion of age and symptom burden as covariates.

Lastly, a compositional isotemporal substitution was conducted to examine theoretical changes in recovery time by reallocating time spent in different movement behaviours. Predicted changes in recovery time by increasing time spent in one behaviour (at the expense of the other three behaviours) were estimated from 0 to ± 60 minutes in 15-minute intervals. The reallocations of time were proportional to the time spent in each behaviour.

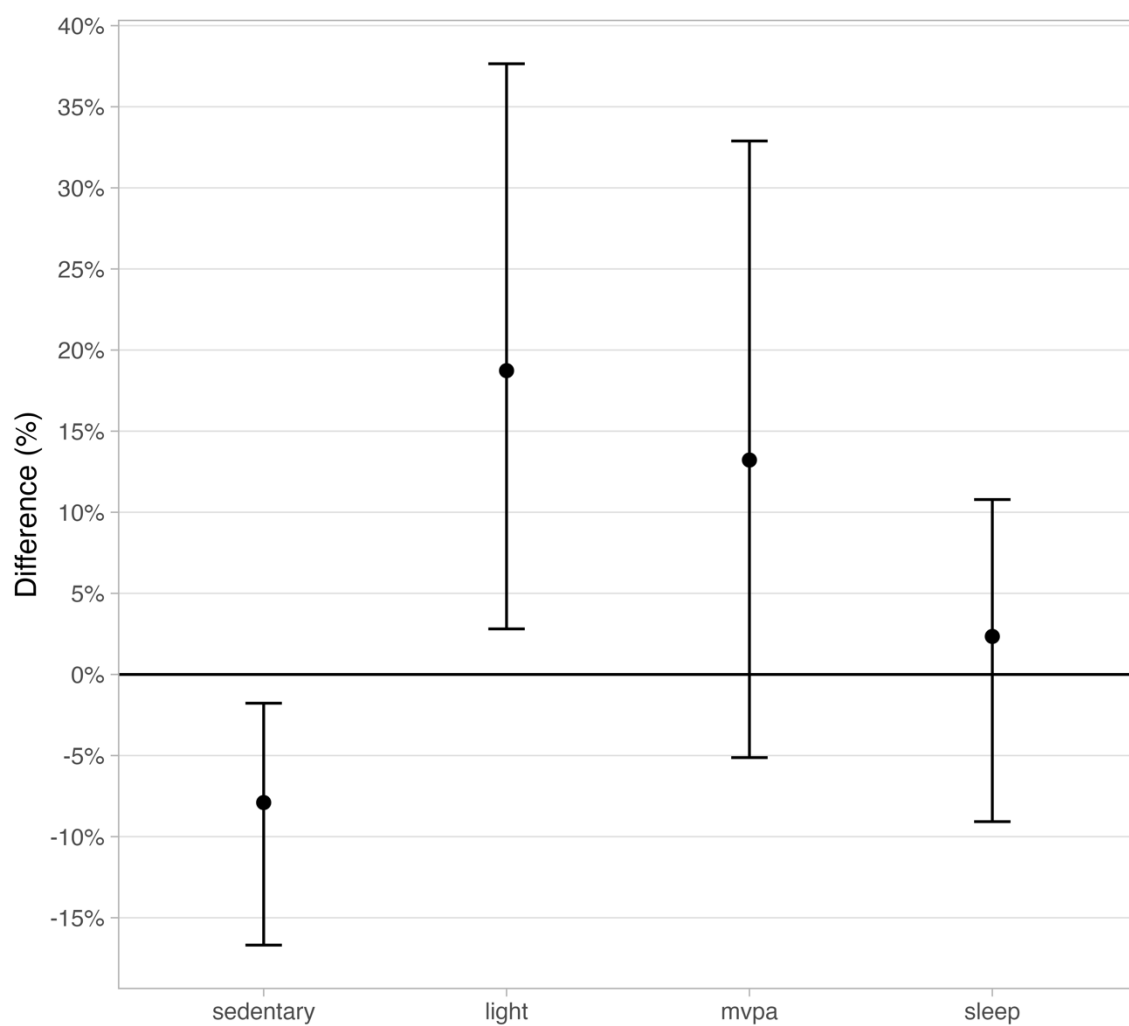
Results

Analysis One: Group Comparison Concussions versus Controls

A MANOVA was conducted to determine if group membership (concussion or control) was associated with the proportion of time spent in the four movement behaviours (sedentary behaviour, light PA, moderate-vigorous PA, sleep). The MANOVA was not statistically significant, $F(1,3) = 1.94$, $p = 0.13$. Results indicated that only 7.0% of the variance in the time-use-composition of participants' behaviour could be explained by the group that they were in ($\eta_p^2 = 0.07$). Comparative group data was generated alongside the MANOVA and can be found in Table 2 (a summary of average movement behaviours by group), Figure 2 (an illustration of the percentage difference between groups) and Figure S1 in the Supplementary Materials (a log ratio comparison).

Table 2*Average Movement Behaviours for Concussion and Control Groups*

	<i>N</i>	Proportions				<i>N</i>	Minutes			
		Sed	LPA	MVPA	Sleep		Sed	LPA	MVPA	Sleep
Concussion	35	48%	13%	8%	30%	697	194	113	436	
Control	45	52%	11%	7%	30%	754	161	99	426	

Figure 2*Percentage Differences in Movement Behaviours for Concussions versus Controls*

Reference group: Control

Note. This figure illustrates between-group differences in movement behaviours as percentage differences, with the control group as the reference group and bootstrapped 95% confidence intervals (i.e. positive percentages indicate the concussion group spent more time engaged in that movement behaviour compared to the control group).

Analysis Two: Time-Use-Composition Association with Recovery

A compositional linear regression model was used to analyse the association between time-use-composition and recovery time within the concussion group, with participant age and initial symptom burden (total BIST scores) included as covariates. Time spent sleeping was significantly associated with recovery time ($p = 0.03$), with a positive association between sleep and recovery ($\beta = 50.54$). However, once the model was adjusted for age and initial symptom burden, the association between sleep and recovery was no longer significant ($p = 0.06$). Time spent in sedentary, light PA and moderate-vigorous PA were all negatively correlated with recovery, but these associations were not statistically significant (see Table 3 for a summary of results and Table S1 in Supplementary Materials for a complete breakdown of the models adjusted with age only and with both age and BIST score).

Table 3

Relationship Between Movement Behaviour Compositions (expressed as isometric log-ratio coordinates) and Recovery Time

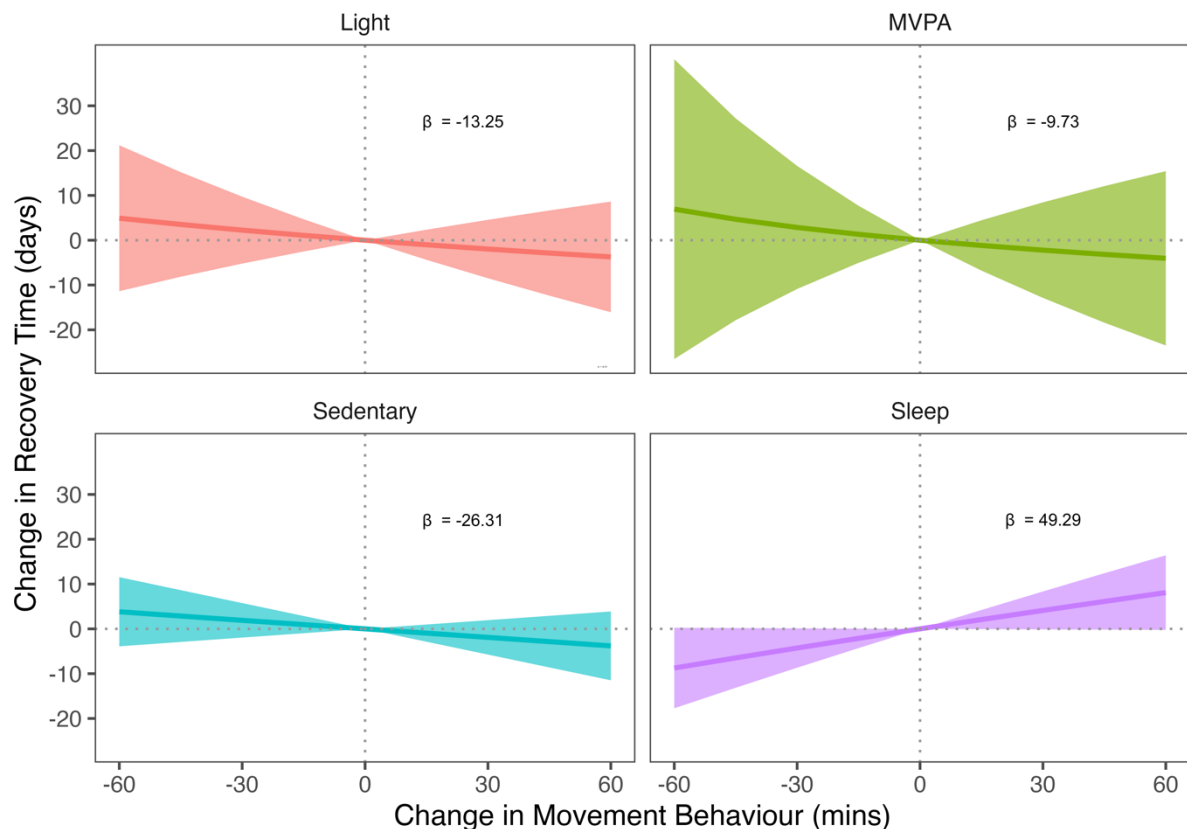
Isometric log-ratio predictor	Unadjusted Model			Adjusted Model (age and BIST score)		
	β	P-value	R ²	β	P-value	R ²
sed/lpa*mvpa*sleep	-26.95	0.24	0.16	-26.31	0.32	0.01
lpa/sed*mvpa*sleep	-15.02	0.42	0.16	-13.25	0.54	0.01
mvpa/sed*lpa*sleep	-8.58	0.64	0.16	-9.73	0.67	0.01
sleep/SB*lpa*mvpa	50.54	0.03*	0.16	49.29	0.06	0.01

Note. * indicates statistical significance at $p < .05$

A compositional isotemporal substitution model was also conducted, of predicted changes in recovery time when time from one movement behaviour is reallocated to/from the remaining movement behaviours (see Figure 3). For example, reallocating more time to moderate-vigorous PA, proportionately from sedentary behaviour, light PA and sleep, was associated with reduced recovery time, however, this association was not statistically significant. Specifically, the model suggests that a theoretical increase in light or moderate-vigorous PA of 60 minutes per day, for example, proportionate to the other movement behaviours, would result in a reduction in recovery time by approximately 4 days. Conversely, a theoretical 60-minute increase in sleep per day, proportionate to the other movement behaviours, would result in a 8-day increase in recovery time. See Table S2 in Supplementary Materials for a complete table of the reallocation results.

Figure 3

Reallocation of Movement Behaviour Time on Recovery Time



Note. The above figure illustrates the adjusted compositional isotemporal substitution model for the four movement behaviours; light PA (top left), moderate-vigorous PA (top right), sedentary behaviour (bottom left) and sleep (bottom right). This shows the predicted theoretical changes in recovery time (in days) when time from one movement behaviour (in minutes) is reallocated proportionately to/from the remaining movement behaviours.

Discussion

Despite a growing shift toward more active, individualised approaches to concussion management, uncertainty remains regarding the optimal type and timing of PA following injury. This study sought to address that gap by investigating how PA influences clinical recovery, focusing on four key movement behaviours: light PA, moderate-to-vigorous PA, sedentary behaviour, and sleep. To the author's knowledge, this is the first study to examine time-use behaviours in individuals recovering from concussion using CoDA. This innovative approach provided novel insights into how reallocating time between different behaviours may support improved recovery outcomes.

Our compositional linear regression analysis revealed no significant associations between moderate-to-vigorous PA, light PA, or sedentary behaviour and recovery time. However, sleep showed a significant positive correlation with recovery time, suggesting that spending more time sleeping - relative to other movement behaviours - may be linked to longer recovery durations. When the model was adjusted for age, the association between sleep and recovery remained significant (see Table S1 in the Supplementary Materials), however when initial symptom burden (as indicated by total BIST score) was added to the model, this association was no longer significant. This suggests that the initial link between sleep and delayed recovery may reflect a higher acute symptom burden, with individuals requiring more sleep due to the severity of their injury. In other words, those who slept more

may have also experienced more severe symptoms and, consequently, slower recovery. However, as this is a correlational finding, it remains unclear whether increased sleep contributes to prolonged recovery, or if individuals with more severe symptoms and thus slower recovery, simply tend to sleep more. Future experimental studies are needed to investigate this relationship directly.

We also conducted an exploratory compositional isotemporal substitution analysis to examine whether theoretical changes in time-use composition were associated with recovery outcomes. Results from this model suggested that reallocating more time to sleep, proportionally away from the other movement behaviours, was linked to a longer recovery duration. Although these findings were not statistically significant, the model provides valuable insights into potential behavioural reallocations that could hold clinical relevance. For instance, increasing time spent in light or moderate-to-vigorous PA, relative to other behaviours, may be associated with faster recovery. Importantly, these types of time-use recommendations should be considered on a case-by-case basis with regards to the individual's personal activity and sleep needs. Further research with a larger sample is needed to validate these preliminary findings and support their application in clinical practice.

In our group comparison, there were no statistically significant differences between the concussion group and healthy controls in the proportion of time spent in each of the four movement behaviours. Group status accounted for only 7% of the variance in movement behaviours, indicating that we cannot conclude whether individuals with sports-related concussions engaged in more or less PA of varying intensities, or sleep, during recovery. These findings may suggest that acutely concussed individuals in this sample were able to participate in physical activity at levels comparable to their healthy counterparts, without adverse effects on recovery. Further validation is needed, however, these results add to the body of literature emphasising PA as a safe component of recovery interventions.

Deepening our understanding of the complex relationship between PA, sleep, and concussion recovery is essential, as significant uncertainty remains in this area. For decades, the standard approach involved strict physical and cognitive rest until full symptom resolution (Howell et al., 2019; Leddy et al., 2019; Markovic et al., 2021; Micay et al., 2018; Willer et al., 2019). However, growing evidence now indicates that prolonged strict rest may hinder recovery. Instead, current guidelines recommend a brief period of relative rest (24–48 hours), followed by a gradual, stepwise return to activity for optimal recovery outcomes (Buckley et al., 2022; Coslick et al., 2020; Dobney et al., 2017; Grool et al., 2016; Lawrence et al., 2018; Leddy et al., 2016; Leddy et al., 2019; Patricios et al., 2023; Schneider et al., 2017; Seehusen et al., 2021; Silverberg & Iverson, 2013; Thomas et al., 2015; Wilson et al., 2020). Multiple factors have been identified as influencing the risk of prolonged recovery. For example, McGeown et al. (2020) reported that individuals who are female, present with a higher initial symptom burden, or exhibit cervicogenic and/or vestibulo-ocular dominant symptoms are more likely to experience extended recovery periods (>14 days). As our understanding of these risk factors continues to evolve, it becomes increasingly important to identify strategies that actively support optimal recovery - highlighting the need to refine and individualise rehabilitation approaches through a better understanding of PA's role in recovery.

One potential mechanism underlying the beneficial effects of PA on concussion recovery is its ability to modulate inflammation (Swain et al., 2023; Metsios et al., 2020). PA may help attenuate the post-concussion inflammatory response by reducing chronic microgliosis, altering cytokine profiles, and lowering systemic low-grade inflammation (Ma et al., 2013; Markovic et al., 2021; Nimmo et al., 2013; Paolucci et al., 2018; Piao et al., 2013). It exerts these effects through the release of inflammatory mediators from leukocytes, adipose tissue, and skeletal muscle. During acute bouts of PA, skeletal muscle releases anti-

inflammatory cytokines such as interleukin-6, with concentrations increasing in proportion to PA intensity, duration, fitness level, and muscle mass (Szostak & Laurant, 2011). Interleukin-6 initiates a cascade of anti-inflammatory processes by suppressing pro-inflammatory cytokines such as interleukin-1 β and tumor necrosis factor-alpha, while promoting the release of the anti-inflammatory cytokine interleukin-10 (Nimmo et al., 2013). Additionally, PA has been associated with reductions in C-reactive protein, a widely recognised marker of systemic inflammation (Abramson & Vaccarino, 2002; Fedewa et al., 2003; Ford, 2002). For instance, Nilsson et al. (2018) demonstrated that replacing 30 minutes of sedentary or light activity with moderate-to-vigorous PA significantly lowered C-reactive protein levels. Furthermore, using a rodent model of TBI, Kim et al. (2022) demonstrated that early initiation of exercise training reduced microglial activation and infiltration, as well as the expression of pro-inflammatory cytokines such as IL-1, IL-13, and IL-1 β , which had initially increased following the injury. Collectively, these findings underscore the important role of PA in regulating inflammation, which may be a key contributor to its positive effects on concussion recovery.

PA also stimulates the production of proteins associated with neural plasticity, such as brain-derived neurotrophic factor (BDNF) (Cordingley et al., 2024; Kreber & Griesbach, 2016; Mastrorilli & Vecchioli, 2024; Szuhany et al., 2015). BDNF, a key member of the neurotrophin family, is highly concentrated in brain regions critical for cognitive and motor function, including the hippocampus, hypothalamus, and cerebellum (Kreber & Griesbach, 2016; Szuhany et al., 2015). It plays a vital role in neuronal growth, differentiation, and survival by supporting neurogenesis, dendritic development, and long-term potentiation (Dinoff et al., 2016; Szuhany et al., 2015). Research has shown that BDNF levels acutely increase in peripheral blood following PA, with the extent of change dependent on the type, intensity, and duration of activity (Bazarian et al., 2023). Even a single session of exercise can elevate BDNF, with regular exercise amplifying this effect over time (Szuhany et al., 2015). Aerobic exercise, in particular, has been associated with increased resting BDNF concentrations (Dech et al., 2019). Since BDNF expression is often suppressed following concussion, PA may aid brain recovery by promoting BDNF production and enhancing neuroplasticity (Cordingley et al., 2024; Dech et al., 2019). Through its involvement in ionic regulation, metabolic support, and structural repair processes, BDNF may play a critical role in neural repair and functional recovery after brain injury (Cordingley et al., 2024; Dech et al., 2019; Kreber & Griesbach, 2016).

Expanding our understanding of PA engagement following concussion and identifying the optimal time-use composition of movement behaviours may have important clinical implications. If individual variations in time-use composition influence recovery, then reallocating time from one movement behaviour to another could enhance outcomes. For example, if increasing time spent in moderate-to-vigorous PA, relative to light PA, sedentary behaviour, and sleep, is found to accelerate recovery, clinicians could incorporate this evidence into rehabilitation guidelines. Conversely, if excessive sleep relative to other movement behaviours is shown to impede recovery, recommendations could be adjusted to help patients structure their daily routines more effectively. Given the high prevalence of SRC and the significant burden it places on individuals and society, identifying strategies to improve recovery outcomes is of considerable value. A more nuanced understanding of how reallocations of movement behaviours influence recovery trajectories could provide clinicians with additional, evidence-based tools to support patient rehabilitation and promote more effective recovery.

A key strength of this study is the extended wear time of the tracking devices ($M = 11.5$ days). This provided a robust dataset for calculating daily averages, thereby enhancing the internal validity of the findings. Another major strength is the use of an objective device -

the Axivity AX3 wrist-worn sensor - to record movement behaviours. This allowed for precise quantification of PA and sleep, improving data reliability while minimising recall bias and subjective reporting errors. Additionally, this method imposed a lower burden on participants compared to frequent self-reported activity logs. Although objective recording devices have been used in prior research (e.g., Neely et al., 2022; Petit et al., 2022; Seehusen et al., 2021), much of the existing literature on daily PA and concussion recovery relies on subjective measures (e.g., Boisgontier et al., 2020; Buckley et al., 2022; Coslick et al., 2020; Grool et al., 2016; Howell et al., 2016; Krainin et al., 2021; Remigio-Baker et al., 2020; Wilson et al., 2020). This study contributes to bridging that gap by employing an objective approach that reduces measurement error and enables robust statistical analysis.

The use of CoDA is another significant strength of the study. This approach considers movement behaviours holistically, recognising them as interdependent components of a 24-hour cycle rather than isolated variables. Since increasing PA inherently reduces time spent in other behaviours (e.g., sleep), understanding the most beneficial time reallocations is critical for optimising recovery. For example, clinicians could engage patients in discussions about “time budgets” that illustrate the trade-offs between behaviours on a day-to-day basis. This might involve strategies for reallocating time from sleep to light or moderate-vigorous PA at appropriate times, considering the patient's symptom exacerbation levels. If such collaborative planning between clinician and patient were implemented during the acute phase post-concussion, it could foster individualised time-use plans that potentially shorten recovery and facilitate a more efficient return to play.

Interpreting these findings requires consideration of potential limitations, particularly the limited sample size and reduced statistical power. Additionally, the limited variability in PA among participants may have hindered the detection of statistically significant results. Since concussion participants were primarily recruited from the same clinic, they likely received similar rehabilitation recommendations (e.g., structured exercise protocols such as daily stationary cycling). Consequently, the proportion of time spent in different movement behaviours may have been relatively uniform, which could have diminished the ability to identify meaningful associations with recovery. Future research should aim to recruit a more diverse sample from multiple sources, over a longer period of their recovery, to increase variability in movement behaviours and enhance the generalisability of findings.

Additionally, the external validity may be limited due to the homogenous, male-only sample. If both sexes were to be included, separating them into distinct groups and comparing them would be most sensible, as there may be sex differences in presentation following concussion (e.g., due to differences in hormones at the time of injury). Conducting such between-group comparisons would require a larger sample size, which could have impacted the feasibility of the study. Future research should aim to expand the sample size and include an accurate representation of both sexes and explore group differences, such as the influence of estrogen and progesterone during the acute phase of injury and how these hormonal factors may interact with the relationship between PA and recovery. Furthermore, although efforts were made to recruit participants as soon as possible post-injury, PA monitoring began within a 14-day window, limiting the ability to assess movement behaviours during the very acute phase. To enhance understanding of the optimal timing for PA initiation, future studies should aim to commence monitoring earlier in the recovery process, thus improving insights into the clinical applicability of PA interventions.

While the current study may have been underpowered to detect significant associations, future research should continue to explore time-use composition in individuals recovering from concussion. With more robust and objective evidence, concussion rehabilitation guidelines could be refined to incorporate specific PA recommendations. Given that sub-symptom PA is both feasible and cost-effective, a structured, stepwise return to

activity could prove to be an effective treatment strategy, ultimately supporting safer and more efficient recovery pathways.

Conclusion

This is the first study to prospectively examine movement behaviours using wearable accelerometers and time-use compositions in the acute phase following sports-related concussion. Our findings indicate that, on average, physical activity did not differ between the concussed and control groups, supporting the tolerability of physical activity in the early weeks after a concussion. Additionally, increased relative time spent sleeping was associated with longer recovery times. In an exploratory analysis, we observed that a theoretical increase of 60 minutes per day in light or moderate-to-vigorous physical activity, proportionate to the other movement behaviours, would result in a reduction in recovery time by approximately four days. Although limited by statistical power, these findings contribute to the growing understanding of the complex interactions between physical activity and concussion recovery. With further validation, compositional data analysis could inform the development of personalised time-use plans in clinical settings, potentially accelerating recovery and supporting a safer return-to-play. Larger studies with more diverse concussion cohorts are essential to validate these findings and facilitate clinical translation.

Conflicts of Interest:

None to declare.

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Data Availability:

The data that support the findings of this study are available on request from the corresponding author

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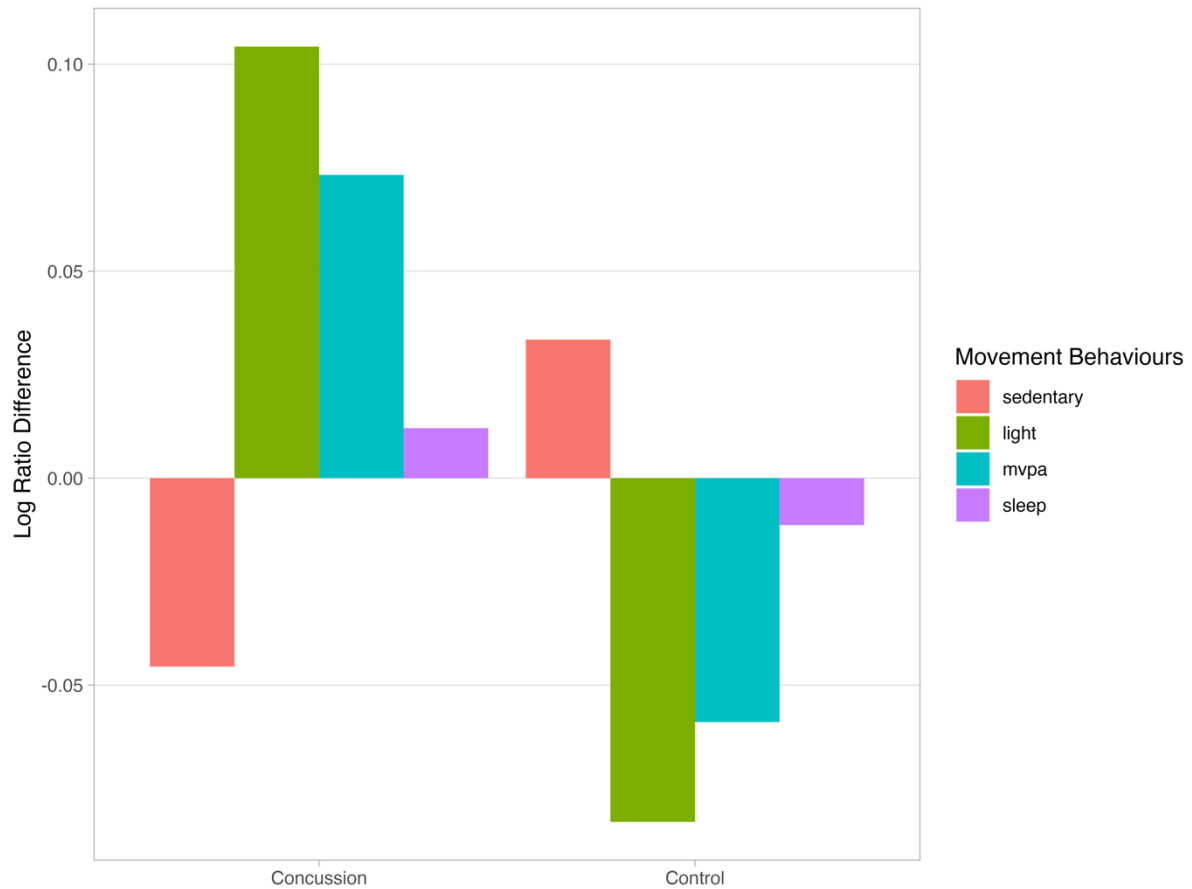
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Supplementary Materials

Figure S1

Log Ratio Differences in Movement Behaviours for Concussions versus Controls



Note. The above figure illustrates the between-group differences in movement behaviours (sedentary behaviour, light PA, moderate-vigorous PA, and sleep) by comparing the log ratio mean of each group to the overall log ratio mean. Each bar represents the difference to the overall mean of both groups, for each respective movement behaviour (e.g., the concussion group engaged in less sedentary behaviour but more light PA, moderate-vigorous PA and sleep, compared to the overall mean).

Table S1

Models of the Relationship Between Movement Behaviour Compositions and Recovery Showing Different Levels of Adjustment

Isometric log-ratio predictor	Unadjusted Model			Adjusted Model (Age)			Adjusted Model (Age and BIST score)		
	β	P-value	R ²	β	P-value	R ²	β	P-value	R ²
Sed	-26.95	0.24	0.16	-28.06	0.24	0.05	-26.31	0.32	0.01
LPA	-15.02	0.42	0.16	-16.20	0.42	0.05	-13.25	0.54	0.01
MVPA	-8.58	0.64	0.16	-6.88	0.75	0.05	-9.73	0.67	0.01
Sleep	50.54	0.03*	0.16	51.15	0.03*	0.05	49.29	0.06	0.01

Note. *Sed* refers to the proportion of time spent in sedentary behaviour relative to the other movement behaviours, *LPA* refers to the proportion of time spent in light PA relative to the other movement behaviours, *MVPA* refers to the proportion of time spent in moderate-vigorous PA relative to the other movement behaviours, and *Sleep* refers to the proportion of time spent in sleep relative to the other movement behaviours. * indicates statistical significance at $p < .05$

Table S2

Compositional Isotemporal Substitution Model of Predicted Theoretical Changes in Movement Behaviours and their Impact on Recovery from Concussion

Movement Behaviour	Reallocated Time (mins)	Predicted Change in Recovery (days)	Lower 95% C.I.	Upper 95% C.I.
Sedentary	-60	3.82	-3.90	11.54
Light PA	-60	4.91	-11.37	21.19
MVPA	-60	6.94	-26.51	40.39
Sleep	-60	-8.74	-17.72	0.25
Sedentary	-45	2.86	-2.92	8.64
Light PA	-45	3.52	-8.15	15.19
MVPA	-45	4.67	-17.84	27.18
Sleep	-45	-6.48	-13.14	0.19
Sedentary	-30	1.90	-1.94	5.75
Light PA	-30	2.25	-5.21	9.71
MVPA	-30	2.85	-10.88	16.57
Sleep	-30	-4.27	-8.67	0.12
Sedentary	-15	0.95	-0.97	2.87
Light PA	-15	1.08	-2.51	4.68
MVPA	-15	1.32	-5.04	7.68
Sleep	-15	-2.11	-4.29	0.06
Sedentary	15	-0.95	-2.87	0.97
Light PA	15	-1.01	-4.37	2.35
MVPA	15	-1.17	-6.78	4.45
Sleep	15	2.07	-0.06	4.21
Sedentary	30	-1.90	-5.74	1.94
Light PA	30	-1.97	-8.48	4.55
MVPA	30	-2.21	-12.87	8.44
Sleep	30	4.11	-0.12	8.34
Sedentary	45	-2.85	-8.61	2.91
Light PA	45	-2.87	-12.37	6.64
MVPA	45	-3.16	-18.40	12.08
Sleep	45	6.12	-0.18	12.41
Sedentary	60	-3.80	-11.48	3.88
Light PA	60	-3.72	-16.06	8.62
MVPA	60	-4.03	-23.48	15.41
Sleep	60	8.09	-0.23	16.42

Note. For all reallocations, a negative value indicates a reduction in the corresponding movement behaviour, relative to all other movement behaviours, while a positive value indicates an increase. All reallocations with a * indicate a significant association with an alpha of 0.05.

R Scripts

Code for Extracting Data from Raw .cwa Files

```
library(GGIR)

datadir= "/Users/mayanbedggood/Documents/Axivity_AX3/Raw_Data/"

outputdir= "/Users/mayanbedggood/Documents/Axivity_AX3/Output/"

g.shell.GGIR(
  desiredtz = "UTC",

  mode = 1:5,
  maxdur = 15,
  do.report = c(2:5),
  visualreport = TRUE,

  do.parallel=TRUE,
  maxNcores = 8,
  doanglez = TRUE,
  overwrite = TRUE,

  datadir=datadir,
  outputdir=outputdir
)
```

Code for Analysis 1

```
#devtools::install_github('TheTS/CodaContrast')
library(zCompositions)
library(tidyverse)
library(compositions)
library(RVAideMemoire)
library(psych)
library(CodaContrast)
library(jmv)
library(lubridate)
library(broom)
library(heplots)
library(readxl)
library(patchwork)

setwd
("/Users/mayanbedggood/Documents/Axivity_AX3/")
df <- read_xlsx("concussion_Data.xlsx")

#Compositional Descriptives
#Overall
df_all <- df %>%
  select(Sedentary,Light, MVPA, Sleep) %>%
  filter(complete.cases(.))

comp <- acomp(df_all)

round(mean(comp),2)

round(clo(mean(comp), total=1440))
```

Code for Analysis 1 (continued)

```
# By Group
dfControl <- df %>%
  dplyr::select(sedentary, light, mvpa, sleep, group) %>%
  filter(group == 'Control') %>%
  dplyr::select(-group) %>%
  filter(complete.cases(.))

dfConcussion <- df %>%
  dplyr::select(sedentary, light, mvpa, sleep, group) %>%
  filter(group == 'Concussion') %>%
  dplyr::select(-group) %>%
  filter(complete.cases(.))

comp_Control <- acomp(dfControl)
mean(aplus(dfControl))
round(mean(comp_Control), 2)
round(clo(mean(comp_Control), total = 1440))

comp_Concussion <- acomp(dfConcussion)
mean(aplus(dfConcussion))
round(mean(comp_Concussion), 2)
round(clo(mean(comp_Concussion), total = 1440))

#Compositional MANOVA

df_all <- df %>%
  select(sedentary, light, mvpa, sleep, group) %>%
  filter(complete.cases(.))

comp <- acomp(df_all[,1:4])

mean(comp)
round(clo(mean(comp), total = 1440))

round(variation(comp), 2)

m1 <- manova(ilr(comp) ~ df_all$group)
summary(m1)

etasq(m1)

# Geomeric mean plot
plot1 <- plot_geo_means(composition = comp, group = df_all$group, type = 'component')

plot1 <- plot1 +
  theme_light() +
  labs(y= "Log Ratio Difference", fill="Movement Behaviours") +
  theme(panel.grid.minor = element_blank(), panel.grid.major.x = element_blank())

ggsave(filename="Plot1.png", plot=plot1, width=8,height=6,dpi=900)

# Contrasts
lr <- log_ratio_difference(composition = comp,
                          group = df_all$group, reference_group = 'Control')
print(lr)

plot2 <- plot_log_ratio_difference(lr,percentage = TRUE)

plot2 <- plot2 + scale_y_continuous(labels = scales::percent, breaks = c(seq(from=-0.25, to=0.44, by=0.05))) +
  theme_light() +
  theme(panel.grid.minor = element_blank(), panel.grid.major.x = element_blank())

ggsave(filename="Plot2.png", plot=plot2, width=6,height=6,dpi=900)

#plot1 + plot2 + plot_annotation(tag_levels = "A")
```

Code for Analysis 2

```
library(compositions)
library(lubridate)
library(tidyverse)
library(car)
library(performance)
library(deltacomp)
library(plyr)
library(readxl)
library(janitor)
library(ggthemes)
library(psych)

setwd ("/Users/mayanbedggood/Documents/Axivity_AX3/")
df <- read_xlsx("concussion_Data.xlsx") %>%
  clean_names()

df_all <- df %>%
  filter(group == 'Concussion') %>%
  dplyr::select(sedentary, light, mvpa, sleep,
    recovery_time,
    participant_age, bist)

mean(df_all$participant_age)
sd(df_all$participant_age)

df_all %>%
  dplyr::select(sedentary, light, mvpa, sleep) %>%
  describe()
comp <- acomp(cbind(df_all$sedentary, df_all$light, df_all$mvpa, df_all$sleep))
round(mean(comp),2)
round(clo(mean(comp), total=1440))
round(var(comp),3)

#Compositional multiple regression
#Building the sequential binary partition matrices

      # sed, lpa, mvpa, sleep

sbp_sed <- matrix(c(1, -1, -1, -1,
  0, 1, -1, -1,
  0, 0, 1, -1),
  ncol=4, byrow=TRUE) # ilr1 = sed/lpa+mvpa+sleep
sbp_lpa <- matrix(c(-1, 1, -1, -1,
  -1, 0, 1, -1,
  -1, 0, 0, 1),
  ncol=4, byrow=TRUE) # ilr1 = lpa/sed+mvpa+sleep
sbp_mvpa <- matrix(c(-1, -1, 1, -1,
  -1, -1, 0, 1,
  1, -1, 0, 0),
  ncol=4, byrow=TRUE) # ilr1 = mvpa/sed+lpa+sleep
sbp_sleep <- matrix(c(-1, -1, -1, 1,
  -1, -1, 1, 0,
  -1, 1, 0, 0),
  ncol=4, byrow=TRUE) #ilr1 = sleep/sed+lpa+mvpa
colnames(sbp_sed) <- c('Sedentary', 'LPA', 'MVPA', 'Sleep')
rownames(sbp_sed) <- c('ilr1', 'ilr2', 'ilr3')
sbp_sed

#Creating isometric log ratios
sbp <- gsi.buildilrBase(t(sbp_sed))
ilr.comp_sed <- ilr(comp, V = sbp)

sbp <- gsi.buildilrBase(t(sbp_lpa))
ilr.comp_lpa <- ilr(comp, V = sbp)

sbp <- gsi.buildilrBase(t(sbp_mvpa))
ilr.comp_mvpa <- ilr(comp, V = sbp)

sbp <- gsi.buildilrBase(t(sbp_sleep))
ilr.comp_sleep <- ilr(comp, V = sbp)
```

Code for Analysis 2 (continued)

```
#Fit model (m0 = unadjusted, m1 = adjusted)
m0_sed <- lm(df_all$recovery_time ~ ilr.comp_sed)
m1_sed <- lm(df_all$recovery_time ~ ilr.comp_sed + df_all$participant_age + df_all$bist)

m0_lpa <- lm(df_all$recovery_time ~ ilr.comp_lpa)
m1_lpa <- lm(df_all$recovery_time ~ ilr.comp_lpa + df_all$participant_age + df_all$bist)

m0_mvpa <- lm(df_all$recovery_time ~ ilr.comp_mvpa)
m1_mvpa <- lm(df_all$recovery_time ~ ilr.comp_mvpa + df_all$participant_age + df_all$bist)

m0_sleep <- lm(df_all$recovery_time ~ ilr.comp_sleep)
m1_sleep <- lm(df_all$recovery_time ~ ilr.comp_sleep + df_all$participant_age + df_all$bist)

#Model Summaries
summary(m0_sed)
summary(m1_sed)

summary(m0_lpa)
summary(m1_lpa)

summary(m0_mvpa)
summary(m1_mvpa)

summary(m0_sleep)
summary(m1_sleep)

##run test to compare Concussion group to control group

#Check assumptions for linear regression model
check_model(m1_sed)
check_model(m1_lpa)
check_model(m1_mvpa)
check_model(m1_sleep)

#Compositional isotemporal substitution
#Increment (mins)
RA = 15
#Substitution
df_pred <- predict_delta_comps(data = df_all,
                              y = "recovery_time",
                              comps = c("sedentary", "light", "mvpa", "sleep"),
                              covars = c('participant_age', 'bist'),
                              comparisons = "prop-realloc",
                              deltas = seq(-60, 60, by=RA)/(24*60),
                              alpha = 0.05)

df_pred %>%
  as_tibble() %>%
  mutate(realloc = rep(seq(-60, 60, by=RA), each = 4)) %>%
  dplyr::select(1:3, 9, 4:8) %>%
  write_csv('reallocations_intensity_zrecovery.csv')

df_pred <- df_pred %>%
  as.data.frame() %>%
  mutate(`comp+`=ifelse(`comp+`=="mvpa", "MVPA", str_to_sentence(`comp+`)))

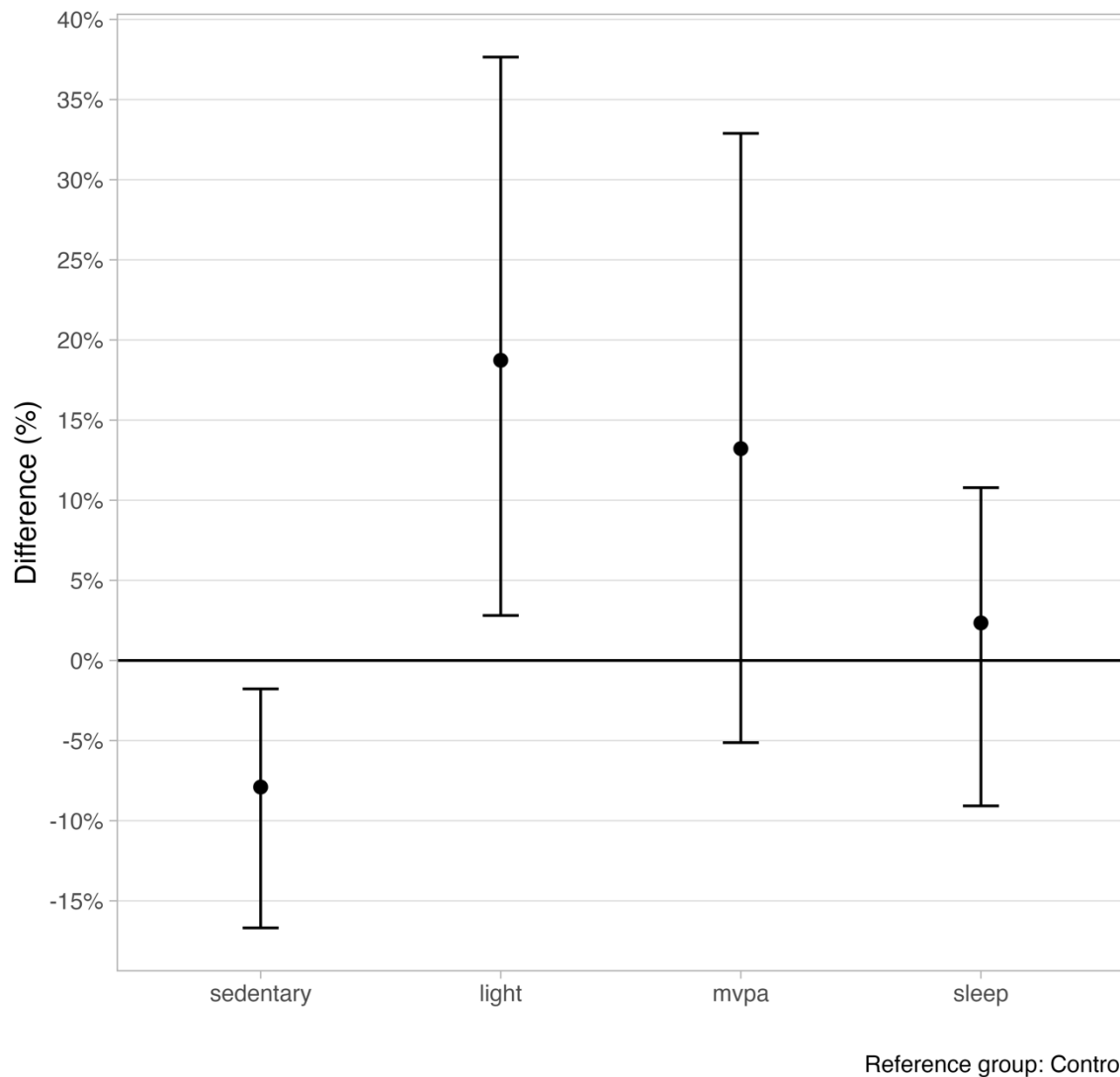
ggplot(df_pred, aes(x=(delta*1440), y=delta_pred)) +
  geom_line(aes(color = `comp+`), size=1) +
  geom_ribbon(aes(ymin=ci_lo, ymax=ci_up, fill = `comp+`), alpha = 0.6) +
  geom_vline(xintercept = 0, size = 0.5, color="grey60", linetype="dotted") +
  geom_hline(yintercept = 0, size = 0.5, color="grey60", linetype="dotted") +
  facet_wrap(`comp+`~.) +
  scale_y_continuous(breaks = c(seq(from=-30, to=30, by=10))) +
  theme_few() +
  theme(legend.position = "none") +
  labs(x="Change in Movement Behaviour (mins)", y= "Change in Recovery Time (days)")

ggsave(filename="Plot3.png", width=7,height=5,dpi=900)
```

Appendix 10: Figure S1

Figure S1

Percentage Differences in Movement Behaviours for mTBI versus Controls



Note. This figure illustrates between-group differences in movement behaviours as percentage differences, with the control group as the reference group and bootstrapped 95% confidence intervals (i.e. positive percentages indicate the mTBI group spent more time engaged in that movement behaviour compared to the control group).