White matter changes and neuropsychological changes in individuals with persistent post-concussion symptoms following mild traumatic brain injury.

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Abstract

Following a mild traumatic brain injury (mTBI) a number of individuals fail to recover within the normal time frame and experience persistent post-concussion symptoms (PPCS). Advances in neuroimaging, have provided a new technique known as Diffusion Tensor Imaging (DTI), capable of examining white matter changes following mTBI. The present study examined individuals who sustained a mTBI (*n*=46) 3-6 months previously and a control group matched for age, gender and education (*n*=20). The mTBI group were further subdivided into two groups of individuals reporting higher levels of persistent post-concussion symptoms (HPPCS), and those reporting lower levels of persistent post-concussion symptoms (LPPCS) based on their self-report on the Rivermead Post-Concussion Questionnaire (RPQ). Specific neuropsychological tests were used to assess cognitive domains (attention, information processing speed, and working memory) and mood (irritability, anxiety and depression) changes commonly reported by individuals with PPCS. Participants underwent magnetic resonance imaging scans including DTI. A whole-brain voxel-based analysis known as Tract-Based Statistics (TBSS) was used to measure white matter microstructure. Analyses were also conducted to examine whether cognitive performance was associated with white matter microstructural properties in the mTBI group. It was hypothesised that the HPPCS group would perform more poorly on cognitive tests trials with increased cognitive demands and complexity, but not on tests that measured simple cognitive functioning. It was also hypothesised that greater white matter disruption would be shown in the HPPCS group compared to the LPPCS group. Lastly, it was predicted that disrupted white matter microstructure in the whole mTBI group would be associated with poorer performance on selected cognitive tests.

Consistent with these predictions, the mTBI performed significantly worse compared to the control group in two out of the four cognitive tests, the Paced Auditory Serial Additions Test (PASAT) and the Symbol Digit Modalities Test. The HPPCS group also performed significantly worse compared to the LPPCS group in two out of four cognitive tests, including the PASAT and Computerised Topography Information Processing (CTIP), specifically on the last trial on the CTIP, which involves the greatest cognitive demand. TBSS analysis revealed that the mTBI group displayed significantly disrupted white matter microstructure as indicated by reduced Fractional Anisotropy (FA) and increased Mean Diffusivity (MD) and Radial Diffusivity (RD) compared to the control group. Strikingly, the HPPCS group also displayed significantly disrupted white matter compared to the LPPCS group, specifically reduced FA and increased RD. Finally, the regression analyses showed a number of regionally specific relationships between disrupted white matter microstructure and cognitive performance in the whole mTBI group. The

results contribute to a better characterisation of the neuropsychological and neural changes that occur in individuals with PPCS, and suggest ongoing disruptions in neural functioning contribute to prolonged symptoms of mTBI.

To Granny Krol, you were so loved and are dearly missed.

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List of Abbreviations

A	Average
aCC	Anterior of the Corpus Callosum
ACR	Anterior Corona Radiata
ACT	Auditory Consonant Trigrams
AD	Axial Diffusivity
ALIC	Anterior Limb of Internal Capsule
ANOVAs	Analysis of Variance
bCC	Body of the Corpus Callosum
CTIP	Computerised Test of Information Processing
CT	Computerised Topography
CC	Corpus Callosum
CR	Corona Radiata
CST	Corticospinal Tract
CTIP	Computerised Test of Information Processing
DAI	Diffuse Axonal Injury
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EC	External Capsule
ED	Emergency Department
FA	Fractional Anisotropy
fMaj	Forceps Major
fMin	Forceps Minor
gCC	Genu of Corpus Callosum
GCS	Glasgow Coma Scale
HPPCS	High Post Concussion Symptoms
ICD-10	International Classification of Disease-10
IC	Internal Capsule
IDAS	Irritability Depression Anxiety Scale
IFOF	Inferior Fronto-Occipital Fasciulus
ILF	Inferior Longitudinal Fasciculus

LOC	Loss of Consciousness
LPPCS	Low Post Concussion Symptoms
MCP	Middle Cerebellar Peduncle
MD	Mean Diffusivity
ML	Medial Lemniscus
MRI	Magnetic Resonance Imaging
MSVT	Medical Symptom Validity Test
mTBI	Mild Traumatic Brain Injury
OR	Optic Radiation
PASAT	Paced Auditory Serial Addition Task
PPCS	Persistent Post-Concussion Symptoms
PCR	Per correct response
PTA	Post-Traumatic Amnesia
PTR	Posterior Thalamic Radiation
R	Range
RD	Radial Diffusivity
ROI	Region of Interest
RT	Reaction Time
Sec	Seconds
sCC	Splenium of the Corpus Callosum
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SLF	Superior Longitudinal Fasciculus
TBI	Traumatic Brain Injury
TBSS	Tract Based-Statistics
T/CR	Time per correct response
TOPF	Test of Premorbid Functioning
UF	Uncinate fasciculus
VBA	Voxel based analysis
WB	Whole brain

Preface

This thesis investigated changes in neuropsychological performance and changes in the white matter structure of the brain in individuals who have sustained a mild traumatic brain injury and have persistent post-concussion symptoms. Neuropsychological performance was examined using a highly selected battery of neuropsychological tests and mood changes were assessed using a specific mood measure. Changes to white matter were assessed using a specialist form of Magnetic Resonance Imaging, Diffusion Tensor Imaging. This study was first conceptualised by Dr Gjurgjica Badzakova-Trajkov supported by an Aotearoa Fellowship, Keith Woods a clinical neuropsychologist, and Professor Lynette Tippett. Dr Nicole Mckay provided brain imaging support in the analysis stages. As part of the team, I recruited and assessed half of the participants and I conducted all of the neuropsychological and imaging analyses.

Chapter 1 provides a review of the literature relevant to thesis. It begins with background information on mild traumatic brain injury (mTBI), and proceeds to review neuropsychological studies and then brain imaging studies of mTBI. Finally it reviews persistent post-concussion symptoms and current theories of the aetiology of this condition. This chapter concludes with an overview of the research conducted in this thesis, including general aims. *Chapter 2* describes the general methodology for the whole thesis. *Chapter 3 and 4,* describe the methods and results of the two studies in this thesis, with each chapter concluding with a discussion of findings. *Chapter 3* focuses on the neuropsychological study and *Chapter 4* focuses on the neuroimaging study. Lastly, a general discussion of these findings is provided in *Chapter 5*.

Chapter One

General Introduction

More than 50 million people worldwide have a traumatic brain injury (TBI) each year. As a result, TBI is a major public health concern and leading cause of disability (Maas et al., 2017). Of all TBI's worldwide and within New Zealand, 70-95% are classified as mild in severity (Feigin et al., 2013; Steyerberg et al., 2019). For some individuals who have had a mild TBI, however, the injury is "far from mild", as 5-35 % of individuals experience persisting post-concussion symptoms (PPCS) beyond three months, which is the expected time of recovery (Reuben, Sampson, Harris, Williams, & Yates, 2014; Van der Naalt et al., 2017). Further, some individuals can experience symptoms that last months, sometimes years, which significantly impacts their quality of life (McCrory et al., 2013). Individuals who struggle to recover from a mTBI in the expected time frame have been referred to as "the miserable minority" and have perplexed researchers for decades. Despite many factors being suggested to explain this presentation, there are currently no clear underlying mechanism/s that account for the enduring symptoms reported by individuals and it remains a contentious debate in the literature (Jones & Jarvis, 2017; King, & Kiriwilliam, 2011). The majority of studies have focussed on psychological explanations for enduring symptoms following mTBI, attributing an individual's ongoing symptoms to their pre-morbid psychological functioning (e.g. anxiety) or their response to the injury (Hellstrøm et al., 2017; Silverberg et al., 2015; van der Naalt et al., 2017). Neural factors have also been proposed as an explanation for PPCS, with some authors arguing that ongoing symptoms can be related to underlying neural damage occurring at the point of injury (Bigler & Maxwell, 2012; Dean, Sato, Vierira, McNamara & Sterr, 2015; Waljas et al., 2015). This view, however, has received limited support in the general TBI literature, as conventional neuroimaging methods, such as computerised topography, typically report insignificant findings. Considering that there is huge heterogeneity in how individuals respond and recover from mTBI within the context of seemingly similar injuries (Taylor, da Silva, Blamire, Wang, & Forsyth, 2020), models that incorporate multiple interacting psychological, psychosocial and neural factors have been considered (Pollinder et al., 2018; Rickards Cranston, & McWhorter, 2020). Given the significant impact that persistent symptoms have on lives of individuals, identifying factors that may contribute to persistent problems, or help to identify at-risk individuals would be beneficial. Findings could additionally inform the development of treatments and enable targeted treatment to those at elevated risk of persistent problems.

In the following studies, we investigate the potential contribution of one neural mechanism, namely damage or dysfunction of white matter tracts in the brain, to PPCS. Results from a number of studies using diffusion tensor imaging (DTI), a form of magnetic resonance imaging (MRI) that measures the integrity of white matter, have shown changes in white matter in individuals who have sustained a mTBI compared to healthy controls in acute and subacute phases post-injury, although the patterns of findings are mixed (Arfrankis et al., 2002; Bazarian et al., 2005; D'Souza et al., 2015; Mayer et al., 2010). The following study will explore whether there are persisting changes in white matter in individuals experiencing PPCS three to six months following a mTBI, and whether these are associated with ongoing difficulties in cognitive processes.

This chapter provides an overview of the current understanding of mTBI and the definition used in this thesis, the neuropathological injuries believed to occur following a mTBI and the neuropsychological consequences. This will be followed by an explanation of PPCS, an outline of symptomology and a discussion around the challenges of diagnosis/definition criteria. The debate regarding the aetiology of PPCS will be detailed, explaining both the psychological and neural arguments. This will lead onto the present study and overall research aims.

Prevalence and Definition

Mild TBIs are the most common type of TBI, accounting for 70-95% of all TBIs (Steyerberg et al., 2019) and approximately 2.5 million emergency department visits per year in the United States of America (Taylor, Bell, Breiding, & Xu, 2017). Similarly, in New Zealand it is estimated that up to 95% of all TBIs sustained each year are mild in severity (Feigin et al., 2013).

There is considerable variation in diagnostic criteria for mTBI and there is currently no universally accepted definition, which influences both research and clinical practice (Iverson et al., 2020; Mayer, Quinn, & Master, 2017; Pollinder et al., 2018). Furthermore, researchers use various terms interchangeably to refer to mTBI, including head injury, mild/minor head injury, minor brain injury, minor head trauma, closed head injury, concussion and sports-related concussion (Rosenbaum, & Lipton, 2012; von Holst & Cassidy, 2004). Inconsistent terms and definitions make it difficult to summarise and compare research findings, which in turn hinders the broader understanding of mTBI sequelae (Bigler, 2008; Karr, Areshenkoff, & Garcia-Barrera, 2014). However, common elements of most definitions include the Glasgow Coma Scale (GCS), length of post-traumatic amnesia (PTA), length of loss of consciousness (LOC) and intracranial imaging findings (Kristman et al., 2014). The GCS consists of three subscales that evaluate motor responsiveness, verbal response and eye-opening response, with total possible scores ranging

from 3 to 15, where 3 indicates deep unconsciousness and 15 indicates a patient is fully awake, orientated and following commands (Teasdale & Jennet, 1974). PTA refers to the period immediately after injury during which the person is unable to form continuous day-to-day memories, typically accompanied by disorientation (Marshman, Jakabek, Hennessy, Quirk, & Guazzo, 2013). Length of LOC refers to a state of alteration or lack of awareness and an inability to respond to environment but does not include transient confusion of other alterations in mental state (e.g. disorientated or confused) (Petchprapai & Winkelman, 2007). Neuroimaging may be used if individuals present at a hospital; typically a computerised topography scan (CT) is used to identify the presence of lesions that may need intervention (e.g. intracranial haemorrhages, or swelling).

The most commonly used operational diagnostic criteria for mTBI was proposed by the World Health Organisation Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury (Caroll et al., 2004). They define mTBI as an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: i) one or more of the following: confusion or disorientation, LOC of 30 minutes or less, PTA for less than 24 hours, and/or transient neurological abnormalities such as focal signs or seizures; and presence of intracranial lesion not requiring surgery; ii) GCS score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of mTBI must not be due to any substance, medications, be caused by other injuries or treatment for other injuries (e.g. systemic injuries), caused by other problems (e.g. psychological trauma, or coexisting medical conditions) or caused by penetrating craniocerebral injury (Caroll et al., 2004; Cassidy et al., 2004). This current study will use this definition of mTBI.

Mild TBI's can also vary in severity, with some individuals experiencing a momentary state of altered consciousness, others are knocked unconscious; while others experience a skull fracture. Evidence indicates that individuals who suffer a depressed skull fracture and/or a trauma-related abnormality experience significant acute dysfunction and poorer neuropsychological outcome than mTBI individuals who do not have these complications, although functional outcome in these patients typically remains normal (Borgaro, Prigatano, Kwasnica, & Rexer, 2003; Dikmen, Machamer, Fann, & Temkin, 2010; Iverson et al., 2012; Lee et al., 2008). Consequently, however, mTBI's have been further differentiated as 'complicated' and 'uncomplicated', where 'complicated' mTBI is defined by the presence of a depressed skull fracture and/or a trauma-related abnormality (e.g. haemorrhage) (Iverson et al., 2012).

mTBI pathology: Primary and secondary injury

Diffuse neuropathology, often referred to as primary injury occurs as a direct consequence of the biomechanical forces of injury that place high strain on axons and microvasculature causing rotation, stretching and shearing (Bigler et al., 2016; Smith, Meaney, & Shull, 2003). Whilst axons and microvasculature can accommodate a degree of strain, their viscoelastic capacities are exceeded by the sudden and rapid application of force (Johnson et al., 2013; Smith, 2016) resulting in diffuse axonal injury (DAI). For microvasculature, rapid acceleration-deceleration leads to rupturing of small end arteries where they terminate at the grey/white matter interface, resulting in microhaemorrhages (Bigler, 2013). Microhaemorrhages result not only from damage to small blood vessels, but also from axonal injury. The rotation, stretching and shearing of axons disrupt cellular membranes and metabolic processes, thereby triggering a "neurometabolic cascade" which is referred to as the secondary injury (Giza, & Hovda, 2014; King, 2014; MacFarlane & Glenn, 2015; Meaney & Smith, 2011). These cascades are delayed responses and can take several hours to days to manifest (Granacher, 2012). The mechanical disruption of cell membranes results in abrupt neuronal depolarisation and release of glutamate, an excitatory neurotransmitter. Increased levels of glutamate lead to neuronal excitotoxicity causing alteration of normal cellular metabolism, neurofilament compaction and microtubule disassembly. This leads to impaired axonal transportation, axonal swelling and axotomy (Barkhoudarian, Hovda, & Giza, 2011; Niogi, & Mukherjee, 2010). Other common secondary injuries include ischemia, oedema, hypoxia, epilepsy and increased intracranial pressure (Lucas & Addeo, 2006; McKee & Daneshvar, 2015).

Early histological studies of human and animal brains first provided empirical evidence of DAI (Adams et al., 1989; Bigler, 2004). DAI is indicated by the presence of axonal bulbs and swellings at the site of injury and Wallerian degeneration of white matter months following injury (Adams et al., 1989; Johnson et al., 2013). The extent of axonal injury is dependent on the magnitude and rate of strain on the brain and the severity of DAI is hypothesised to correlate with the impairments, prognoses and recovery from TBI (Bigler, 2008). DAI usually causes microstructural injuries, which can rarely be seen on CT or conventional MRI scans, as these techniques lack the sensitivity required to detect damage at the microstructural level (Bigler, 2013; Bigler & Maxwell, 2012). However, new advances in neuroimaging, including a form of MRI called diffusion tensor imaging (DTI), are enabling *in vivo* explorations of the neural consequences of mTBI.

Outcomes Following mTBI

Normal recovery

In the days and weeks following a mTBI (also known as concussion) individuals can experience a cluster of symptoms known as *post-concussion symptoms* (Barkhoudarian, Hovda, & Giza, 2011; Dischinger, Ryb, Kufera, & Auman, 2009). These symptoms are commonly grouped into *physical* complaints (e.g. headaches, fatigue, dizziness, and sensitivity to noise/light), *cognitive* complaints (e.g. attention impairment, concentration issues, slow processing speed and memory difficulties) and *emotional* complaints (irritability, depression, anxiety) (Hiploylee et al., 2017). An individual can experience one or a combination of many symptoms. Symptom resolution varies greatly, from several hours, days to weeks, but "normal recovery" from a mTBI is considered to occur from 14 days up to three months (Carroll et al., 2004; 2014). The rate and duration of symptom resolution is influenced by factors including the nature of the head injury itself, such as the presence of intracranial abnormalities and mechanism of injury and physical factors such as the presence of other trauma-related injuries, e.g. pain; and medication in the early post-injury period (Broshek, De Marco, & Freeman, 2015; Iverson, 2006; Jacobs et al., 2010; Landre, Poppe, Davis, Schamus & Hobbs, 2006; Meares et al., 2008). Recovery following mTBI is typically categorised into *acute, sub-acute and chronic*, where acute refers to hours following injury up to a week; subacute refers to one week up to three months; and chronic refers to symptoms that occur at three months and beyond.

Neuropsychological changes following mTBI

Cognitive impairments are reported to be the most common mTBI complaint (Ponsford et al., 2000) and can significantly affect an individual's quality of life, leisure activities and ability to work (Levin & Diaz-Arrastia, 2015; Mani, Cater, & Hudlikar, 2017; Wise et al., 2010). Neuropsychological tests are used as an objective measure of cognitive functioning post-mTBI. Common cognitive impairments following mTBI are in the domains of attention, processing speed, executive functions, and/or memory, although there is differential recovery across these domains over time (Kay, Newman, Cavallo, Ezrachi, & Resnick, 1992; Rabinowitz, & Levin, 2014; Williams, Potter, & Ryland, 2010). There is a breadth of research examining cognitive impairment acutely post-injury, where considerable cognitive impairments across many domains are identified. However, the picture is less clear for changes occurring in the later stages of recovery.

The cognitive sequelae of mTBI are often conceptualised as acute, short-lived, and a direct result of the biomechanical forces of injury and associated biochemical changes (Bigler, 2003). A

consistent pattern of reduced cognition has been documented in the first 24 hours and within the first week post-mTBI (Bloom et al., 2017; de Freitas Cardoso et al., 2019; Kou et al., 2013; Silverberg, Luoto, Ohman, & Iverson, 2014). In the first week post-injury reductions in attention, information processing speed, language, memory and executive function have been shown in mTBI individuals compared to controls (de Freitas Cardoso et al., 2019; Sivák et al., 2014; Veeramuthu et al., 2015) .

Within the sub-acute period, comprehensive neuropsychological testing can be conducted rather than limited to specific tests or brief screens used in the acute phase. Cognitive deficits at 1 week to three months post-mTBI are shown in the domains of attention, information processing, reaction time, memory and executive functions compared to controls (Barker-Collo et al., 2015; Heitger et al., 2006; Landre et al., 2006; Levin et al., 2013; Mathias, Beall, & Bigler, 2004; McCauley et al., 2014; Ponsford et al., 2000, 2011, Shanmukhi & Panigtahi, 2003). Individual studies, meta-analyses and reviews have shown that cognitive deficits in the sub-acute period are more subtle than in the acute period, which is suggestive of recovery (Karr et al., 2014; Rohling et al., 2011).

Whether these cognitive impairments persist in the later stages of recovery is debated. While a large proportion of studies have suggested that cognitive deficits at the acute phase of recovery dissipate one to three months post-injury (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Frencham, Fox, & Maybery, 2005, Ponsford et al., 2000; Rohling et al., 2011), other studies have shown that persistent impairment can be present in mTBI individuals three months, 1 year and up to 8 years post-injury (Bernstein, 2002; Leininger, Gramling, Farrell, Kreutzer, & Peck, 1990; Kwok, Lee, Leung, & Poon, 2008; Vanderploeg, Curtiss, & Belanger, 2005). It remains controversial as to whether all individuals who have sustained a mTBI recover from mTBI-related neuropsychological deficits within three months, or whether it is possible that a small group of individuals continue to have neuropsychological deficits related to their injury which last a prolonged period of time.

Neuroimaging post-mTBI

CT is the most commonly used imaging technique to assess mTBI acutely within a hospital/medical setting (Douglas et al., 2018). CT's are used acutely after mTBI, as they are fast to complete and identify the location and extent of damage e.g. if a skull fracture or haemorrhage are present and whether immediate medical and/or surgical interventions are required (Niogi & Mukherjee, 2010; Gonzalez & Walker, 2011). However, CT scans tend to show only macroscopic damage (e.g. hemorrhage) which occur in only the minority of mTBI cases (10%) (Bigler, 2016; Shelton et al., 2012). CT is not sensitive enough to identify subtle pathology or microstructural

alterations, such as DAI which are believed to occur in mTBI (Bigler & Maxwell, 2011; Douglas et al., 2018; Koerte, Hufschmidt, Muehlmann, Lin, & Shenton, 2016).

In some clinical centres MRI is also used regularly in the acute and sub-acute period (up to weeks/ months) post-mTBI, particularly when symptoms are present, but no damage has been detected by CT (Bigler et al., 2016; Le & Gean, 2009; Suri & Lipton, 2018; Wheble & Menon, 2016). MRI is considerably more sensitive than CT (Bigler et al., 2016; Guenette, Shenton, & Koerte, 2018), with MRI abnormalities identified in 30% of people with mTBI who had normal CT scans (Niogi & Mukherjee, 2010). In addition to identifying macroscopic damage (e.g a haemorrhage) in the acute phase, MRI can also be used in the subacute and chronic phases following mTBI to measure structural damage (Bigler & Maxwell, 2012; Koerte et al., 2016). Although more sensitive than CT, standard clinical MRI scans also underestimate microstructural damage (DAI), and therefore the assessment of neural injury post-mTBI (Koerte et al., 2016).

Persistent Post-Concussion Symptoms (PPCS)

Definition and diagnosis

Whilst, the majority of individuals have recovered within 3 months post-injury (Losoi et al., 2016), 10-35% of individuals experience post-concussion symptoms beyond the typical recovery period and in some cases, up to a year or longer (Ahman, Saveman, Styrke, Björnstig, & Stålnacke, 2013; Belanger, Barwick, Kip, Kretzmer, & Vanderploeg, 2013; Ruff, 2005; Theadom et al., 2016). Individuals who experience symptoms beyond three months are considered to have persistent post-concussion symptoms (PPCS) (Begaz, Kyriacou, Segal, & Bazarian 2006; Stålnacke, Elgh, & Sojka, 2007; Willer & Leddy, 2006). Similarly to mTBI, various terms are used to refer to PPCS in research and clinical settings including: post-concussion syndrome, post-concussive disorder and persistent post-concussion syndrome (Caroll et al., 2004; Kashluba, Paniak, & Casey, 2008; Marshall et al., 2012). Different diagnostic criteria are also used to diagnose the unresolved symptoms following mTBI. The two most used clinically are: The Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV, American Psychiatric Association, APA, 1994) (despite the revisions made in the fifth edition) (APA, 2011) and the International Classification of Diseases 10th revision (ICD-10, World Health Organization, 1992). The DSM-IV and ICD-10 have similar criteria with good concordance between the symptoms involved (McCauley et al., 2018), however, the DSM-IV includes additional criteria of neuropsychological testing and the ICD-10 includes loss of consciousness criteria. These different specifications influence the rates of classification, where fewer individuals are diagnosed with PPCS using the DSM-IV criteria compared to the ICD-10 (McCauley et al., 2018). As there is no consensus on diagnostic criteria and terms, enduring

symptoms following mTBI will be referred to as persistent post-concussion symptoms for this thesis.

A number of studies have shown that individuals who have sustained a mTBI may report a variety of persistent post-concussion symptoms up to a year post-injury. Individuals report persistent physical symptoms, such as headaches, sensory sensitivity, nausea and dizziness three months (or more) post-mTBI (Tator et al., 2016). Headaches are frequently reported as the most common PPCS at three months post-mTBI (Cooksley et al., 2018; Silverberg, 2019) and 36.1% of individuals report headaches up to a year post-injury (Theadom et al., 2016). Noise sensitivity is present in 35% of individuals at three months post-injury (Kashluba et al., 2004), in 30.6% of individuals at 6 months post-injury (Theadom et al., 2016), and 27.5 % of individuals at 1 year post-injury (Theadom et al., 2016). Persistent emotional difficulties including irritability, emotional lability, depressed mood and anxiety are also commonly reported. The presence of anxiety is commonly reported at six months and up to a year post-injury (Delmonico, Theodore, Sandel, Armstrong, & Camica, 2017; Ponsford et al., 2012; Walker, Franke, McDonald, Sima, & Keyser-Marcus, 2015). Depression is also present up to a year post-injury (Bombardier et al., 2010). Irritability is less commonly studied, but has also shown to be present up to a year post injury (Hovland & Mateer, 2000). Cognitive difficulties are frequently reported by individuals with PPCS, including 39%- 44.9% at six months (Stulemeijer, Vos, Bleijenberg, & Van der Werf; 2007; Theadom et al., 2016) and 34-40.9% a year post injury (Theadom et al., 2016). Although controversial, a range of persistent cognitive neuropsychological impairments have been shown including attention, information processing speed, working memory and executive function from three months and up to eight years post-injury (Barker-Collo et al., 2015; Dall'Acqua et al., 2017; Grossman et al., 2013; Kinnunen et al., 2011; Konrad et al., 2011; Oldenberg, Lundin, Edman, Nygren-de Boussard, & Bartfai, 2016). Other studies however, report no cognitive impairments in the key domains beyond three months following mTBI (Clarke, Genat, & Anderson 2012; Vanderploeg, Curtiss, & Belanger, 2005; Walijas et al., 2015; Zhou et al., 2013).

A variety of questionnaires are used studies to measure the frequency/severity/number of symptoms associated with PPCS (Dikmen et al., 2010; Meares et al., 2008; Sigurdardottir, Andelic, Roe, Jerstad, & Schanke, 2009; Stulemeijer, van der Werf, Borm, & Vos, 2008). These include the: Concussion Symptom Inventory (Randolph et al., 2009); Post-Concussion Checklist (Gouvier, Cubic, Jones, Brantley, & Cutlip 1992) and the Rivermead Post-Concussion Questionnaire (RPQ; King, Crawford, Wenden, Moss, & Wade, 1995). The individual questionnaires (except the RPQ) have clearly defined criteria, which determine whether PPCS is present, or not. However, there is no specified criteria for the RPQ, and different studies specify their own PPCS cut off criteria (Barker-Collo et al., 2019; Theadom et al., 2016).

In summary, there are several different diagnostic criteria proposed for PPCS including the DSM-IV and ICD-10 criteria, and a range of questionnaires used to assess ongoing symptoms. There is still no consensus, however, regarding a definition of PPCS for use in research or clinical settings, which makes it difficult to compare studies and make conclusions (Marshall et al., 2012; Fayol et al., 2009).

Aetiology of PPCS

The aetiology of PPCS is an area of ongoing debate and with little agreement as to the mechanisms underlying PPCS. Two dominant arguments, frequently presented as opposing viewpoints, focus on psychological factors or on neural factors.

Psychological and psychosocial perspective. An extensive literature has focused on the view that psychological factors underlie the enduring problems experienced by individuals with PPCS. There is considerable evidence suggesting psychological factors can be significantly related to the development, level of symptom report and maintenance of PPCS (Hellstrøm et al., 2017; Lange, Iverson, & Rose, 2011; Massey, Meares, Batchelor, & Bryant, 2015; Ponsford et al., 2000, 2002; Silver, 2014; Silverberg et al., 2015; van der Naalt et al., 2017; Walijas et al., 2015). Pre-injury psychological disorders have been associated with PPCS from three months up to a year post injury (Broshek, De Marco & Freeman, 2015; Cnossen et al., 2017; Meares et al., 2011; Ponsford et al., 2019). Ponsford et al. (2012) argues that individuals with pre-injury psychological disorders are more likely to react to post-concussion sequelae with anxiety and catastrophic interpretations, which exacerbates their symptoms and symptom report. Others have suggested that individuals with pre-injury psychological disorders do not have effective coping mechanisms and therefore experience greater adjustment difficulties following mTBI (MacMillan, Hart, Martelli, & Zasler, 2002; Rapoport, Kiss, & Fernstein, 2006). Van Veldhoven et al. (2011) argued that pre-injury stress may complicate recovery from mTBI, and may predispose an individual to develop prolonged emotional disturbances, as well as physical or cognitive symptoms in response to injury.

Early post-injury psychological distress has also been shown to be predictive of PPCS development and long-term outcomes following mTBI (Dischinger et al., 2009; King et al., 1999; Meares et al., 2011; Ponsford, 2012; Ponsford et al., 2000, 2002; Silverberg & Iverson, 2011). In a number of studies, acute post-injury anxiety (5-10 days) was the strongest predictor of PPCS development at three months (Dischinger et al., 2009; Ponsford, 2012), and greater than a year post-injury (King, & Kiriwilliam, 2011). As pre-existing psychological disorders may contribute to the post-injury anxiety two studies excluded individuals with pre-existing psychological disorders (Dischinger et al., 2009, King, & Kiriwilliam, 2011) and then examined the relation

between acute post-injury psychological disturbances and PPCS. Although both found an association, they were not able to determine whether the psychological disturbance caused PPCS. For example, it is possible that the psychological difficulties some individuals experience following mTBI may be caused response to the severity and impact of their concussion symptoms, rather than a driver of ongoing symptoms. Furthermore, as anxiety and depression are included as symptoms of PPCS, it might be expected that pre-existing/ post-injury psychological difficulties are likely to predict a component of PPCS. However, psychological difficulties cannot solely explain all of the PPCS symptoms, such as light sensitivity, suggesting other factors must be contributing to the picture (Phillips & Reddy, 2016).

Personality styles and/or traits have also been suggested to be contributing factors to PPCS. Certain personality styles may influence an individual's symptom report and their response to their injury. Specific personality traits including: narcissism, neuroticism, histrionic, perfectionistic, compulsive and borderline traits have been associated with greater symptom report (Merz, Zane, Emmert, Lace, & Grant, 2019; Ruff, Camenzuli, & Mueller, 1996; Wood, McCabe, & Dawkins, 2011). Hou et al. (2012) found that individuals with "all or nothing" personality traits often present with perfectionism, predicted PPCS at three and six months post-injury. Additionally, traits of negativity, somatisation and dependency were also associated with PPCS (Garden, Sullivan, & Lange, 2010; Morgan et al., 2015; Ponsford et al., 2012; Trinh, Brown, & Mulcahey, 2020; Yuen, Tsai, Lin, Yang, & Huang, 2016). Wood, O'Hagan, Williams, McCabe, & Chadwick (2014) showed that the severity of PPCS was predicted by individuals with higher levels of sensitivity to their bodily sensations (believed to be a personality characteristic, but could also be explained as a trauma response).

Negative coping styles and individuals' reactions to the injury or recovery have been also been associated with greater PPCS (Anderson & Fitzgerald, 2020; Belanger et al., 2013; Snell, Siegert, Hay-Smith & Surgenor, 2011; Wijenberg, Stapert, Verbunt, Ponsford, & Van Heugten, 2017). In contrast, Sullivan, Kempe, Edmed, & Bonanno, (2016) argued that positive coping styles such as higher levels of resilience (where resilience is broadly defined as positive adaptation and the ability to return to baseline following adversity) acts as a protective factor against the development of PPCS. They found that higher levels of resilience related to less PPCS, whilst lower levels of resilience related to greater PPCS symptomatology.

Cognitive biases have shown to influence symptom report (Iverson, Lange, Brooks, & Rennison, 2010; Lange, Iverson, & Rose, 2010; Mittenberg, DiGiulio, Perrin, & Bass, 1992; Whittaker, Kemp, & House, 2007). The *"Good Old Days Bias"* is a term first proposed by Mittenberg et al. (1992) who suggested that individuals' expectation of symptoms after mTBI contributes to individuals' misattribution of common symptoms and complaints (e.g, headaches)

to the injury, and minimisation of other aetiologies driving their symptoms e.g. stress. Additionally, Mittenberg et al. (1992) claimed that individuals minimised their preinjury symptoms and overestimated their pre-morbid functioning as better than it was. Finally, some findings indicate that how individuals appraise their injury, interpret their symptoms and their beliefs about the injury influences the susceptibility to PPCS (Anderson & Fitzgerald, 2020; Hou et al., 2012; Whittaker et al., 2007). Snell, Surgenor, Hay-Smith, Williman, & Siegert, 2015) found that individuals who endorsed stronger negative beliefs about the identity, chronicity, expected consequences, predictability and emotional impact of their injury experienced enduring symptoms beyond seven months compared to individuals who reported positive beliefs and returned to normal faster.

Some authors have further argued that PPCS is not a real syndrome because studies have shown that post-concussion-like symptoms exist in healthy populations (Edmed, & Sullivan, 2014; Iverson & Lange, 2003; Voormolen et al. 2019; Zakzanis & Yeung 2011), as well as in patients with a non-head injury trauma (Lagarde et al., 2014; Meares et al., 2008) or individuals with chronic pain (Iverson & McCracken, 1997). However, given the broad range of cognitive, physical and affective symptoms in PPCS, it is important to examine the symptom profiles of non-mTBI patients reporting PPCS-like symptoms. Van der Vlegel, Polinder, Toet, Panneman, & Haagsma (2021) compared the PPCS-like symptoms of individuals who sustained an accident without a head injury (e.g. sports accident or road traffic accident) with those of individuals who sustained a mTBI. In addition to the high prevalence of PPCS in mTBI participants (24.1%), a considerable proportion of non-head injury patients also reported PPCS (20.6%) a year after injury. Notably, however, there were differences in symptom profiles for patients with and without head injury: all cognitive complaints (poor memory, poor concentration, and taking longer to think) and most of the physical complaints (headaches, dizziness, blurred vision, double vision, light sensitivity) were significantly more prevalent in mTBI patients. Whereas, most of the emotional complaints (irritably, frustration, restlessness) were similarly present in mTBI and non-head injury patients. These results suggest that the cognitive and physical symptoms may be associated with the brain injury itself, whereas the emotional/behavioral symptoms may be generally linked to psychological distress. These findings are similar to those of Dean, O'Neill, & Sterr (2012), who compared the scores for each RPQ item between patients with a history of mTBI and healthy controls with no history of mTBI. The mTBI group had significantly higher scores for headaches, dizziness, nausea, light sensitivity and taking longer to think than healthy controls. These factors suggest a need for a diagnostic measure to fully, but selectively, capture the experience of individuals with PPCS.

Another argument made in support of the view that psychological factors underlie PPCS is that there is significant variation in findings in those studies exploring cognitive functioning in the chronic phase post-mTBI (Alsalaheen, Stockdale, Pechumer, Giessing, He, & Broglio, 2017). Findings from studies that have examined cognitive outcome beyond three months mTBI in an unselected group are inconsistent. A number of studies have shown mTBI participants display reduced cognitive performance in the chronic period (>3 months post-mTBI on tasks that assess attention (Catale, Marique, Closset, & Meulemans, 2009; Chan, 2005; Kumar, Rao, Chandramouli & Pillai, 2013; Maruta et al., 2016; Sterr et al. 2006), information processing (Johansson, Berglund, & Rönnbäck, 2009; Kinnunen et al., 2011; Lachapelle, Bolduc-Teasdale, Ptito, & Mckerral, 2008; O'Jile et al., 2006), memory (Catale et al., 2009; Chen et al., 2007; Vanderploeg et al., 2005) executive function (Bar-Haim Erez, Rothschild, Katz, Tuchner, & Hartman-Maeir, 2009; O'Jile et al., 2006; Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009; Sterr et al., 2006). However, there is also research that observes no deficit in cognitive performance in mTBI patients in the chronic stage of recovery (Heitger et al., 2006; Karr et al., 2014; Konrad et al., 2011; Walijas et al., 2015; Zhou et al., 2013). Neuropsychological tests are used as objective outcome measures of function following mTBI, and it is argued that if PPCS develops and has a neural origin, a decline in cognitive performance is expected in individuals in the chronic phase. Authors argue that a subgroup of individuals with enduring symptoms following mTBI are unlikely to exist because a number of meta-analyses have failed to detect significant difference between those who have sustained a mTBI compared to controls (Belanger, Curtiss, Demery , Lebowitz, Vanderploeg, 2005; Frencham, Fox, Maybery, 2005; Rohling et al., 2011). This has been used as evidence supporting a psychological basis for PPCS. However, there are a number of factors which might explain why there are mixed results in functioning. Firstly, the majority of studies have measured an unselected group of individuals who have sustained a mTBI three or more months prior compared to controls. This sample of mTBI participants is likely to include individuals who are experiencing PPCS and those who are not. It is plausible that a minority group of individuals with subtle cognitive impairment on neuropsychological tests would be concealed, as their deficits would be obscured within a larger group of individuals who have recovered (Bigler et al., 2013; Iverson, 2010). Such individuals may be difficult to detect because they are likely to constitute a very small portion of the overall participant sample. A few studies have directly examined neuropsychological performance in individuals with PPCS perform compared to controls and have found individuals with PPCS perform worse (Dean et al., 2015; Miller, Hayes, Lafleche, Salat, & Verfaellie, 2016). Secondly, the majority of these studies compare a group of individuals who have sustained a mTBI with a healthy control group. A stronger design would compare individuals who report enduring symptoms post-TBI with those

who have recovered. This would make it possible to delineate and examine the subtle cognitive differences frequently reported by individuals with PPCS.

To date, the limited number of studies who have taken this approach have found that individuals with PPCS, up to a year post-injury, performed more poorly on neuropsychological tests that measure attention (divided, sustained and selective), reaction time, working memory and learning compared to individuals without PPCS following a mTBI and controls (Bohnen, Jolles, & Twijnstra, 1992; Chen et al., 2007; Messé et al., 2012; Sterr, Herron, Hayward, & Montaldi, 2006).

An additional factor influencing why reduced neuropsychological performance may not be indicated beyond 3 months relates to the sensitivity of conventional neuropsychological tests. Bigler (2013) argues many of these measures are insufficiently sensitive to reveal the subtle cognitive dysfunction experienced by individuals with PPCS. Instead, tests requiring complex cognitive skills that place greater demands on cognitive systems may detect the subtle changes experienced by individuals with PPCS (Allen, Wu, & Bigler, 2011). A number of studies incorporating tests that measure complex cognitive functioning have shown that mTBI participants perform more poorly than controls on tasks that place high demands on the attentional and executive systems (Cicerone, 1996; Ozen & Fernades, 2012; Paré, Rabin, Fogel,& Pépin, 2009; Vanderploeg, Curtiss, & Belanger, 2005). For example, dividing attention between two concurrently performed tasks has shown to decrease information processing speed (Cicerone, 1996; Pare et al., 2008), as well as accuracy (Bernstein, 2002; Paré et al., 2008), in mTBI participants in the chronic phase compared with controls. Ozen and Fernades (2012), found that mild TBI participants did not differ from controls on simple processing speed measures, Trail Making Tests and Stroop Test. However, they did significantly differ in average response times on a non-standard assessment of a visual working memory task that included a ‘low load’ and a ‘high load’ condition. The mTBI group performed more poorly with the increase in load resulting from an additional concurrent task compared to the controls. Pare et al. (2009) corroborated these findings using a divided attention task, in which reductions in processing speed were shown in mTBI individuals and were associated with the increased complexity of the additional task. This highlights it is not the simple division of attentional resources, but the complexity of the additional task that impairs the speed of information processing. Vanderploeg, Curtiss, & Belanger (2005) also argue that subtle deficits in cognition following mTBI can be detected using non-standard and more sensitive measures of cognitive performance. They report no effect of mTBI on cognitive functioning using standard neuropsychological measures on a test battery of 15 tests. However, they found significant differences on the Paced Auditory Serial Addition Test;

(PASAT); by measuring trial completion rates. Individuals who sustained a mTBI's one year prior performed significantly more poorly over the four trials than healthy controls.

The role that psychological factors can have in the development and maintenance of PPCS has received a lot of focus in PPCS research. Studies have revealed that both pre-injury and post-injury mood disturbances are associated with PPCS up to a year post-injury. It has been argued that this explains the presence of PPCS. However, it can also be explained that greater psychological difficulties post-injury are presented with the distress associated with unresolved, enduring symptoms. Specific personality traits, coping styles and cognitive biases have been shown to influence PPCS report. Finally, the inconsistency of cognitive studies in the chronic stage post-mTBI, and particularly the studies that show no cognitive difficulties, have been used as evidence to support the psychological argument for PPCS.

Neural perspective. An alternate perspective proposes that PPCS may be the result of injury-related neuropathology. This viewpoint is based on the biomechanics of the injury and subsequent metabolic and pathophysiological changes, and evidence of how these injury mechanisms affect the function and structure of the brain (Martin, 2016; MacFarlane, & Glenn 2015). The evidence to support this argument will be discussed below and separated into sections including evidence related to DAI, focussing on studies using DTI measures of white matter organisation, differences in individual's brain reserve capacity and the cognitive dysfunction resulting from cumulative TBI's.

The neural argument was first proposed following evidence from animal and post-mortem human autopsy studies (Adams et al., 1989; Bigler, 2001). These studies demonstrated damage to axons, referred to as diffuse axonal injury (DAI), and microvasculature well beyond the typical recovery period (e.g 7 months) (Bigler, 2004). DAI is thought to occur as a result of the stretching and shearing of axons that comprise the brain's deep white matter tracts (Su & Bell, 2016). More recently, an MRI-based technique called Diffusion Tensor imaging (DTI; Basser, Mattiello & LeadBihan, 1994) has enabled researchers to identify and quantify microstructural changes following mTBI *in vivo* (Bigler, 2013). Research has been conducted on all stages of recovery following mTBI (acute, subacute, and chronic).

The technique of DTI will be discussed in further detail in *Chapter Four*. However, in brief, DTI is a technique that uses the diffusion of water molecules within the brain to identify the integrity of white matter structure; where altered water diffusion is commonly interpreted as a marker of axonal injury (Assaf & Pasternak, 2008). In healthy white matter, water diffusion is highly directional and moves readily along the axonal fibres. Diffusion metrics are used to quantify the *amount* and *directionality* of diffusion and research has demonstrated that changes in DTI metrics are indicative of microstructural changes. The two most reported metrics are

Fractional Anisotropy (FA) and Mean Diffusivity (MD). FA is a normalised measure that evaluates the degree of *directionality* of diffusion (Le Bihan et al., 2001). A value of 1 is given when diffusion is exclusively restricted movement along the axis, and a value of 0 is given for unrestricted movement of water in all directions. MD refers to the total diffusion within a voxel (Dodd et al., 2014; Strauss et al., 2015). With damage to the white matter structure, the most commonly reported changes include: a decrease in FA and an increase in MD (Niogi & Mukherjee, 2010). These findings suggest reduced structural integrity of the white matter tract, and are considered markers of DAI (Beaulieu, 2002). Other diffusion metrics, such as Radial Diffusivity (RD) and Axial Diffusivity (AD), are used less frequently in mTBI research, despite purported sensitivity to relevant pathologies such as axonal damage (AD) and changes in myelination (RD) (Alexander, 2008; Song et al., 2003; Song et al., 2005).

As shown in *Table 1*, bidirectional changes in DTI metrics are shown in mTBI participants in the acute and subacute phases. Compared to control subjects, a number of studies reveal increased FA and decreased MD in mTBI participants, while others have found reduced FA and increased MD, or even no differences compared to healthy controls. Variation in DTI metrics is most evident within the first month post-injury with almost equal numbers of studies reporting reduced FA as did increased FA (Dodd et al., 2014). These variable findings may be due to the effects of secondary injury. More specifically axonal swelling that occurs post-injury due to intracellular influx of water (i.e. cytotoxic oedema) leads to restriction of diffusion within the extracellular space, resulting in increased anisotropic diffusion and therefore higher FA leads (Alexander, 2008).

There is a more consistent pattern of findings shown in *Table 1* for the chronic stage of recovery. The majority of studies report that mTBI participants' show reduced FA, or both reduced FA and increased MD compared to controls. Of these, most have found changes in the corpus callosum or frontal association pathways (Niogi & Mukherjee, 2010). Damage to these areas are congruent with many of the cognitive symptoms reported by mTBI participants (e.g. attention, working memory). There are a few studies, however, that report no differences in FA or MD between mTBI and control groups.

Table 1

DTI Neuroimaging Studies for the Acute and Subacute Phases

Injury phase	First author and year	Time since injury	Analytical method	DTI results mTBI versus controls
Acute	Arfanakis et al., 2002	<24 hours	ROI	↓FA in IC, CC
	Huisman et al., 2004	≤ 7 days	ROI	↓FA in sCC, IC ↓MD in sCC;
	Bazarian et al., 2005	<4 hours	WB, ROI	No FA differences
	Wilde et al., 2008	R: 1-6 days	ROI	↑FA and ↓MD and ↓RD in CC
	Ilvesmaki et al., 2014	48 hours	WB, TBSS	No group differences in FA, ADC, AD, RD
	Zhu et al., 2014	5.5 days	WB, VBA, TBSS	↓FA in CC, all lobes
Acute & Subacute	Inglese et al., 2005	R: 1-10 days	WB, ROI	↓FA and ↑MD in sCC, IC
	Miles et al., 2008	R: 1-10 days	ROI	↓FA and ↑MD in centra semiovala, CC, and IC
	Mayer et al., 2010	≤ 20 days	ROI	↑FA and ↓RD in gCC, CR, UF
	Toth et al., 2013	T1:72 hours; T2: 1 month	TBSS	↓FA and ↑MD aCC, CR and IC at both time phases.
	Yuh et al., 2014	A: 11.2 days	WB, VBA, ROI	↓FA in IC, EC, gCC, UF, ACR
Subacute	Lange et al., 2012	A: 47 days	ROI	No FA or MD differences
	Xiong , 2014	A: 32.1 days	VBA, TBSS	↓FA and ↑MD in UF, SLF, and IC
Subacute & Chronic	Rutgers et al., 2008	R: 0.1-109.3 months	WB	↓FA in cingulum, CC
	Niogi et al., 2010	R: 1-65 months	ROI	↓FA in ACR, UF, gCC, cingulum, ILF
	Messé et al., 2012	T1: R: 7-28 days; T2: R: 3-4 months	VBA, TBSS	PO ↑MD in fMaj & fMin; IFOF, ILF; no FA, AD, RD differences
Chronic	Veeramuthu et al., 2015	6 months	TBSS, ROI	↓FA in CR, IC, cingulum, SLF, OR, gCC
	Henry et al., 2011	6 months	VBA	↑FA, ↓MD and ↑AD in CC and CST
	Kraus et al., 2007	>3 months	ROI	↓FA and ↑AD in OR, SLF
	Lipton et al., 2009	>8 months- 3 years	WB, VBA	Whole-brain ↓FA
	Lo et al., 2009	R: 2.6–10.8 years	ROI	↓FA and ↑MD in gCC
	Sugiyama et al., 2009	R: 1-20 years	VBA, tractography	↓FA in CC, fornix, cingulum, all lobes
	Grossman et al., 2013	>9 months	TBSS	↑MD in CC, cingulum, thalamus, EC,OR,
	Wada et al., 2012	R:6-88 months	TBSS	↓FA in SLF, insula, fornix
	Bouix et al., 2013	R: 2.6- 138 months	ROI	No group differences in FA, MD, AD, or RD
	Dean et al., 2015	>1y	VBA	↓FA in ACR, ALIC
	Astafiev et al., 2015	R:3 months - 5.5 years	ROI, TBSS	No differences in FA, MD, RD, or AD
	Maruta et al., 2016	R: 90days – 5 years	WB, ROI	No FA differences
	Karlsen et al., 2019	3 months	TBSS	↓ FA in gCC, SFOF cerebellar peduncle, IC, CR and PTR.

Note. R; Range; A: Average. WB: Whole brain; ROI: Region of interest; VBA: Voxelwise analysis; TBSS; Tract-based spatial statistics. FA; Fractional Anisotropy; MD; Mean Diffusivity; Radial Diffusivity; AD Axial Diffusivity. CC; Corpus callosum; aCC; Anterior of the corpus callosum; gCC; Genu of the corpus callosum; sCC; Splenium of the corpus callosum fMaj; Forceps major; fMin; Forceps minor; IC; Internal capsule; ALIC; Anterior limb of IC, EC; External capsule, CR; Corona radiata; ACR; Anterior corona radiata; UF; Uncinate fasciculus; SLF; Superior longitudinal fasciculus; IFL; inferior longitudinal fasciculus; IFOF; inferior fronto-occipital fasciculus; SFOF; superior fronto-occipital fasciculus; OR; Optic radiation; PTR; posterior thalamic radiation.

The majority of studies that have used DTI in mTBI individuals in the chronic phase of recovery have used unselected groups. Unselected mTBI groups are likely to include individuals who have recovered from mTBI and individuals who are experiencing enduring symptoms and reporting PPCS, which may reduce sensitivity. To date a small number of studies have directly studied individuals with PPCS following mTBI and compared them to individuals without PPCS and control participants (Bartnik-Olson et al., 2014; Karlsen et al. 2019; Messé et al. 2012). Messé et al. (2012) reported that individuals with PPCS (poor outcome) displayed higher MD values compared to both those with no PPCS (good outcome) and controls three months post-mTBI in the corpus callosum (forceps major and minor) inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus. Bartnik-Olson et al. (2014) found no differences in diffusion metrics when comparing the whole mTBI group to controls at three months post-mTBI. However, when the mTBI was split into two groups between those experiencing enduring cognitive symptoms (PPCS) compared to those who are not, reduced FA and increased RD was shown in those with enduring symptoms. In contrast, however, Karlsen et al. (2019) found no differences between individuals reporting PPCS compared to those without PPCS, despite displaying reduced FA in the whole mTBI sample compared to controls. A small number of studies have compared PPCS compared to no PPCS in the sub-acute phase (less than 3 months post-injury) (Kinnunen et al., 2011; Lange et al., 2015; Waljas et al., 2014). While these studies included measures of PPCS, we have not included these studies as they do not meet our classification of PPCS. Given the promising results coming from studies utilising DTI, more research is needed to delineate further the meaning of alterations in DTI metrics, as well as understanding the relationship between changes in white matter and functional changes.

A second line of support for a neural basis for PPCS comes from theoretical constructs termed brain reserve capacity (BRC) and cognitive reserve capacity (CRC), which have been used to explain how individuals display different functional outcomes following similar mTBIs. The BRC is a construct referring to a critical or threshold level of brain size/ synapse count with functional deficits occurring when the pathology burden is such that the brain substance is reduced below a critical level. BRC was first proposed by Satz (1993) who suggested that compared to those with less BRC, individuals with more BRC may be deficit-free for longer after similar sized lesions or require larger lesions to generate symptoms. Variables such as head circumference and brain volume are proxies for BRC (Stern, 2013). CRC is considered an active model of reserve, where the brain actively attempts to cope with brain damage by using alternative pre-existing cognitive processes and/or by enlisting compensatory processes (Stern, 2013). Cognitive reserve capacity has been estimated based on pre-morbid intellectual quotient (IQ), level of educational attainment or current occupational cognitive demands, all with higher levels leading to greater

reserves (Oldenberg et al., 2016: Levi, Rassovsky, Agranov, Sela-Kaufman, & Vakil, 2013). TBI studies have shown that individuals with greater CRC (as measured by either IQ, education level or occupational demands) show some degree of resilience to the impact of injury or neurodegenerative disease, as they can withstand greater levels of pathology before exhibiting outward signs of a given disorder (Bigler, 2015). In contrast, lower cognitive reserve has been associated with greater PPCS report at three months post-mTBI (Luis, Vanderploeg, & Curtiss, 2003; Oldenberg et al., 2016) and six months post-mTBI (Stulemeijer, Van der Werf, Borm, & Vos, 2008) and one year post injury (Leary et al., 2018). One possible mechanism by which cognitive reserve might affect PPCS relates to the processing efficiency of underlying neural networks. Individuals with lower CRC who experience a mTBI might have lower processing efficiency than those with higher CRC, and thus in the presence of mild neural dysfunction be more likely to have ongoing difficulties evident as PPCS. Lower CRC is likely to be also associated with a diminished capacity to mobilise compensatory neural and/or cognitive strategies in the face of neural dysfunction. Thus, individuals have different amounts of 'reserve' buffers when the brain is injured, which contributes to differences in their functional outcome and whether they develop PPCS or not.

A third line of evidence supporting a neural basis of PPCS following mTBI comes from studies showing some individuals with a history of multiple mTBIs have long lasting cognitive difficulties that are disproportionate to the most recent injury (Collins, 1999; Giza et al. 2013; Morgan et al., 2015; Stephens, Rutherford, Potter, & Fernie, 2010; Wall et al., 2006). This is particularly evident if individuals sustain a second mTBI within 10 days of the first injury or have greater than three mTBIs (Giza et al. 2013; Morgan et al., 2015; Ponsford et al., 2000). Collins (1999) reported that athletes with a history of two or more mTBIs performed more poorly on Trail Making (a measure of visual attention, task switching, processing speed and executive function) and Symbol Digit Modalities (a measure of psychomotor processing speed, and visual scanning) and report more enduring symptoms than athletes with no prior history. Similarly, Iverson (2005) reported that individuals with three or more mTBIs reported more subjective symptoms and performed more poorly on neuropsychological tests. Wall et al. (2006) compared jockeys who sustained one and multiple concussions and found that individuals who sustained two or more mTBIs experienced worse long-term executive/ attentional function compared to those with a single mTBI. More specifically, some studies have found that individuals with two prior concussions recover more slowly (Gronwall & Wrightson, 1975; Guskiewicz et al., 2003). However, not all findings support this; others studies have not found differences in neurocognitive functioning in individuals with multiple previous mTBIs (Broglio, Ferrara, Piland, & Anderson, 2006; Iverson, Brooks, Collins, & Lovell, 2006; Macciocchi, Barth, Littlefield, & Cantu, 2001;

Thornton, Cox, Whitfield, & Fouladi, 2008). There are a number of methodological design issues, which might explain these different findings. For example, Iverson, Brooks, Lovell and Collins (2006) and Broglio et al. (2006) used a computer screening measure (IMPACT) to measure cognitive impairment in individuals with multiple mTBIs. This tool is used to gather an overview of cognitive functioning and despite measuring attention and working memory, it fails to measure processing speed or complex attention e.g. divided attention, which are the common complaints of individuals' who fail to recover from mTBI. Additionally, the majority of participants in these studies were young sports players, who were tested pre-season. If an athlete had enduring symptoms following the previous season, they may have not undergone baseline testing because they may not be participating in sport that season. The number of previous concussions reported was based on athlete self-report and information on time since injury and severity of injury was not available in the majority of studies. In the study conducted by Macciocchi et al. (2001), only six percent of individuals had multiple prior injuries and this was within a small sample, and therefore their sample may not adequately represent the population of players who typically sustain multiple injuries.

In summary a range of models and factors have been proposed to explain the basis of persistent symptoms following mTBI, yet this remains unclear and controversial. Despite a lot of evidence implicating psychological factors, these do not explain all PPCS symptoms or account for a range of other findings. In a systematic review, Silverberg et al. (2015) proposed that a multifactorial model is more likely to predict outcome following mTBI. They argue that the existing models leave a considerable amount of variance unexplained and no single model could accurately predict individual recovery. However, the models included in this review used conventional MRI, which did not yield significant findings. This further reinforces the point that in order to understand individual recovery following mTBI, it is critical to use more sensitive imaging techniques.

Research Questions

This introductory chapter provides a brief overview of mTBI, associated recovery and PPCS. Three key research questions arise out of this overview that guide the overarching structure for this thesis. The overall aim of the thesis is to explore whether neural changes in white matter are present in individuals experiencing PPCS and whether these changes are associated with cognitive difficulties. To do this we will measure cognitive outcomes, microstructural properties of white matter tracts (as measured by DTI), the relationship between reported PPCS and DTI metrics, and the association between cognitive performance and DTI metrics in individuals 3-6 months post a mTBI.

The first research question explored in Study One, builds upon two key aspects of previous research. Firstly, the discrepancy between subjective reporting of enduring symptoms following mTBI and limited objective evidence of cognitive dysfunction at three months and beyond. Secondly, the proposal that the use of cognitive demanding and complex tasks may facilitate detection of ongoing subtle cognitive changes. Thus, the aims of Study One are to determine whether specific neuropsychological tests designed to assess complex cognitive abilities can differentiate between individuals with mTBI and matched healthy controls, and between individuals reporting high levels of PPCS compared to those who are not.

The second research question explored in Study Two builds upon existing research suggesting axonal injury following mTBI can be examined using the MRI metrics captured with DTI. In this study, the aims are first to examine whether DTI can identify white matter changes in a group of individuals who have sustained a mTBI and are 3-6 months post-injury, when compared to healthy matched controls. The second aim is to compare these same DTI metrics in individuals within the mTBI group, specifically comparing those experiencing high levels of PPCS with those whose symptoms are fewer or have largely resolved.

The third and final research question seeks to determine whether changes to white matter following mTBI are associated with objective performance on tests of cognitive function. There is a small amount of evidence suggesting that symptoms following mTBI are associated with markers of white matter tract damage using DTI, although findings across studies are not consistent. Whether or not performance on objective measures of cognition is also related to markers of white matter tract damage is poorly understood. Empirical evidence directly linking changes in white matter tract microstructure to cognition is needed in order to advance understanding of the contribution of one aspect of neural factors to individual recovery following mTBI. Thus, the third aim of this thesis explored in Study two is to determine whether injury-related white matter tract microstructural changes can predict poorer cognitive performance following mTBI.

Chapter Two

General Method

This chapter provides an overview of the general methodology and design applicable to both studies, including details of participants and procedure.

Participants

A total of 66 participants were involved in this study comprising two groups, a mTBI group and control group. All participants were required to be between 18 and 64 years of age, and to speak fluent English. Participants were also required to be free from taking any major psychiatric medications, having substance abuse dependence, a history of moderate or severe mTBI, or other neurological conditions. All participants involved in the study passed the Medical Symptom Validity Test suggesting good effort made during the assessments.

mTBI group

The mTBI group comprised 46 participants, with a mean age of 34.72 years (*SD* = 11.8) who were within 3-6 months of sustaining an mTBI (see Table 1). In this study, mTBI was classified as an individual sustaining an injury to the head and experiencing the following four criteria 1) PTA of less than 24 hours, 2) LOC of less than one hour, 3) GTA of 13-15, and 4) no intracranial or invasive medical procedures as a result of injury.

Self-identified ethnicity revealed the mTBI group comprised 35 European (29 New Zealand European), two Māori, four Asian, one Pacific individual and four 'other'. The 'other' category included South American and African ethnicities. The group contained 22 males and 24 females. The mechanism of injuries involved: motor vehicle accidents (*n*=12), falls (*n*=4), assaults (*n*=9), sports (*n*=12), and other (*n*=9). The 'other' category included injuries as a result of an individual hitting their head on stationary object (e.g. cabinet or basin) (*n*= 6) or being hit on the head by a stationary or moving object (e.g. a rock or a roof panel) (*n*=3). A total of 24 mTBI participants reported a history of one or more previous mTBIs, while 22 participants reported no previous injury.

The main source of participants (40 of the 46) was the Emergency Department (ED) at Auckland Hospital. Those individuals who attended the ED after experiencing a TBI, who met the above criteria, were asked by hospital staff whether they would be willing to be contacted study 3-6 months later about this study. Those individuals' who agreed to this, provided the potential participant pool for the researcher. Of individuals approached by hospital staff, 120 agreed to being contacted 3-6 months later. Of these, when contacted, 58 individuals did not return

calls, 13 individuals expressed they were no longer interested, 2 individuals had moved away, and 5 individuals did not meet the study criteria. One participant who attended a testing session was excluded upon the discovery of a diagnosis of Multiple Sclerosis, whilst another participant did not want to undergo the scan on the day, leaving a total of 40. The remaining six participants were recruited from concussion services in the wider Auckland region.

Control group

The control group comprised 20 participants who closely matched the mTBI group with respect to age, gender, and educational level. Controls were recruited by advertising at the University of Auckland and from the wider Auckland community. The group contained 10 males and 10 females, of whom 15 self-identified as European (11 New Zealand European), one as Asian, four as other and one as Maori. 'Other' included African and American ethnicities. Only one individual reported a history of a previous mTBI (falling off a horse) and this occurred during childhood. The participant described a complete recovery and no lingering symptoms. The other 19 participants reported no history of a previous injury.

Table 2

Demographic Characteristics of mTBI and Control Groups and High and Low Persistent Post Concussion Symptom Groups

Measure	Group			
	Controls *n*=20 M (*SD*)	mTBI *n*=46 M (*SD*)	HPPCS *n*=24 M (*SD*)	LPPCS *n*=22 M(*SD*)
Gender (male/ female)	10/10	22/24	9/15	13/11
Age	32.85 (15.00)	34.72 (11.82)	36.46 (12.18)	32.82 (11.37)
Range	18-63	18-63	19-63	18-51
Years of education	15.35 (3.08)	15.51 (3.10)	14.85 (3.08)	16.23 (3.04)
Range	10-22	11-23	11-20	11-23
TOPF	114.35 (10.49)	105.02 (13.9)	103.04 (13.24)	107.8 (14.74)
Range	87-127	74-127	77-124	74-127
Hx of previous mTBI *(yes/no)*	1/19	24/22	12/12	12/10

Note. M; Mean; SD; Standard Deviation. M; Male; F; Female. TOPF; Test of Pre-Morbid Functioning performance converted into a standard score. HPPCS; High Persistent Post-Concussion Symptom group and LPPCS: Low Persistent Post-Concussion Symptom Group based on their self-report on the Rivermead Post-concussion Questionnaire. Hx; History.

Demographic characteristics of the control and mTBI groups of participants are displayed in *Table 2*. There were no significant age differences between mTBI and control groups ($t_{(64)}$ = .54, p = .59) or years of education completed ($t_{(64)}$ = .45, p = .65). However, there was a significant difference on the Test of Premorbid Functioning (TOPF) scores between mTBI and controls ($t_{(64)}$

= -2.67, p = .010), with the control group scoring higher than the mTBI group. No significant differences in the gender proportions (χ^2 (1, N=66) =.26, p =.71), or proportions of ethnicity (χ^2 (2, N=66) =3.37, p =.19) were observed between the two groups (with ethnicity collapsed to three groups).

mTBI Group Classification of PPCS: HPPCS and LPPCS

The presence and severity of PPCS in the mTBI group was measured with the Rivermead Post- Concussion Questionnaire (RPQ; King, Crawford, Wenden, Moss, & Wade, 1995). *Figure 1* displays the distribution of the scores on the RPQ self-report questionnaire report for the total mTBI sample. Table 3 displays the percentage of each symptom reported on the RPQ for the whole mTBI group. As there is no accepted definition for post concussion syndrome, the mTBI participants were divided into two groups based on the median of the total scores on the RPQ. As seen in *Figure 1*, there was a natural break in the scores at the point of the median. Individuals who scored 17 and above on the RPQ comprised a group experiencing higher levels of persistent post-concussion symptoms (high PPCS group; HPPCS), while individuals who scored 15 and below comprise the group experiencing lower levels of symptoms (low PPCS group; LPPCS), in which individuals were more likely to have recovered. A total of 24 participants made up the HPPCS group, and 22 made up the LPPCS group.

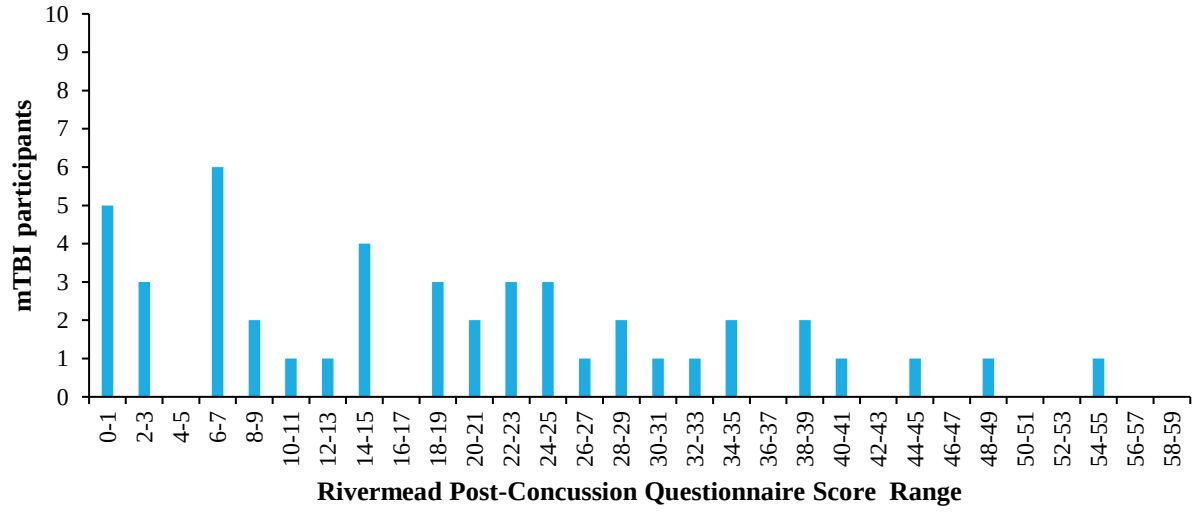


Figure 1

The Distribution of Scores on the RPQ for mTBI Participants

Table 2 provides a summary of the demographic characteristics of the low and high PPCS groups. There were no significant age difference between these two groups $t_{(44)}$ = -1.05, p = .30, no significant difference in years of education completed $t_{(44)}$ = .77, p = .44 or in gender distribution $\chi^2_{(1,46)}$ = 2.14 p = .14. There were no significant difference between high and low PPCS groups on the TOPF $t_{(44)}$ = .99, p = .32. Chi square analyses also revealed that there was no

difference between HPPCS and LPPCS with regards to whether or not they had experienced a previous mTBI χ^2 (1,N=45) =2.30, p = .63.

Participants were also asked a *"yes"* or *"no"* question as to whether they felt they had recovered from their mTBI. A chi-squared test was performed to test whether participants' classifications using the RPQ median cut-off were consistent with their subjective global evaluation of the presence of ongoing symptoms. There was a significant relationship between RPQ classifications and PPCS self- report χ^2 (1,N=66) =7.00, p =.008), with 32 out of 46 participants' PPCS self-report corresponding with the RPQ median split classifications (low and high PPCS). However, seven participants gave a self-report of "*yes"* to ongoing PPCS symptoms, but fell in the low PPCS group (recovered group) and seven said *"no",* but fell in the high PPCS group.

Table 3

Percentage of Participants Reporting a Score of ≥ 2 on the Individual Post-Concussion Symptom Items on the RPQ

Symptom	Group		
	mTBI	HPPCS	LPPCS
Headaches	59%	79%	36%
Feelings of dizziness	46%	63%	27%
Nausea/vomiting	17%	29%	5%
Noise sensitivity	48%	71%	23%
Sleep disturbance	41%	67%	14%
Fatigue/tiring more easily	59%	83%	32%
Being irritable/easily angered	37%	58%	14%
Feeling depressed or tearful	46%	79%	9%
Feeling frustrated or impatient	50%	83%	14%
Forgetfulness/poor memory	61%	92%	27%
Poor concentration	63%	92%	32%
Taking longer to think	61%	92%	27%
Blurred vision	28%	50%	5%
Light sensitivity	33%	46%	18%
Double vision	11%	21%	0%
Restlessness	33%	63%	0%

Measures

The Medical Symptom Validity Test (MSVT; Green, 2003)

The MSVT is a brief computerised verbal-memory screening and effort test. This effort measure evaluates whether an individual has exerted sufficient effort and provides an indication

of whether their performance on neuropsychological measures is considered valid or not. The MVST involves four trial conditions: the immediate recognition trial, delayed recognition trial, the paired associate trial and the consistency (free recall) trial. The MVST requires the participant to learn a list of 10 word pairs, which comprise of everyday nouns (e.g. ball and skateboard). Words are presented in pairs (two at a time) and are presented at a rate of one per six seconds. The participant is shown the same list of words twice before the immediate recognition trial (IR). The IR involves the participant being presented with 20 new word pairs; one of the words in each pair is from the original 10-word pair list (e.g. ball-hoop). The participant is required to choose the word from the original list and respond by clicking the word with the mouse. After 10 minutes, a delayed recognition trial (DR) is presented and this trial involves same structure as the IR. Following DR, the participant completes a paired associate trial, where the assessor states the first word from each pair and the participant is asked to respond with the appropriate paired word. The final trial is the consistency trial, where the participant is asked to recall as many words as possible from the original list. Pass or fail cut offs are defined as: Pass – all IR, DR and Consistency trial scores above 85%; Fail - at least one of IR, DR or Consistency trial scores are at or below 85%.

Test of Premorbid Functioning Record Form (TOPF; Weschler, 2011)

The TOPF is a reading test designed to estimate pre-morbid intelligence in people with suspected neurological disorders or brain injury. The measure comprised of 70 phonetically irregular words (e.g. acquiesce, ceilidh), which are free of context and ordered in increasing difficulty. Participants are asked to read each word out loud and are warned that some words may be unfamiliar to them. Responses are scored correct or incorrect (0 or 1) and aggregated into a total raw score, which is converted into a standard score based on age. The TOPF has a very high degree of reliability (.96-.99), test-retest reliability, (.89-.95) and concurrent validity with the WAIS-IV Full Scale Intellectual Quotient (r= .70) (Holdnack & Whipple Drozdick, 2009).

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ; King, Crawford, Wenden, Moss, & Wade, 1995)

The Rivermead Post-Concussion Symptoms Questionnaire is a self-reporting tool specifically developed for identifying the presence and severity of symptoms experienced after mTBI. The measure consists of 16 symptoms commonly reported by individuals who have experienced an mTBI including headaches, feelings of dizziness, nausea and/or vomiting, noise sensitivity, sleep, disturbance, fatigue, irritability, depression, frustration, forgetfulness, poor concertation, taking longer to think, blurred vision, light sensitivity, double vision and restlessness. Participants are asked to rate the severity of each symptom on a zero to four scale,

(0= *not experienced at all; 1=no more of a problem than before; 2= a mild problem; 3=a moderate problem; 4= a severe problem*). All scores greater than or equal to 2 (indicative that the symptom is a problem in daily life) are aggregated into a total score. Potential total scores range from 0 (experiencing no symptoms after injury) to a maximum score of 64 (most severe symptoms). *(Appendix D)*

General Procedure

Individuals who sustained a mTBI and attended the Emergency Department at Auckland Hospital and community concussion services who expressed interest in the study, were contacted three-six months post-injury for screening. The screening questions involved questions around the mTBI, ensuring they met the eligibility criteria, and included details around the mechanism of injury, their history of any previous mTBIs, learning difficulties, psychological difficulties or substance abuse and their current support system *(Appendix A).* Individuals who met the inclusion criteria and who were willing to participate in the study read the Participant Information Sheet gave written consent *(Appendix B)* and an appointment was scheduled. Control participants underwent the same screening procedures for the general eligibility criteria without the injury criteria.

Once recruited into the study, each participant attended a full day session to undertake an MRI scan and complete the neuropsychological testing and questionnaires. When the participant arrived for their scheduled session, they were greeted at the reception of the Centre Advanced MRI, Auckland by the researcher. The researcher explained the process of the day, answered any questions the participant had and the participant completed the MRI consent form *(Appendix C).* The researcher and radiographer then escorted the participant to the MRI changing room, where they changed in a gown for the scan. Once in the scanning room, each participant underwent the scanning (described in the *Chapter 4*). This procedure took approximately 30 minutes. After completing the MRI scan, each participant was escorted to the research room in the psychology department of the University of Auckland to complete neuropsychological testing. This took approximately one hour and was conducted by the researcher. Once the neuropsychological testing was completed, the participants were given the questionnaires to complete. The researcher remained in the room to offer support and answer the participant's questions. At the end of the testing day, the participant was given a supermarket voucher and a paid parking ticket to thank them for their time and participation in the study.

The investigation was approved by the Health and Disability Ethics committee (reference:13/STH/177).

Chapter Three

Study One: Neuropsychological Changes in Individuals with Persisting Post-Concussion Symptoms Following mTBI

Study one investigated whether specific neuropsychological tests can provide evidence of cognitive dysfunction at three months post-mTBI, particularly in individuals reporting ongoing symptoms. The neuropsychological assessment was comprised of a structured protocol of cognitive tests that were selected to examine the cognitive domains commonly affected in mTBI populations including speed of information processing, attention and working memory (Karr et al., 2014). One psychological questionnaire was also included which assesses three mood states: irritability, anxiety and depression, as research has shown mood disturbances following mTBI (Lamontagne et al., 2021; Solberg, & Riggio, 2021). In addition to selecting tests specific to cognitive domains, other criteria were taken into account. Firstly, tests which increase in cognitive demand (either by multiple cognitive tasks being performed concurrently or tests with increased complexity within a task) were chosen in order to capture the subtle differences believed to occur in individuals who have sustained a mTBI. Another criterion used for test selection was to ensure that the tests were not currently used in standard assessments in mTBI clinics within the community, to limit practice effects both for this study and for any future clinical assessments participants in this study might undertake. To reduce the possibility of sub-optimal effort, all participants were administered a standard measure of effort/motivation which was embedded into the cognitive test battery.

Considering these factors, the neuropsychological tests chosen included the following: Paced Auditory Serial Addition Task (PASAT); Computerised Test of Information Processing (CTIP); Auditory Consonant Trigrams (ACT); and the Symbol Digit Modalities Test (SDMT). The Medical Symptom Validity Test (MSVT) was used as the effort test and TOPF was used as the measure of premorbid functioning (both described in *Chapter Two*). The properties of all other tests and descriptions are discussed below.

All of these tests are used in research and clinical settings and have shown to be sensitive to the cognitive deficits experienced by individuals who have sustained a mTBI. The PASAT and the ACT tests are both tests which involve multiple cognitive demands occurring concurrently and assess processing speed, attention and working memory. The PASAT was adapted first by Gronwall and Wrightson (1975) to assess subtle cognitive deficits in information processing in mTBI. The PASAT has demonstrated utility in identifying cognitive impairments among individuals with neurological disorders, such as multiple sclerosis (Tombaugh, 2006). ACT has

been shown to be sensitive to cognitive difficulties in the acute and chronic stages post mTBI (Stuss, Stethem, Hugenholtz, & Richard, 1989).

The CTIP measure involves three subtests which increase in difficulty and cognitive load; increased reaction time is correlated with increase in subtest difficulty (Tombaugh, Rees, Stormer, Harrison, & Smith, 2007). The CTIP is used clinically to discriminate between mTBI individuals and healthy controls (Willison & Tombaugh, 2006). The SDMT has demonstrated high sensitivity in detecting processing speed deficits in a variety of populations including mTBI (McCauley et al., 2014). The Irritability Depression Anxiety Scaled (IDAS) was chosen as a brief measures of three mood states (irritability, anxiety and depression) commonly reported by individuals who sustain a mTBI.

As outlined in *Chapter Two,* the Rivermead Post Concussion Questionnaire (RPQ) was administered to individuals within the mTBI group to identify levels of ongoing symptoms. This enabled examination of differences in neuropsychological performance between individuals who were experiencing greater levels of persistent symptoms compared to those who were experiencing lower levels.

A number of predictions were made for this study. Firstly, it was hypothesised that the mTBI group would perform more poorly on the targeted neuropsychological measures than control participants because it is expected that this group would contain individuals experiencing PPCS. The mTBI group was also predicted to show higher levels of mood disturbance. The second prediction, which addresses the primary aim of this study, was that individuals with higher levels of persisting post-concussion symptoms (HPPCS) would show poorer performance on neurocognitive tests compared to mTBI individuals reporting lower levels of persisting post-concussion symptoms (LPPCS). These differences were expected to be shown specifically on the most sensitive measures and trials that place the most demands in terms of speed or complexity. Finally, it was predicted that individuals in the HPPCS group would report greater levels of mood disturbances compared to the LPPCS group on all measures of mood, given their enduring symptoms.

Method

Materials

Neuropsychological test measures

Properties of all measures are detailed in *Table 4.*

Table 4

Properties of Neuropsychological Tests for the Study

Tasks	Construct measures	Instruction modality	Response modality	Timed	Performance measures
PASAT	Auditory information processing speed; divided attention; and auditory-verbal working memory	Verbal / Auditory	Verbal	Yes	Accuracy under time constraints.
CTIP	Visual information processing speed; and reaction time	Visual (Computerised)	Computer keypad	Yes	Accuracy; RT
ACT	Auditory information processing speed; complex attention; and auditory-verbal working memory	Verbal	Verbal	Yes	Accuracy
SDMT	Psychomotor processing speed; and visual scanning.	Visual	Pencil & paper	Yes	Accuracy
MSVT	Verbal-memory screening; and effort test	Verbal	Computer keypad; verbal	Yes	Accuracy
TOPF	Reading test; pre-morbid intelligence	Visual- verbal	Verbal	No	Accuracy

Note. PASAT; Paced Auditory Serial Addition Task; CTIP; Computerised Test of Information Processing; ACT; Auditory Consonant Trigrams; SDMT; Symbol Digit Modalities Test; RT; Reaction time; TOPF; Test of Premorbid Functioning.

Paced Auditory Serial Addition Task (PASAT; Gronwall & Sampson, 1974). The PASAT is a measure of an individual's auditory information processing ability or speed of thinking, divided attention and auditory-verbal working memory (Grownall, 1977). The PASAT involves the assessor playing the participant a pre-recorded series of 61 single-digit numbers read aloud. The participant is instructed to add the two most recent numbers together and say the additional answer out loud, ignoring previous numbers and answers given. The numbers are presented at four different speeds (four trials): 2.4, 2.0, 1.6, and 1.2 second inter-stimulus intervals. A practice trial of 10 digits at the 2.4 second pacing is presented prior to commencing the first trial. The total number of correct responses for each speed are calculated and converted into z-scores that are based on age-corrected normative data (Stuss et al., 1989). The mean time

per correct response (total length of trial divided by the number of correct responses) is also calculated for all four trial paces (Gronwall, 1977; Tombaugh, 2006). The PASAT is considered a reliable instrument as it has been found to have high internal consistency (*r*=.90) (Crawford, Obansawin, & Allan, 1998) and good test-retest reliability (*r* = .90 to .97) (Tombaugh, 2006).

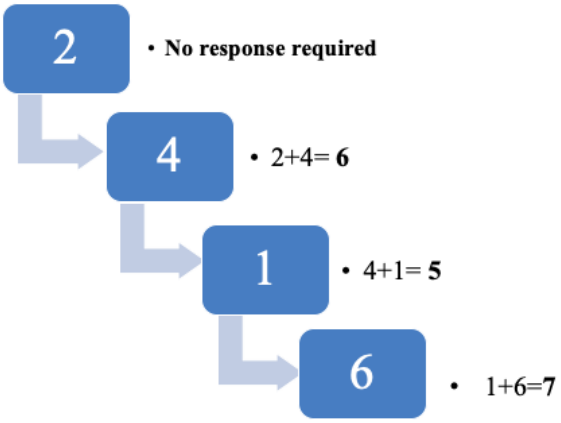


Figure 2

Paced Auditory Serial Addition Task (PASAT). Participants were required to add the two most recent numbers they heard.

Computerised Test of Information Processing (CTIP; Tombaugh, & Rees, 2008). The CTIP is a computerised tool for evaluating visual speed of information processing and reaction time (Tombaugh, & Rees, 2008). The test is composed of a series of three reaction time (RT) subtests – Simple RT, Choice RT and Semantic Search RT, which progressively increase in the amount of information processing demands and decision making required. The Simple RT measures the amount of time required to process and react to a simple stimulus and serves as a baseline for the other two subtests. Participants are instructed to press the spacebar as fast as they can when they see a fixation cross (X) appear in the centre of the screen. The subsequent subtests (Choice RT and Semantic RT) increase in complexity by incorporating a decision-making component based on presented stimuli. For the Choice RT, the participant is presented with either the word 'DUCK' or 'KITE' in the centre of the screen and the participant is required to press the right key (M) if 'DUCK' is presented or the left key (Z) if 'KITE' is presented. The Choice RT measures time required to process the information and respond differentially. The complexity of processing is further increased in the Semantic RT task by adding a conceptual component to the decision process. In this subtest, the participant has to decide if a specific word belongs to a certain category or not. On each trial, one of four categories (weapon, furniture, bird, and fruit) is presented in the centre of the screen. Approximately 2.0 seconds later, a word appears below the category that either is or is not a member of that category (e.g. tool - hammer or tool - orange). If the word belongs to the category the participant presses the right key (M) and if not the participant

presses the left key (Z). For all three subtests, 10 practice trials are given followed by 30 test trials. Individual median reaction time for each trial is recorded. Median scores for each individual are compared to the appropriate normative group, based on age and gender.

Simple RT **Choice RT** **Semantic RT**

Figure 3

Computerised Test of Information Processing. Participants were required to press the allocated key when the appropriate stimulus from each subtest was in the middle of the computer screen

Auditory Consonant Trigrams (ACT; Stuss et al., 1989). ACT is a test developed to evaluate, processing speed, working memory and complex attention in the absence of rehearsal and in the presence of a distractor (Struss et al., 1989). The examiner says three consonants (e.g. NDJ or TDH) at an even pace, followed by a specified number (e.g. 75 or 194). The participant is instructed to count backwards from the specified number (e.g. 75, or 94), out loud in increments of threes (apart from the 0 second trial). After a specified time, either 0, 9, 18 or 36 seconds, the examiner signals to the participant to stop counting back using a knock on the table; at which point the participant is asked to recall the three consonants. There are 20 trials in total, with 5 trials for each time interval (0, 9, 18, 36 seconds). The total number of correct responses for each trial is calculated and converted into z-scores using age-based normative data (Stuss et al., 1989). ACT demonstrates adequate psychometric properties; internal reliability and validity (Shura, Rowland, & Miskey, 2016).

Symbol Digit Modalities Test (SDMT; Smith, 1963). The SDMT is a test used to assess psychomotor processing speed, and visual scanning (Forn, Ripollés, Cruz-Gómez, Belenguer, González-Torre, & Avila, 2013; Kiely, Butterworth, Watson, & Wooden, 2014). The participant is presented with a key consisting of 9 symbols paired to a number. Using the key, the participant is given 90 seconds to fill in a sheet of paper (using a pencil) the numbers that correspond with the relevant symbols as quickly as possible. Total correct responses are recorded and converted into z-scores, adjusted for age and education. The SMDT has proven to be a reliable psychometric test with good test-retest reliability (r = .79) (Pereira, Costa, & Cerqueira, 2015; Strauss et al., 2006).

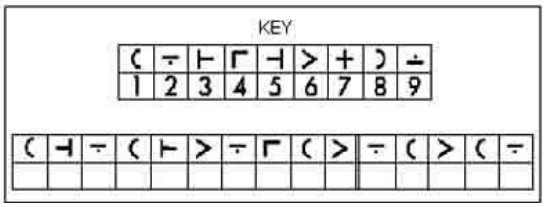


Figure 4

The Symbol Digit Modalities Test. Key and first line of test.

Psychological measure

Irritability-Depression-Anxiety Scale (IDAS*) *(Snaith, & Taylor, 1985). The IDAS is a self-administered questionnaire used to measure levels of irritability, depression and anxiety. It contains 14-items, five questions measuring depression, five questions measuring anxiety and four questions measuring irritability. Responses are based on relative frequency of symptoms over the past week using a four point (scored 0-3) Likert scale, in which individuals have to choose and underline the response that was most relevant to how they have been feeling that week (e.g. "I feel cheerful"/"I can sit down and relax quite easily", yes, definitely (0); yes, sometimes (1); no, not much (2); no, not at all (3). Responses are calculated for each mood dimension, with possible scores ranging from 0-15 for anxiety, 0-15 for depression and 0-12 for irritability. The subscales scores are classified as 'normal', 'borderline' or 'abnormal' for the respective mood based on scoring criteria. Individuals are encouraged to respond with their immediate reactions, rather than a long thought-out response *(Appendix E).*

Self-reported history of psychological difficulties. As pre-injury levels of mood on the IDAS are unattainable, whether or not individuals reported a history of psychological difficulties (met clinical criteria according to their general practitioner) and whether or not they received professional treatment (medication or therapeutic intervention) for their psychological difficulties were used as an indicator of pre-injury psychological difficulties.

Procedure of the testing session

As described in *Chapter Two*, participants first completed an MRI scan, which took approximately 30 minutes. After completing the MRI scans, each participant was escorted to the research room in the Psychology Department of the University of Auckland or a quiet room at CAMRI to complete neuropsychological testing. All tasks were conducted by the researcher and lasted approximately an hour. All of the tests were administered in the same order for all participants and the order of tests are presented: Paced Auditory Serial Addition Task (PASAT), Computerised Test of Information Processing (CTIP), Medical Symptom Validity Test (MSVT) part one, Auditory Consonant Trigrams (ACT); Symbol Digit Modalities Test (SDMT); MSVT

part two; and Test of Pre-morbid functioning (TOPF) and Irritability-Depression-Anxiety Scale (IDAS). Distractions were minimised, for example participants were asked to turn off their phones. The duration of the testing session was roughly an hour, including a brief structured interview, neuropsychological testing, and psychological questionnaire. For the computer tasks, participants were seated in a comfortable distance from the computer screen and responded by pressing keypad buttons. The researcher remained in the room for these computerised tasks, to offer support and answer the participant's questions.

Statistical Analysis

All analyses were performed using the Statistical Software SPSS-IBM 22 (IBM Corp). Data were inspected for accuracy of data entry, missing values and normality.

Non-parametric statistics were used for variables with non-normalised distributions. Split-plot Analysis of Variance (ANOVA) was used to examine differences between groups (mTBI and control groups; and HPPCS and LCPS) on tests with within-subject conditions. If Mauchly's Test of Sphericity was violated the Greenhouse-Geisser correction was applied (Brace, Kemp, & Sneglar, 2003). Bonferroni pairwise comparisons were used to test for differences within subjects and interactions. For significant group effects, the Games-Howell (1976) post-hoc test procedure was used as it has been found to be accurate with unequal sample sizes and unequal population variances while remaining a powerful test (Field, 2009). Pearson correlations were used to assess associations between variables. Multiple regression analyses were conducted to investigate whether PPCS severity predicted cognitive performance in the mTBI group (independent of subgroup categorisation).

The Chi-square test of independence was used for between-group comparisons of categorical data. For 2x2 tables, the Continuity Correction was used for overestimates of the chi-square value. If the 'minimum expected cell frequency' assumption was violated, the Fisher's Exact Test value was used, rather than the Continuity Correction or the Pearson.

For all of the between-group analyses, a significance level of $p < 0.05$ was applied. Exact p values are reported for all statistical analyses, unless the p value is less than 0.001 reported as ($p < 0.001$). All levels of significance reported are two tailed values, unless noted otherwise.

Given age is known to affect the performance on PASAT (Tombaugh, 2006) and one of the PASAT measures, mean time per correct response, did not have age-adjusted scores, age was used as a covariate in analyses with this variable.

Results

Neuropsychological performance: Comparisons between controls and the total mTBI group

As reported in *Chapter Two*, there was a significant difference in TOPF scores between these two groups, with the control group displaying higher scores than the mTBI group. Although there was no difference in education levels of the two groups, to reduce the chance that any between-group differences might simply reflect different levels of ability, the TOPF was entered as a covariate in all between-group comparisons. A summary of neuropsychological performance for mTBI and control groups is presented in *Table 5*.

All participants passed the MVST, the test effort measure. Five participants completed the first two trials on the PASAT only. This was because either the participant became highly distressed performing the test or they refused to continue the test. One participant did not complete any of the PASAT trials because they were unable to grasp the practice trial. Three participants did not complete ACT: Two participants became very distressed during the test and one participant refused to continue the test.

To examine differences in performance on number of correct responses on the PASAT (age-adjusted z-scores), a split-plot ANCOVA was conducted, with Trial Speed (2.4, 2.0, 1.6, 1.2) as the within subjects factor, Group (mTBI and control) as the between subjects factor, and TOPF scores entered as a covariate. There was no significant main effect of group, $F_{(1,57)} = .11$, $p = .74$ when adjusting for TOPF, but the TOPF was significant, $F_{(1,57)} = 20.16$, $p < .001$. However, there was a significant main effect of Trial Speed, $F_{(2.52,143.33)} = 5.69$, $p = .002$ and a significant interaction between Group and Trial Speed $F_{(2.52,143.33)} = 4.73$, $p = .006$. Pairwise Bonferroni comparisons revealed there were no significant differences between Groups on any of the Trial Speeds. Interestingly, the control group performed significantly better on the two fastest speeds of presentation compared to the slowest speeds (1.6 seconds, $p = .003$ and 1.2 seconds, $p = .002$). The mTBI group also performed significantly better on the 1.6 second pacing speed only compared to the 2.0 seconds ($p = .001$) and 1.2 second pacing speed ($p = .001$).

Table 5

Neuropsychological Test Performance of mTBI and Control Groups

Measure		Groups		
		mTBI		Control
	N	Total *n* = 46 M(*SD*)	*N*	Total *n* = 20 M (*SD*)
PASAT (accuracy z-score)				
Trial 2.4 sec	45	-1.01 (1.17)		
Completed all 4 trials	40	0.84 (1.09)	20	-.92 (.86)
Trial 2.0 sec	45	-1.05 (.95)		
Completed all 4 trials	40	-.94 (.93)	20	-.66 (.78)
Trial 1.6 sec	40	-.61 (.76)	20	-.52 (.51)
Trial 1.2 sec	40	-.86 (.80)	20	-.51 (.50)
Mean T/CR 4 trials	40	4.72 (2.25)	20	4.08 (1.40)
Mean T/CR first 2 trials	45	4.70 (1.73)	20	4.21 (1.39)
ACT (accuracy z-score)				
Delay 9 sec	43	.02 (.96)	20	.23 (.91)
Delay 18 sec		.10 (.97)		.57 (.72)
Delay 36 sec		.32 (.88)		.92 (.80)
CTIP (ms)	46		20	
Simple Median RT		266 (58)		255 (16)
Complex Median RT		491 (110)		459 (95)
Semantic Median RT		763 (190)		633 (110)
SDMT (accuracy z-score)		-.17 (1.10)		.59 (.71)

Note. M; Mean; *SD*; Standard Deviation, Sec; Seconds; PASAT; Paced Auditory Serial Addition Task the number of correct responses converted into a z-score. T/CR; Time per correct response. ACT; Auditory Consonant Trigrams converted into a z-score; CTIP; Computerised Test of Information Processing Median Reaction time. SDMT; Symbol Digit Modalities Test**.** The number of participants differed across PASAT trials, as not all participants completed each trial. Similarly, not all participants completed the ACT test.

To compare the performance of 45/46 of the mTBI participants with the control group, an additional split-plot ANOVA was conducted on number of correct response on PASAT (age-adjusted accuracy z-score) with Trial speed over the first two trials (2.4 and 2.0 second pacing) as the within-subjects factor, Group (mTBI and controls) as the between subject factors, and TOPF as a covariate. There was no significant main effect of group $F_{(1,62)} = .38$, $p = .54$ when adjusting for TOPF, but TOPF was significant, $F_{(1,62)} = 31.28$, $p < .001$. There was no main effect of Trial Speed, $F_{(1,62)} = 3.27$ $p = .08$. However, there was a significant interaction between Group and Trial Speed $F_{(1,62)} = 4.73$, $p = .02$ with the mTBI group performing differentially poorer on the second trial speed.

A one-way ANCOVA was conducted to compare the differences between Groups (mTBI and control) PASAT mean time per correct response over all four trials, whilst adjusting for age and TOPF. There was no significant difference between groups over the four trials $F_{(1,56)}$= .26, p =.61 when adjusting for age and TOPF. The covariate age was not significant $F_{(1,56)}$= .01, p =.91, but TOPF was significant $F_{(1,56)}$= 6.13, p =.02. Similarly, there was no significant difference between groups over the mean time per correct response for the first two trials only $F_{(1,61)}$= .08, p =.78, nor was age significant $F_{(1,61)}$= .29, p =.59. Once again, TOPF was significant $F_{(1,56)}$= 6.13, p = < 0.01.

No statistical differences were shown using a split-plot ANOVA to compare group (mTBI and control) performances on accuracy z-scores on the ACT, with Trial Delay (9, 18, and 36 seconds) a within subjects factor, group a between-subjects factor, and TOPF scores a covariate. Contrary to predictions, there was no significant main effect of Group $F_{(1,60)}$ = .82, p = .37 when adjusting for TOPF, but the effect of TOPF was significant $F_{(1,60)}$ = 20.34, p <.001. There was also no significant main effect of Trial Delay $F_{(2,120)}$ = 2.74, p = .07 although it approached significance and no significant interaction between Group and Trial Delay, $F_{(2,120)}$=2.38, p =.10. This indicates that the mTBI group did not perform differentially more poorly than the controls on any trial.

Reaction times on the CTIP were analysed using a repeated measures ANCOVA with Trial Complexity (Simple, Choice and Semantic) a within-subjects factor, Group (mTBI and control) as a between subjects factor, and TOPF scores entered as a covariate. There was no significant main effect of Group $F($1, 63)= 3.08, p = .08, between the mTBI (M = 501, SE = 100) and control (M = 460, SE = 200) group, when adjusting for TOPF, but TOPF was significant , $F_{(1, 63)}$= 5.98, p = .02. There was a significant main effect of Trial Complexity $F_{(1.61,101.2)}$ = 15.96, p <.001 with all participants displaying significantly longer reaction times (p < 0.001) during the Semantic Condition (M = 705, SE = 220) compared to both the Choice Condition (M = 477, SE = 14) and Simple Condition (M = 260, SE = 7). However, there was no significant interaction between Group and Trial Complexity $F_{(1.61,101.15)}$ = 2.67, p = .09.

A univariate analysis was used to examine differences in the groups (mTBI and controls) performance on the SDMT using age and education adjusted z-scores and TOPF scores as a covariate. There was a significant main effect of Group $F_{(1, 63)}$= 4.29, p =.04 when adjusting for TOPF, indicating that the mTBI group performed significantly more poorly than controls. There was also a significant main effect of TOPF $F_{(1, 64)}$= 5.76, p = .02.

Neuropsychological performance: Comparisons between HPPCS and LPPCS group

Table 6

Neuropsychological Test Performance for High PPCS and low PPCS Groups

Measure	*N*	Groups		
		HPPCS		LPPCS
		Total *n* = 24 M (*SD*)	N	Total *n* = 22 M (*SD*)
PASAT (accuracy z-score)				
Trial 2.4 sec	23	-1.38 (.80)	22	-.63 (1.38)
Completed all 4 trials	20	-1.27 (.71)	20	-.42 (1.26)
Trial 2.0 sec	23	-1.37 (.84)	22	-7.2 (.96)
Completed all 4 trials		-1.28 (.85)	20	-.59 (.90)
Trial 1.6 sec	20	-.85 (.65)	20	-.37 (.81)
Trial 1.2 sec	20	-.1.13 (.70)	20	-.58 (.83)
Mean T/CR all 4 trials	20	5.43 (2.56)	20	4.03 (.61)
Mean T/CR first 2 trials	23	5.08 (1.41)	22	4.30 (1.96)
ACT (accuracy z-score)				
Delay 9 sec	22	.25 (1.10)	21	.30 (.72)
Delay 18 sec		.10 (1.05)		.32 (.85)
Delay 36 sec		.17 (.92)		.46 (.84)
CTIP (ms)	44		22	
Simple Median RT		263 (59)		270 (58)
Complex Median RT		496 (122)		486 (90)
Semantic Median RT		820 (202)		701 (160)
SDMT (accuracy z-score)		2.63 (1.14)		-0.8 (.71)

Note. M; Mean *SD*; Standard Deviation; Sec; Seconds; PASAT; Paced Auditory Serial Addition Task converted into a z-score. T/CR; Time Per Correct Response; ACT; Auditory Consonant Trigrams converted into a z-score; CTIP; Computerised Test of Information Processing SDMT; Symbol Digit Modalities Test**.** The number of participants differed across PASAT trials, as not all participants completed each trial. Similarly, not all participants completed the ACT test for various reasons.

The performance of the two mTBI subgroups (LPPCS and HPPCS) was compared on all neuropsychological measures to determine whether there is a relationship between self-reported symptoms consistent with enduring post-concussion and neuropsychological performance. There was no significant difference between these two groups on education $t(_{44}) = .77$, $p = .17$ or TOPF $t(_{44}) = 1.04$, $p = .68$ and therefore no covariate was included. A summary of neuropsychological performance is provided in Table 6. CTIP Performance is illustrated in Figure 5.

To examine differences in performance between the two groups, performance on the PASAT (age-adjusted accuracy z-scores) was subjected to a repeated measures ANOVA, with

Trial Speed (2.4, 2.0, 1.6, 1.2) as the within subjects factor, and Group (HPPCS versus LPPCS) as the between subjects factor. There was a significant main effect of group, $F_{(1,38)}$= 6.52, p = .02, with the HPPCS group (M = -1.13, SE = -1.8) performing more poorly overall than the LPPCS group (M =-.49, SE=.18). There was also a significant main effect of Trial Speed $F_{(2.49, 94.62)}$=5.17, p = 0.04, however, there was no significant interaction between Group and Trial Speed $F_{(2.49, 94.62)}$=1.56, p =.21. Pairwise Bonferroni comparisons revealed that overall participants performed significantly worse on the 2.0 second pacing speed (M= -.94, SE = .14, p =.001) and 1.2 pacing speed (M = -.86, SE = .123, p = .001) compared to the 1.6 second pacing speed.

Once again an additional split-plot ANOVA was conducted to examine the difference in performance for the two groups on age-adjusted accuracy z-scores of the PASAT so that the performance of 45/46 of the mTBI participants was included. Trial speed over the first two trials (2.4 and 2.0 second pacing) was the within-subjects factor, and Group (HPPCS versus LPPCS) the between subject factors. There was a significant main effect of group $F_{(1,43)}$ = 5.89, p = .02, with the HPPCS group performing more poorly overall than the LPPCS group. However, there was no main effect of Trial Speed, $F_{(1,62)}$ = .19, p = .66 and no significant interaction between Group and Trial Speed $F_{(1,62)}$ = .36 p = .55.

Separate ANCOVAs were used to compare the differences between groups (HPPCS and LPPCS) on their mean time per correct response over four trials and two trials on PASAT, whilst adjusting for age. There was a significant difference between groups $F_{(1,37)}$= 5.56, p = .02 for mean time per correct response over four trials adjusting for age, with the HPPCS group performing more poorly than the LPPCS group. However, there was no significant difference between groups for the two trial analysis, $F_{(1,42)}$= 3.85, p = .06, although it approached significance. The covariate age was significant $F_{(1,42)}$= 5.62, p = .02.

A split-plot ANOVA was used to compare performance of the two groups on z-scores of accuracy of performance on ACT. Trial Delay (9, 18, 36 seconds) was the within subjects factor and Group (LPPCS and HPPCS) was the between-factor. There were no significant main effect of Group, $F_{(1,41)}$ =3.42 p=.07, although it was approaching significance. There was also no significant main effect of Trial Delay, $F_{(2,82)}$ = 2.19 p =.12 and no significant interaction between Group and Trial Delay, $F_{(2,82)=}$ .38, p =.68). This indicates that the HPPCS group performed overall slightly, but not significantly, worse than the LPPCS group on the ACT test.

To assess whether there were differences between the groups (LPPCS and HPPCS) on reaction times on the CTIP, a split-plot ANOVA was conducted with Trial Complexity (Simple, Choice and Semantic) a within-subjects factor, and Group a between subjects factor (see Figure 2). There was no significant main effect of Group, $F_{(1, 44)}$= 2.280, p = .14, but as expected, there was a significant main effect of Trial condition $F_{(1.54, 67.79)}$ = 240.84, p < .001, with participants

responding more slowly during the Semantic Condition (*M=761, SE=27*) compared to both Choice (*M*= 491, *SE*= 16) and Simple (*M*= 266, *SE*= 9) conditions; and also longer reaction times during the Choice condition compared to the Simple condition. Notably, there was a significant interaction between group and Trial Condition $F_{(1.54, 67.79)} = 4.54$, $p = .022$. Pairwise Bonferroni comparisons indicated that the HPPCS group (*M*=820, *SE* = 37) took significantly longer to perform the Semantic Trial than the LPPCS group (*M =701*, *SE*= 39, $p = .03$). However, there were no significant differences between groups for the Simple Trial ($p = .71$) or the Choice Trial ($p = .75$).

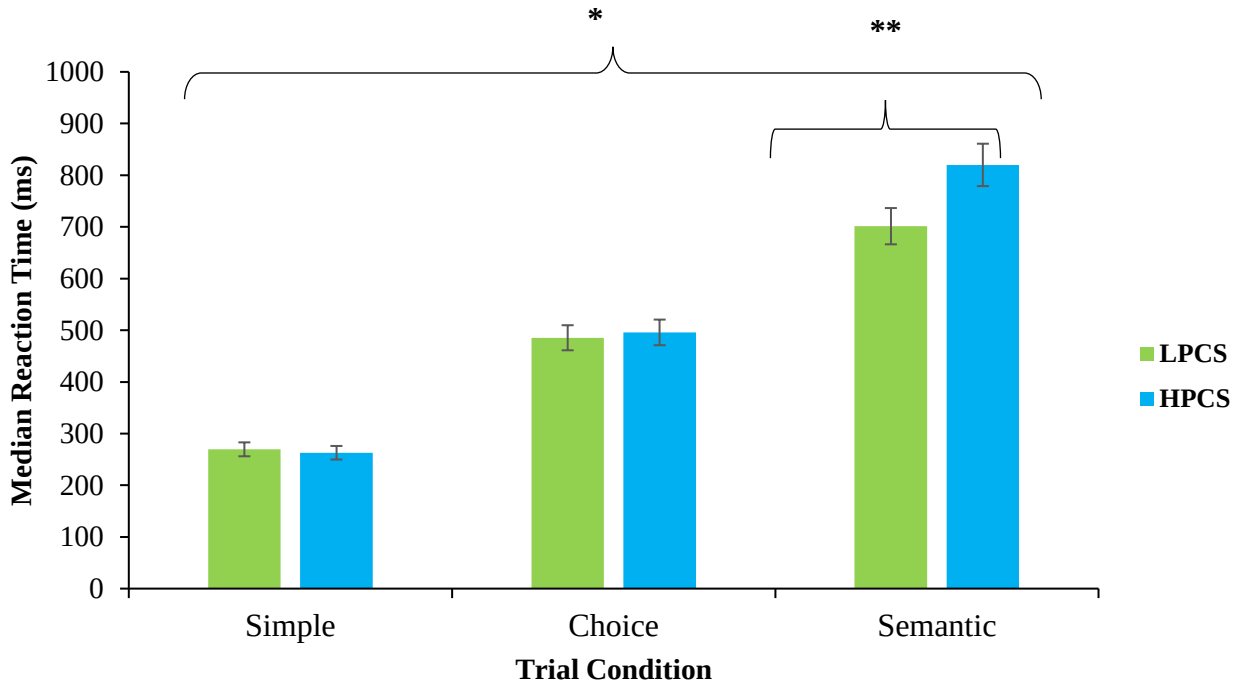


Figure 5

*Median Reaction Time (ms) for Each Trial Condition (Simple, Choice and Semantic) on the CTIP. Note. *** p< .001 and * p = .05 indicate significant differences. Error bars represent standard error.*

Independent t-tests were used to determine whether there were differences between the between the two mTBI groups (HPPCS and LPPCS) on the SDMT. There were no significant differences between groups (HPPCS and LPPCS) on the SDMT (age and education adjusted z-scores), $t(44) = .57$, $p = .57$.

Pearsons correlations were conducted in the combined mTBI group to examine whether there were significant associations between total score on the RPQ and performance on SDMT and the final trials of the PASAT, CTIP and ACT, as cognitive demand increases with trial condition on these tests. The results indicated that there were no significant associations between

the RPQ and any cognitive variable: CTIP Semantic trial (*r*= .24. *p*= *.11*), ACT 36 second trial (*r*=-1.23, *p*=*.42*), the SDMT (*r*=-.16, *p*=*.30*) or PASAT trial 4, although it was approaching significance (*r*=-.30, *p*=*.06*).

Psychological scores: Comparisons between the control group and the total mTBI group

Table 7 presents the mean scores for levels of outward irritability; depression and anxiety reported using the IDAS mood questionnaire for the mTBI and control groups. Independent t-tests indicated that there were no significant differences found between groups for irritability $t(64) = -1.83$, $p = .07$ anxiety $t(64) = 1.56$, $p = .12$ or depression $t(64) = 1.49$, $p = .14$. Although these tests were approaching significance, mean scores on all three mood states for both groups were low. The number of individuals in each group whose scores fell in the abnormal range on the psychological measures are also shown in Table 8. Fisher's Exact tests were used to compare the proportion of participants in each group, whose scores fell in the abnormal ranges for irritability, depression and anxiety. The Fisher's Exact test, indicated that the proportion of the mTBI group with 'abnormal' levels of irritability $p = 1.0$, depression $p = .71$, or anxiety $p = .55$ were not significantly higher than the controls.

Fisher's Exact analyses revealed that the proportion of mTBI individuals who reported a history of psychological difficulties prior to injury was not significantly higher than the control group ($p = .30$). Similarly, the number of mTBI individuals who reported receiving professional interventions prior to injury was not significantly higher than the control group ($p = .23$).

Table 7

Means and Standard Deviations for mTBI and Controls Groups and HPPCS and LPPCS Groups on the IDAS Questionnaire

	Groups			
	mTBI	Control	HPPCS	LPPCS
IDAS	*n* = 46	*n* = 20	*n* = 24	*n* = 22
IDAS Irritability Scale (0-12)				
Total score: mean (SD)	3.37 (2.05)	2.40 (1.82)	3.79 (2.15)	2.91(1.88)
% in abnormal range	2.17 (1)	0.00 (0)	4.55 (1)	0.00 (0)
Depression Scale (0-15)				
Total score: mean (SD)	3.80 (2.52)	2.80 (2.53)	4.96 (2.40)	2.55(2.02)
% in abnormal range	15.21 (7)	10.00 (2)	29.17 (7)	0.00 (0)
Anxiety Scale (0-15)				
Total score: mean (SD)	4.89 (3.13)	3.65 (2.54)	6.17 (2.62)	3.50(3.10)
% in abnormal range	6.52 (3)	0.00 (0)	8.33 (2)	4.54 (1)

Note. SD; Standard Deviation; IDAS: Irritability, Depression and Anxiety Questionnaire. Numbers in brackets e.g. (1) account for number of participants with this classification.

Table 8

The Number of Individuals in the mTBI and Control Groups, and HPPCS and LPPCS Groups, who have Experienced Psychological Difficulties and Received Treatment prior to injury

Psychological history	Groups			
	mTBI	Controls	HPPCS	LPPCS
	n = 46	*n* = 20	*n* = 24	*n = 22*
Psychological difficulties (Y/N)	16/30	6/14	10/14	6/16
Received treatment (Y/N)	15/31	3/17	9/15	6/16

Note. Y= Yes and N= no

Psychological scores: Comparisons between HPPCS and LPPCS groups

Table 7 also shows the means and standard deviations for irritability, depression and anxiety subscales of the IDAS for the LPPCS and HPPCS groups. There were no significant differences between groups for irritability $t_{(44)} = -1.48$, $p = .15$. However, significant differences were found between these two groups for depression $t_{(44)} = -3.67$, $p < 0.01$, and for anxiety $t_{(44)} = -3.16$, $p = .003$, with the HPPCS group having higher levels of depression and anxiety compared to the LPPCS group.

Fisher Exact tests revealed that the proportion of HPPCS individuals with 'abnormal' levels of anxiety, $p = 1.0$ was not significantly greater than that of the LPPCS group. However, the proportion of HPPCS individuals with abnormal levels of depression was significantly greater than the LPPCS group, $p = .01$. This indicates that individuals with HPPCS report more depressive symptomology compared to the LPPCS group. However, the proportion of HPPCS individuals who received professional treatment in the past was not significantly greater than the LPPCS group, Fisher Exact Test, $p = .54$.

Additionally, Fisher's exact analyses were conducted to identify whether members of the HPPCS group who sought professional treatment in the past (pre-injury) were more likely to experience abnormal levels of anxiety and depression on the IDAS post-injury. The results revealed that the HPPCS group who had received treatment prior to their mTBI, were not more likely to have abnormal levels of anxiety, $p = 1.0$ or depression, $p = .19$ on the IDAS. Specifically, of those in the HPPCS group who had received professional treatment for their prior psychological difficulties ($n = 9$), only one individual revealed abnormal depression levels on the IDAS and one individual revealed abnormal anxiety. In contrast, of the HPPCS individuals who reported no history of receiving a professional intervention for prior psychological difficulties ($n = 15$), six individuals displayed abnormal levels of depression, one individual displayed abnormal levels of anxiety, and one individual displayed abnormal levels of irritability on the IDAS. In summary, in

this sample a history of pre-injury psychological difficulties or pre-injury treatment for psychological difficulties does account for elevated mood post-injury.

Parametric Pearson's correlations were calculated to explore the relationship between symptom report on the RPQ and mood measures (only depression and anxiety) for the whole mTBI sample. There was a significant positive relationship between both depression and RPQ scores, r =.56, p= <.001 and anxiety and RPQ scores r=.47, <.001, with higher levels of depression and anxiety associated with greater levels of PPCS report (Figure 6).

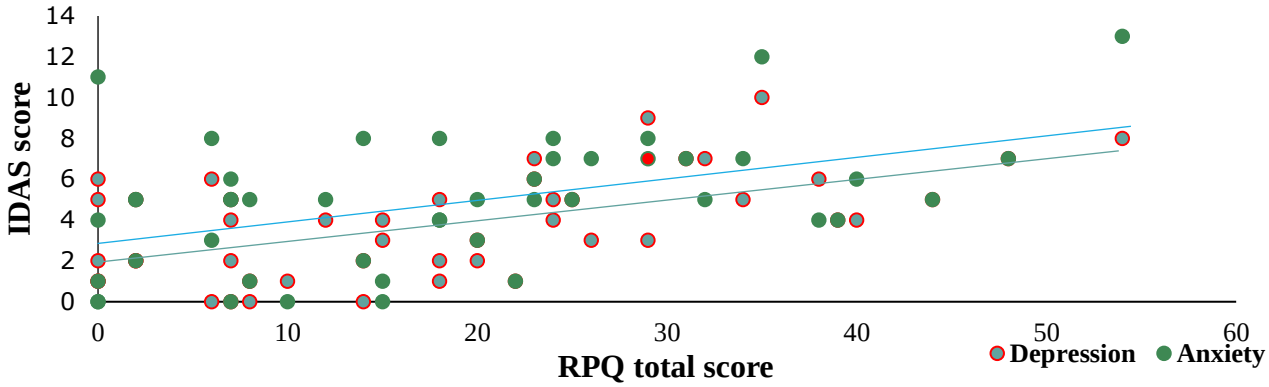


Figure 6

Correlations Between PPCS Symptom Report on the RPQ and Reported Depression and Anxiety Symptoms on the IDAS. Pearson r= .56 p < 0.01.for Depression and Pearson r= .56 p < 0.01.

mTBI group neuropsychological performance and mood measures

Pearson's correlations were calculated to explore the relationship between neuropsychological tests and mood measures (irritability, depression and anxiety) for the whole mTBI sample. There was a significant negative correlation between both depression and accuracy on PASAT 4-trial, r =-.35, p= <.03 and anxiety and PASAT 4-trial, r=.-.38, <.02, with higher levels of depression and anxiety associated with poorer performance on the PASAT. There was a significant positive relationship with irritability and CTIP semantic trial r =.29 p= <.05, with higher levels of irritability associated with longer reaction times on the test (poorer performance). There was a significant negative relationship with irritability and ACT =-.30, p= <.05.

Prior to conducting multiple regression analyses, Pearson's correlations were calculated between anxiety, depression and RPQ, to check for collinearity. Subsequently a multiple regression was conducted to explore whether anxiety, depression and RPQ directly influenced PASAT trial 4 accuracy (z-score) performance in the mTBI group. The analysis indicated that the model was not significant, $F_{(3,39)}$= 2.54., p =.07, although it was approaching significance.

A multiple regression was also conducted to investigate whether anxiety, depression and RPQ scores predict the mTBI's group performance on the CTIP semantic trial. The results of the regression indicated that the model was not significant, although it was approaching significance $F_{(3,45)}$= 2.68., p =.06. Anxiety was a significant independent predictor (B=.41, p = 0.03) of performance on the CTIP semantic trial, but depression (B=-.20), p = .30) and RPQ (B=.16, p=.36) were not.

Discussion

The aim of *Study One* was to determine whether neuropsychological tests, sensitive to subtle cognitive changes following mTBI can differentiate between individuals with mTBI 3-6 months post-injury and matched healthy controls, and between individuals reporting higher levels of persistent post-concussion symptoms and those reporting lower levels. Overall, the results indicate that the mTBI sample performed worse on two of the neuropsychological tests compared to the control participants and the HPPCS group performed worse on two neuropsychological tests compared to the LPPCS group. Overall, the results indicate that the mTBI sample performed worse only on two of the neuropsychological tests compared to the control participants. As predicted, the HPPCS group performed worse than the LPPCS on the most sensitive measures and test trials that involved the most cognitive demand and/or increased with complexity. While there were no significant differences in mood scores between mTBI participants and controls, the HPPCS group reported significantly higher levels of anxiety and depression than the LPPCS group. This was unrelated to a previous history of mood difficulties.

The impact of mTBI on cognition

We predicted that the mTBI group would perform more poorly on four neuropsychological measures and a measure of depression, anxiety and irritability compared to controls 3-6 months post-injury. Contrary to predictions, the mTBI group performed more poorly on two of the four neuropsychological tests, the PASAT (z scores for accuracy) over two trials and the SDMT. No significant group differences were found for the ACT or CTIP, although the difference on the CTIP was approaching significance (p=0.08). Additionally, there were no significant differences between groups on the IDAS mood measure, although these were close to significance.

Our results indicated subtle differences between groups and supported previous studies who found mTBI participants perform more poorly on neuropsychological measures of information processing, attention and memory (Catale et al., 2009; Johansson et al., 2009; Kinnunen et al., 2011; Kumar et al., 2005; Lachapelle et al., 2008 Maruta et al., 2010; Sterr et al. 2006; O'Jile et al., 2006; Vanderploeg et al., 2005).

It is possible that had our control group been better matched to the mTBI participants, further differences would have been evident. For example, despite extensive efforts, the two groups were not matched on the TOPF. In an attempt to account for the possible influence that differences in ability may have had on neuropsychological performance, TOPF performance was used as a covariate. Arguably, however, analysis of covariance is a crude tool to use to control for between group differences on a variable that is also likely to be directly related to the dependent variable (Miller & Chapman, 2001). We predicted the mTBI group would have some degree of neuropsychological dysfunction, but unfortunately this was also the group with the lower TOPF and pre-morbid ability could arguably be related to performance on some neuropsychological tests. Removing the variance associated with the TOPF likely also removed some of the deficits due to having sustained a mTBI. Additionally as three of the four neuropsychological tests used z-scores derived from educationally and age-matched normative data, it is possible that in including TOPF as a covariate we "double corrected" for these differences.

High levels of persisting symptoms and impaired cognitive performance

The second aim of the study was to explore whether individuals reporting higher levels of enduring symptoms (HPPCS) 3-6 months post-mTBI would perform more poorly than those with lower, or no ongoing symptoms. Based on existing literature, it was hypothesised that the HPPCS would perform more poorly on measures that assess processing speed, attention and working memory and on measures that increase in cognitive load. Our results showed this, with the HPPCS group performing more poorly than the LPPCS group on two cognitive measures, the PASAT and CTIP. However, there were no significant group differences on the SDMT or ACT tasks. Our results are consistent with the few studies who have directly measured cognitive performance in individuals with PPCS compared to those individuals who have sustained a mTBI but recovered (Bohnen et al., 1992; Messé et al., 2012, Sterr et al., 2006). These studies have also found that individuals with PPCS perform more poorly on measures of information processing, attention, and working memory compared to individuals without enduring symptoms. The question regarding the neural origin and mechanisms underlying PPCS are not addressed in this study, however the results are in line with that viewpoint.

On the 4-trial PASAT, the HPPCS performed more poorly overall than the LPPCS, both in terms of accuracy (z-scores) and mean time per correct response. Our results are consistent with the proposition that DAI occurs as a result of a mTBI, which affects how rapidly information can be processed (Gronwall, & Sampson, 1974; Gronwall, & Wrightson, 1974). This argument refers to simple processing speed, however, the complaints of individuals with PPCS involves complex information processing. Gronwall and Wrightson (1981) later extended their initial proposal and

argued that the impact of damage to information processing ability is related to performance only when the tasks require complex processing, or where time constraints are imposed. Similarly, Peloso, von Holst and Borg (2004) argued that accuracy and response speed becomes less efficient when the cognitive load exceeds a certain point and that this level may be lower following damage to the brain as a result of mTBI. Our results support both of these interpretations, as response time and accuracy are reduced in the HPPCS group of this task. The results also support past findings that suggest that PPCS may compromise the ability to organise mental resources to accommodate increased processing load which results in problems with working memory and processing speed (McAllister et al., 1999). Additionally three participants from the HPPCS group only completed the first two trials of this test, either because they became highly distressed or they refused to continue the test. Additionally, another individual in the HPPCS group failed to successfully perform the practice trials and therefore did not undertake the test at all. It is highly likely that had these individuals completed the last two trials and their performance included in the study, greater differences between groups would likely be seen.

The HPPCS group did not perform more poorly overall on the CTIP than the LPPCS group, but they were differentially slower on the Semantic trial. The Semantic trial involves greater cognitive demands and internal processing than the Choice and Simple trial, as the cognitive processes involve searching through a semantic representation to determine if the word is in the same or different category, in addition to selecting the appropriate response key. In contrast, the Choice RT requires the recognition and response to a stimulus ("Kite" vs "Duck") response and Simple RT, the response to an "X" being on the screen. Our results indicate that differences between the HPPCS and LPPCS group are most evident on measures that involve increase in cognitive complexity and demand.

The ACT measure has been considered to be a measure sensitive to the effects of mTBI (Stuss et al., 1989), however, it was not a sensitive measure in this sample, as no differences between groups were shown. Of note, however, three participants had their test discontinued, two in the HPPCS and one in the LPPCS group and therefore were not included in the analyses. Individuals who had their test discontinued were struggling to complete the task. This may have masked differences between the two groups. It was predicted that the HPPCS would perform worse than the LPPCS group on this measure, given the high cognitive demand required to complete multiple cognitive tasks concurrently. Anecdotal evidence provided by the participants, however, indicated that they found the ACT task easier than the PASAT (which also increases in cognitive demand with trial condition) because participants stated that they adopted strategies to remember the letters (e.g., MLC they would use "Mum likes cats") which aided their recall.

Previous research suggests that some individuals with a history of one or more mTBI's experience greater and enduring cognitive difficulties than individuals who have not previously sustained a mTBI (Belanger & Vanderploeg, 2005; Collins, 1999; Iverson, 2005; Stephens et al., 2010). Considering this, it raises the question – did the HPPCS group have more people with a history of previous mTBIs? As detailed in *Chapter Two,* there were no significant differences between HPPCS group and LPPCS group on history of prior mTBI. In fact, both groups had 12 individuals who previously sustained a mTBI. This does raise some questions about the composition of the LPPCS group and whether this may have influenced the likelihood of finding differences between these two mTBI subgroups,

The method we used to subdivide the mTBI group in relation to persistent post-concussion symptoms was a median split of the total self-report scores (mild problems ≥ 2) on the Rivermead Post-Concussion Questionnaire (RPQ). Using this method only 14 of the 22 members of the lower PPCS group had RPQ scores less than 8, and additionally 4 individuals in this group had RPQ scores of 14 or 15. The International Classification of Diseases (ICD-10) provide a definition/diagnostic criteria for PPCS, classifying PPCS as the presence of three or more symptoms for a duration longer than three months. According to these criteria, a score of only six on the RPQ could be classified as experiencing PPCS. Clearly our method included individuals who met ICD-10 criteria for ongoing symptoms in the lower PPCS group; in fact 14 of the 22 individuals within the LPPCS group reported three or more enduring symptoms, although these may have been rated as mild in a number of cases. The most commonly reported symptoms in the LPPCS group were headaches, poor concentration, fatigue, and forgetfulness. Had we used the ICD-10 definition we would have had a smaller group of individuals reporting no symptoms, but this may have produced more differences between these two subgroups. Using this more liberal definition of PPCS, however, would raise different issues. For example, Voormolen et al. (2019) found that using the ICD-10 definition, a large proportion of the general population reported PPCS. Nevertheless, given the method we used it is striking that there were still notable differences on tasks that required multiple cognitive processes with increasing demand even though the low PPCS group contained individuals reporting ongoing symptoms. This point again highlights the controversial issue that there is no universally accepted diagnostic criteria or measure for PPCS and/or no accepted "cut off" value on the RPQ, which in turn poses a challenge in distinguishing those who have PPCS from those who do not. The challenge of characterising the severity of PPCS symptoms also remains complicated by the wide heterogeneity of symptoms experienced by individuals.

Depression, anxiety and irritability

A dominantly held perspective, both clinically and in the literature, is that PPCS is driven by psychological factors, particularly as pre- and post-injury mood disturbances have shown to be present in individuals with ongoing symptoms beyond three months post-injury (Broshek, De Marco & Freeman, 2015; Cnossen et al., 2017; Meares et al., 2011; Ponsford et al., 2019). In this study the mTBI group did not display higher levels of mood disturbance compared to controls post injury, or display differences in reported history of psychological difficulties. In contrast, however, individuals in the HPPCS group reported higher levels of anxiety and depression than the LPPCS group. This can be explained in a number of ways. On the one hand it appears consistent with the literature arguing for the causative role of psychological factors in ongoing PPCS. On the other hand, however, it is equally plausible that higher levels of anxiety and depression in the HPPCS group are caused by the distressing nature of unresolved and unexplained symptoms impacting their daily life. Ponsford et al. (2012) reported that pre-injury psychological difficulties are the strongest predictors of PPCS following mTBI. Interestingly in our study, only two (out of 7) individuals in the HPPCS group who displayed abnormal levels mood on the IDAS, reported a history of receiving treatment for psychological difficulties. Additionally, we found no differences between the HPPS and LPPCS group on history of receiving treatment for psychological difficulties. Our results suggest an alternative interpretation to the view that PPCS is driven by pre-psychological disorders. The effort measures embedded in our study provided no indication that individuals were exerting incomplete effort, indicating participants were not intentionally attempting to perform poorly. Since there is no evidence for this, instead we suggest that the mood symptoms experiencing by the HPPCS group relate to the ongoing symptoms caused by the mTBI itself. Other literature is also consistent with our finding, namely greater mood symptomatology post-mTBI in individuals who fail to recover following mTBI and who reported no pre-injury psychological disorder (Bombardier et al., 2010; Dikmen et al., 2010; Meares et al., 2011; Silverberg & Iverson, 2011).

Strengths and Limitations

The present study had a number of methodological limitations. We used a cross- sectional design to capture the functioning of a mTBI group within the three-to-six month post-injury window. Considering the cognitive changes that occur throughout the various phases of recovery, a longitudinal design would be beneficial, potentially provide new insights into different recovery processes following mTBI. The mTBI participants were recruited at the hospital and invited to participate in the study three to six months later. Although, the initial recruitment of mTBI individuals in the emergency department represented an unbiased sample (although their injury,

or other non-brain injuries associated with it, was severe enough to warrant visiting the emergency department), it is possible that participants who agreed to participate in the study 3-6 months later were more likely to be those who were experiencing ongoing symptoms, and therefore were more motivated to attend the imaging and testing session. This would be consistent with the relatively high scores on the RPQ of the mTBI group as a whole in our study. Theadom et al. (2016) classified PPCS if four or more items on the RPQ were reported as *'mild problems'* (≥2). For our study, this would mean that 31/46 (67%) participants would classify as having PPCS, which is higher than the 49.8% participants measured at six months post-mTBI in the Theadom et al study. Compared to the Theadom et al. study, our mTBI participants reported higher levels of each individual symptom on the RPQ at six month post-mTBI (shown in *Chapter Two*). Alternatively, however, Sterr et al. (2006) determined PPCS as three symptoms rated as 'moderate problems' (≥3) on the RPQ. Using this criteria 19/46 (41.3%) of our participants would classify as PPCS with their criteria for PPCS. Additionally, all of the participants who met this criteria were in the HPPCS group. Furthermore, despite our very liberal classification of low level of symptoms, significant differences in neuropsychological performance between the high PPCS group, and the group with lower levels of symptoms were revealed in our study. Additionally, the control group was not optimally matched to the mTBI group as the control group had higher mean TOPF scores. Finally, future studies would benefit from larger sample sizes, as this will increase the statistical power of the investigation and increase the likelihood of obtaining accurately matched control participants for group comparisons.

Notwithstanding these limitations, the study had a number of strengths. Notably, the present study is one of a few studies to directly measure individuals with higher levels of PPCS compared to individuals with lower PPCS or none (Bohnen et al., 1992; Messé et al., 2012, Sterr et al., 2006). This direct comparison, in participants who underwent an effort test, provides insight into the specific cognitive difficulties experienced by individuals with enduring symptoms. We propose that previous inconsistent findings measuring the relationship of neuropsychological performance and PPCS might, in part, be due to the fact that most experiments investigated chronic mTBI consequences by studying a cohort of mTBI participants without taking the status of PPCS specifically into account. These studies also typically used neuropsychological measures with simple cognitive demand. In this study, however, we used measures that involved multiple trial conditions that increase in cognitive demands, which capture the subtle difficulties reported by individuals with PPCS. It is argued that these tests are more sensitive to the subtle cognitive difficulties experienced by individuals with PPCS (Allen, Wu, & Bigler, 2011; Bigler, 2013).

Conclusion

In conclusion, whilst most individuals who sustain a mTBI recover within three months, there is a significant minority of individuals still experiencing difficulties 3 to 6 months later. Our results indicate that that higher levels of PPCS is associated with objectively measurable performance deficits on cognitive measures of processing speed, complex attention, working memory and reaction time. While individuals with the highest symptoms also reported more mood issues, there was no evidence that this related to pre-injury mood disturbance. This suggests their mood disturbances are likely to be reflective of the persisting struggle with ongoing symptoms related to the mTBI. The disruption to cognitive function is consistent with the assumption that DAI may occur at the point of injury and possibly in secondary processes, and causes disturbances of neural function. As a result, information processing may become less efficient or more effortful, which can lead to deficits in neurobehavioral performance.

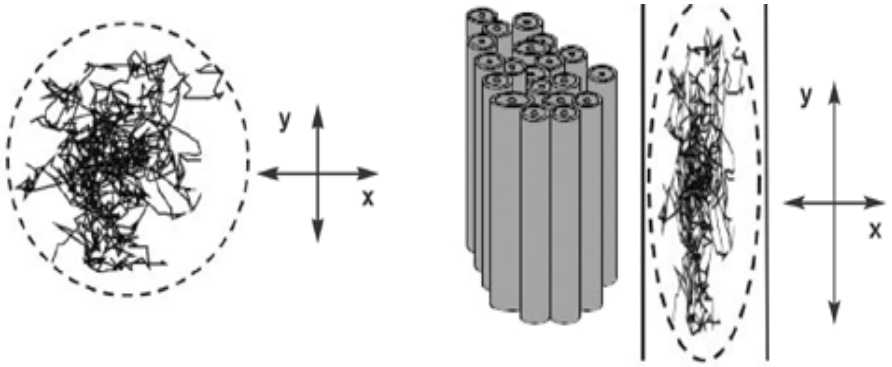
This has implications for our understanding of PPCS and treatment. Mild TBIs are not always, as mild as the name would suggest, and long-term consequence may plausibly have a neural underpinning.

Chapter Four

Study Two Diffusion Tensor Imaging to Examine White Matter Changes in Persistent Post-Concussion Symptoms

Histological and human autopsy studies have revealed that axonal damage may occur following a mTBI (Adams et al., 1989; Bigler, 2004). This evidence supports the proposal that the mechanical forces involved in a mTBI can cause diffuse axonal injuries (DAI) (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013), and raises the possibility that DAI may play a role in persisting symptoms following mTBI. Until recently, these microstructural changes following mTBI have not been able to be shown *in vivo*. Promising findings have been found, however, using a specialist form of magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), which has revealed changes in microstructural properties of white matter following mTBI at all phases (acute, sub-acute and chronic) of recovery (Arfanakis,, et al., 2002, Dean et al., 2015; Messé et al., 2012; Miles et al., 2008; Toth et al., 2013; Yuh et al., 2014).

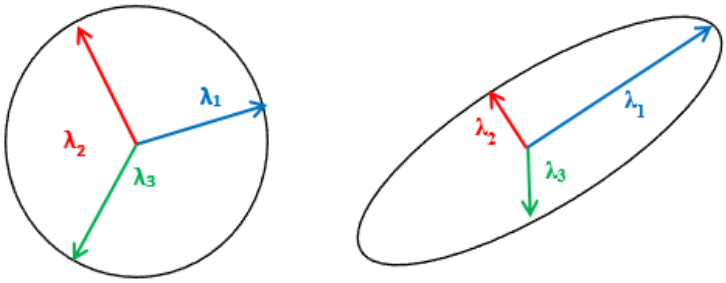
DTI is a technique that allows us to estimate the organisation of white matter pathways and the strength of these pathways, by using the principles of water diffusion. Diffusion is a thermally-driven random motion; water molecules will diffuse freely and equally in all directions unless there are barriers to prevent this. In regions of the brain where there are no microstructural elements to restrict it (such as cerebrospinal fluid) diffusion occurs equally in every direction (Koerte et al., 2016; Suri & Lipton, 2018). This results in a spherical or symmetrical diffusion ellipsoid known as *isotropic* diffusion (Amyot et al., 2015; Huisman, 2010). In white matter regions, however, diffusion is restricted by microstructural components, such as axonal membranes, myelin sheaths, neurofilaments and microtubules (Koerte et al., 2016; Strauss et al., 2015). When these elements are intact, water molecules will diffuse quicker parallel to the long axon axis and will be slower perpendicular to the axon due the restriction. This results in an elongated diffusion ellipsoid, with the principle axis aligned with the axon (Huisman, 2010; Shenton et al., 2012; Suri & Lipton, 2018). This asymmetric/directional diffusion is known as *anisotropic* diffusion (Koerte et al., 2016). See Figure 7 for graphical representation of isotropic and anisotropic diffusion.



Isotropic Diffusion Anisotropic Diffusion

Figure 7

Graphical Depiction of Isotropic and Anisotropic Diffusion (Roceanu, Mihaela, Antochi, & Bajenaru, 2012)



A) Isotropic Diffusion B) Anisotropic Diffusion

Fractional anisotropy (FA):

C) $$\sqrt{\frac{3}{2}}\sqrt{\frac{(\lambda_1-\bar{D})^2+(\lambda_2-\bar{D})^2+(\lambda_3-\bar{D})^2}{\sqrt{\lambda_1^2+\lambda_2^{2+}\lambda_3^2}}}$$

Where $\bar{D}$ is the trace of the diffusion tensor and is defined as:

$$\bar{D} = \lambda_1+\lambda_2+\lambda_3$$

Mean diffusivity (MD): $(\lambda_1+\lambda_2+\lambda_3)/3$

Axial diffusivity (AD) :(λ_1)

Radial diffusivity (RD):($\lambda_2+\lambda_3$) /2

Figure 8

*Graphical Depiction of the Diffusion Tensor Model. (A) Isotropic vector where all three eigenvectors are approximately equal($\lambda_1=\lambda_2=\lambda_3$) (B) Anisotropic vector where one eigenvector is greater than the other two ($\lambda_1>\lambda_2$ & λ_3)). (C) Equations for the key DTI parameters. * λ_1 = first eigenvector; λ_2 = second eigenvector; λ_3 = third eigenvector.*

The diffusion tensor model is able to measure diffusion in three-dimensions; at least six non-collinear diffusion encoding directions are required to calculate the tensor (Basser et al., 1994; Newcombe, Das, & Cross, 2013; Niogi & Mukherjee, 2010; Strauss et al., 2015). Different measures can be calculated from the diffusion tensor (Figure 8 for equations). *Fractional Anisotropy* (FA) measures the predominant diffusion direction/ the extent of directionality of water diffusion. FA values range between 0 and 1, where 0 is completely isotropic diffusion, and 1 is completely anisotropic diffusion (occurring only along one axis). *Mean Diffusivity* (MD; also known as Apparent Diffusion Coefficient; ADC) measures the mean magnitude of diffusion in all directions within the voxel, again ranging from 0 to 1 (Douglas et al., 2018; Koerte et al., 2016). Two other parameters commonly reported are *Axial Diffusion (AD),* which measures the diffusion rate parallel to the fibre, it is the principal diffusion direction; and *Radial Diffusivity* (RD) which measures the average diffusion rate along the transverse diffusion direction (Soares, Marques, Alves & Sousa, 2013). The diffusion metrics are often interpreted as measures of microstructural integrity. In healthy brains, the amount of diffusion is limited by the microstructural organisation of the white matter tracts (Niogi & Mukherjee, 2010). *Higher FA* values reflect motion of water molecules favoured in a specific direction and therefore reflect highly structured axons (white matter fibres) (Shenton et al., 2012), whereas *lower MD* values are associated with organised and aligned fibres, as free diffusion is prevented (Shenton et al., 2012). With damage to the white matter structure, FA is expected to decrease (as less longitudinal orientated microelements hindering diffusion) and MD to increase (fewer microstructural elements hindering diffusion) (Niogi & Mukherjee, 2010). Axial diffusivity reflects the diffusivity parallel to the axon itself, and lower AD is thought to be sensitive to pathology of the axon itself from trauma (Kraus et al., 2007). Radial diffusivity (RD) reflects diffusivity perpendicular to the axonal fibres and appears to be strongly correlated with myelin abnormalities, either demyelination or demyelination (Kraus et al., 2007), such that higher RD is associated with greater myelin damage (Song et al., 2002).

The literature involving the application of DTI in the chronic phase following mTBI is mixed in its findings. A number of studies report reduced FA (only) in a number of tracts, notably, the corpus callosum, fornix, cingulum, superior longitudinal fasciculus, uncinate fasciculus, insula, corona radiata, and internal capsule (Dean, Sato, Vieira, McNamara, & Sterr, 2015; Geary et al., 2010; Kraus et al., 2007; Lipton et al., 2009; Miller et al., 2016; Niogi & Mukherjee, 2010; Sugiyama et al., 2009; Wada, Asano, & Shinoda, 2012; Veeramuthu et al., 2015). Increased MD (only) is also shown in mTBI individuals in this chronic stage compared to controls (Grossman et al., 2013; Messé et al., 2012); as well, both increased MD and reduced FA (Lo, Shifteh, Gold, Bello, & Lipton, 2009). Two studies have found an association between reduced FA shown in mTBI individuals and greater PPCS reported on the RPQ (Dean et al., 2015; Miller et al., 2016).

There are a few studies, however, that show no differences in DTI metrics between the mTBI group and controls in this phase (Astafiev et al., 2015; Bouix, et al., 2013; Maruta et al., 2016).

One way to further understand the role that neural factors have in PPCS, is to compare individuals with PPCS to individuals who have sustained a mTBI, who are not reporting enduring symptoms. This will provide a more direct way to determine whether differences in DTI metrics, thought to reflect DAI, are associated with enduring symptoms. A small number of previous studies have made this direct comparison using the PPCS criteria used in this study (Bartnik-Olson et al., 2014; Karlsen et al. 2019; Messé et al. 2011). Two of these studies displayed DTI changes in the PPCS group compared to the mTBI group without enduring symptoms, specifically increased MD (Messé et al.) and increased RD (Bartnik-Olson et al.). Karlsen et al. failed to yield significant findings in the PPCS group compared to the non-PPCS group, despite the whole mTBI group showing reduced FA compared to controls. Karlsen et al. and Messé et al. used similar experimental design and the same measures, as both used the ICD-10 classification and TBSS to analyse the DTI metrics. It is possible that Karlson et al. failed to detect differences between the PPCS and non- PPCS groups due to the very small sample size in the study of n=25 participants compared to the n=85 in Messé et al..

Previous work in patients with mTBI has typically focused on a limited number of brain locations defined as regions of interest (Astafiev et al., 2015; Bouix et al., 2013; Kraus et al., 2007; Maruta et al., 2016). This approach is a sensitive way of identifying white matter damage, but because it is restricted to assessment of *a priori* defined regions, only a small amount of the total white matter is examined (Niogi et al., 2008). This is problematic for a number of reasons. Mild TBI's are unique injuries, that produce a complex pattern of DAI at variable locations across individuals depending on the physics of each injury, and so it is difficult to define the specific location of white matter disruption. The investigation of a small number of regions may result in a failure to identify significant white matter damage elsewhere in the brain. As the cognitive functions commonly affected by mTBI depend on the functioning of a distributed network, such an approach limits analysis of the structural causes of cognitive impairment. These issues are compounded by our limited knowledge of how tract structure relates to cognitive function in the normal brain, making it important to assess white matter structure after mTBI as comprehensively as possible (Kinnuen et al., 2011).

Tract-based spatial statistics (TBSS) is a voxel-based technique for analysing white matter structure across the whole brain (Smith et al., 2006). TBSS allows complex patterns of white matter disruption to be identified and their relationships with cognitive function to be studied in a data-driven way. Statistical calculations are performed at each point within an individual's white matter 'skeleton', which has been registered to a standard space using a two-stage process

involving non-linear warping and subsequent alignment of individual white matter tracts across subjects.

The present study used TBSS to examine white matter integrity in individuals who have sustained a mTBI 3-6 months prior. Differences in white matter microstructure were explored in individuals who had sustained a mTBI compared to healthy matched controls. All DTI metrics (FA, MD, AD, RD) were examined. To examine the possible role that white matter integrity might have in PPCS, we then investigated whether there were differences in white matter structure in individuals reporting higher levels of post-concussion symptoms (HPPCS) on the Rivermead Post-concussion Questionnaire (RPQ) compared to those reporting lower levels (LPPCS). This study also sought to investigate whether there was a relationship between the white matter microstructural integrity and cognitive performance in mTBI participants on measures that individuals with HPPCS performed more poorly on than the LPPCS group.

Based on previous DTI studies a number of predictions were made. Firstly, it was hypothesised that the mTBI group would display disrupted white matter integrity, specifically reduced FA and increased MD compared to the control group. The second prediction, which addresses the main aim of this study was that, the HPPCS group also would disrupted white matter integrity, specifically reduced FA and increased MD compared to the LPPCS group. Finally, the third prediction was that greater white matter disruption (evidenced by reduced FA and increased MD) would be associated with poorer performance on specific cognitive measures.

Method

Participants

The participant groups included in this study have been described in the general method chapter (see *Chapter Two*).

Neuroimaging

All neuroimaging was performed at the Centre for Advanced MRI (CAMRI) Auckland, New Zealand. Brain images were obtained on a 3 Tesla MAGNETOM Skyra machine (Siemens Healthcare, Erlangen, Germany), with a 32-channel head coil. The neuroimaging protocol was designed to optimise the assessment of mTBI and PPCS and included a number of additional sequences and modalities for future research. This includes structural anatomical scans and resting state functional MRI (fMRI), which are not reported. The total acquisition time for the neuroimaging protocol was 24.67 minutes.

Image acquisition

Participants lay supine inside the scanner with foam padding placed around the head to prevent movement. Diffusion weighted images (DWIs) were acquired with whole brain coverage in an approximately axial orientation, but angulated where needed to avoid the frontal sinuses. A spin-echo, echo planar-imaging sequence was used with the following parameters: echo time (TE) = 95ms; repetition time (TR) = 8900ms; with an in-plane field of view (FOV) = 240 × 240 mm; voxel size = 2 × 2 × 2mm, number of slices = 67 and GRAPPA acceleration factor = 2. Diffusion weighting was encoded using bipolar gradients in 64 non-colinear directions, with a diffusion weighting of b=1000s/mm^2. Six volumes with b=0 s/mm^2 were collected inline, yielding an acquisition time = 10m 51s. A field map for distortion correction of the DWI images was collected with the same FOV, voxel size and number of slices as the DWI, but with two TEs and diffusion weighting of b=0 s/mm^2, in a scan time of 2m 43 s.

Image preprocessing

All DICOM images were imported to a Linux workstation and converted into NIFTI format using MRIcron (Li, Morgan, Ashburner, Smith, & Rorden, 2016). The subsequent image processing steps were performed using FMRIB diffusion toolbox (Behrens et al., 2003; Smith et al., 2004). First, the images were reoriented and FSL Brain Extraction Tool (BET) was applied to remove the skull and all non-brain structures from further consideration (Smith, 2002). Each image was checked manually to determine if additional or specialised extraction steps were necessary. All images were pre-aligned using the FSL Eddy current tool to correct for any eddy current-induced distortions and head motion artefacts (Anderson & Sotiropoulos, 2016). Any slices that were detected to have signal loss were replaced by non-parametric predictions generated by Eddy's underlying Gaussian process. After prealignment, the DTIFIT tool was used to create Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD), and Radial Diffusivity (RD) images for each participant using a tensor model (Behrens et al., 2003).

TBSS

Whole-brain voxel wise statistical analysis of the pre-processed diffusion image was carried out with tract-based spatial statistics (TBSS) (Smith et al., 2006). TBSS allows the implementation of a unique nonlinear registration and projection onto an alignment-invariant tract representation (Andersson, Jenkinson, & Smith, 2007a; 2007b). This technique ensures that only voxels present in all subjects are included and does not require smoothing. All FA images were aligned to the 1x1x1mm FMRIB58_FA standard space target using the nonlinear registration tool FNIRT (Andersson et al., 2007a, 2007b). A standard space version of each subject's FA image

was generated by transforming the FA image to MNI52 standard space (Rueckert et al., 1999). A mean FA skeleton image was created by projecting each participant's FA image onto a skeleton, where the mean skeleton image represents the voxels in the centres of all the tracts common to the subjects and in this way removing partial-volume confounds. Finally, each participant's FA data was projected onto the mean FA skeleton, which was used to carry out voxel-wise cross-subject analyses. Similar steps of processing were carried out to obtain each of the diffusion metrics of interest (MD, AD, RD). MD, AD and RD were first aligned using the same non-linear registration as above, followed by all participants' warped data being merged and then projected onto the mean FA skeleton. Subsequent voxel-wise cross-subject analyses were conducted.

Neuropsychological Measures

All participants completed a standardised neuropsychological test battery customised to test cognitive domains believed to be affected by mTBI (measures described in *Chapter Three*). Two measures, the Paced Auditory Serial Additions Test (PASAT) (Gronwall & Sampson, 1974) and the Computerised Test of Information Processing (CTIP; Tombaugh, & Rees, 2008), were used as variables in imaging analyses. These two measures showed differences in performance between the TBI subgroup with high levels of PPCS symptoms (HPPCS) and the subgroup with lower levels (LPPCS). Both of these tests measure information processing speed. The PASAT also requires divided attention and auditory-verbal working memory and the CTIP measures information processing and reaction time. Both measures have multiple trials that increase with cognitive demands.

Statistical Analyses

Separate TBSS analyses were run to determine if there were any regions of white matter that differed in the DTI parameters between groups. Voxel-wise cross-subject analyses of DTI parameters (FA, MD, AD, RD) were measured using general linear model with permutations analysed with the randomize function from FSL, using the threshold-free cluster enhancement (TFCE) (Nichols, & Holmes, 2002; Smith, & Nichols, 2009). Four permutations were run for each DTI parameter. We used non-parametric permutation testing to correct for family-wise error from multiple comparisons. Significant difference between groups presented as clusters were tested for significance at $p < 0.05$, corrected for multiple comparisons across space using the TFCE approach. The anatomical location of each significant cluster was identified from the John Hopkins University ICDM-DTI -81 using AUTOAQ for automated anatomical labelling of activated clusters (Winkler, 2012) using an arbitrary threshold of $p < 0.05$.

In the combined mTBI group we examined the relationship between cognitive performance and the DTI metrics using separate general linear models (GLM) in the FMRIB

Software Library (FSL), controlling for age. This allowed analyses of the relationship between cognitive performance and white matter measures across voxels. The following neuropsychological variables: PASAT mean time per response over four trials, PASAT mean time per response over two trials, and CTIP semantic trial median reaction time were included as a predictor in separate regression models for each DTI metric (FA, MD, RD, AD).

Results

Comparison of Control and mTBI Groups on Diffusion Metrics

The results of the TBSS voxel-wise analyses are reported in the Table 9, shown visually in Figure 9, and visualised with TBSS fill in *(Appendix F).* Compared to controls, the mTBI group had significantly lower FA ($p < 0.05$) corrected for multiple comparisons) and significantly higher MD in a large number of white matter tracts. In contrast, no regions of lower FA or higher MD in the control group compared to the mTBI group were identified. Additionally, significantly higher RD ($p < 0.05$) was also shown in the mTBI group compared to controls. There were no significant differences between groups in AD ($p < 0.05$).

Table 9

DTI Comparisons for mTBI Compared to Controls

Diffusion metric	Significant differences	Locations in the brain
FA	mTBI group displayed significantly lower FA ↓($p < 0.05$) compared to the control group.	bCC, gCC, sCC right IFOF, right ILF, fornix, bilateral IC, bilateral cerebellar peduncle, bilateral cerebral peduncle, bilateral ML, bilateral PTR, bilateral CR, bilateral CST, and bilateral EC.
MD	mTBI group displayed significantly higher MD ↑($p < 0.05$) compared to control group.	bCC, gCC, sCC right IFOF, right ILF, fornix, bilateral IC, bilateral cerebellar peduncle, bilateral cerebral peduncle, bilateral ML, bilateral PTR, bilateral CR, bilateral CST, left EC and left SLF.
RD	mTBI group displayed significantly higher RD↑ ($p < 0.05$) compared to control group.	bCC, gCC, sCC, bilateral IC and EC, bilateral superior and posterior CR, bilateral cerebral peduncle, right ILF and right IFOF and cingulum.

Note. bCC; body of corpus callosum, gCC; genu of corpus callosum ; sCC; splenium of corpus callosum; IFOF; inferior fronto-occipital fasciculus, ILF; inferior longitudinal fasciculus, IC; internal capsule, ML; medial lemniscus; PTR; posterior thalamic radiation; CR; corona radiata, CST; corticospinal tract; external capsule; SLF; superior longitudinal fasciculus. All comparisons corrected for multiple comparisons using non-parametric permutation testng.

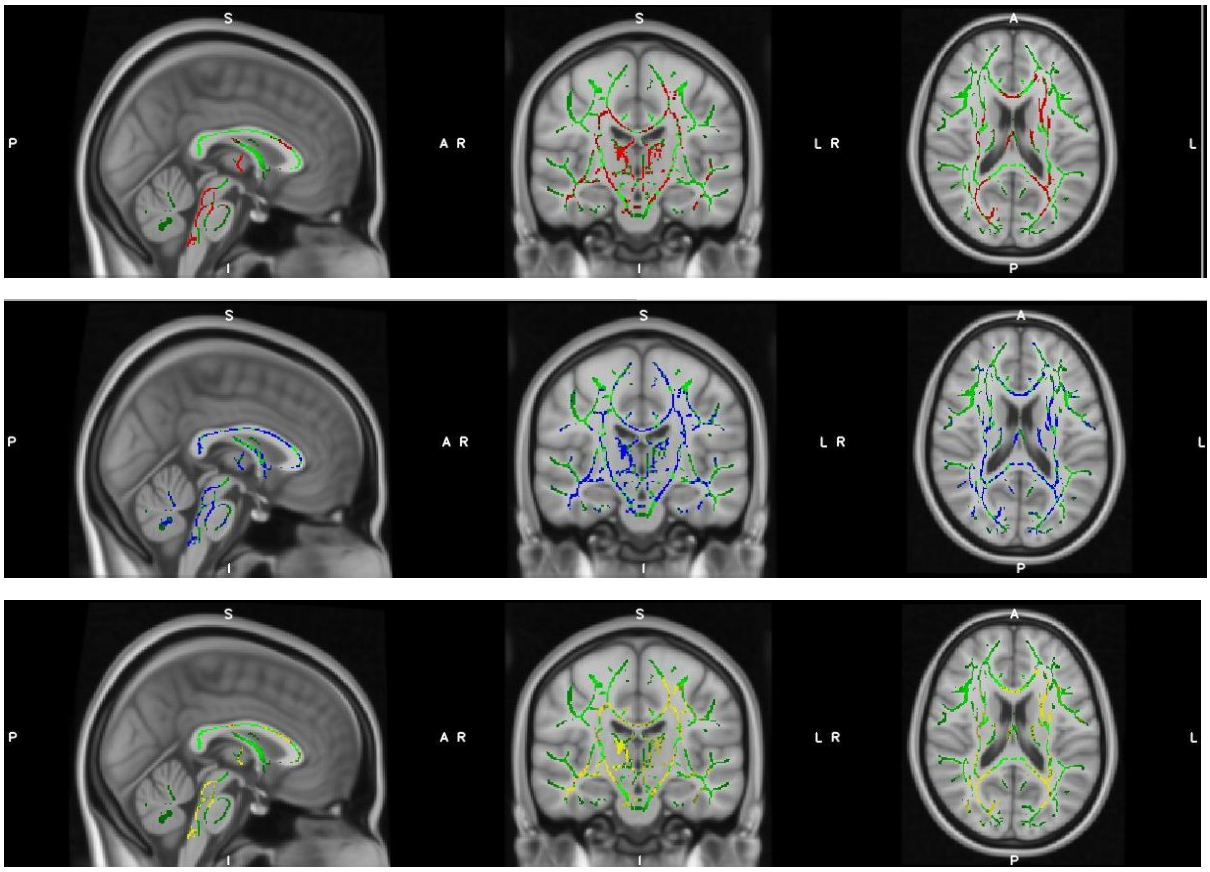


Figure 9

TBSS Contrast Analysis Between Controls and mTBI Groups on Measures of Fractional Anisotropy (FA) (Red), Mean Diffusivity (MD) (Blue) and Radial Diffusivity (RD) (Yellow) in mTBI and Control Groups. Areas in red are regions where FA was significantly lower in mTBI compared to controls. Areas in blue are regions were MD was significantly higher in the mTBI group compared to the controls group. Areas in yellow are regions where RD was higher in the mTBI group compared to controls. The contrasts are overlaid on a standard Montreal Neurological Institute 152 T11mm (MNI52-TI) template and the mean FA skeleton (in green) with display thresholds set from 0.2 to 0.7. The results are thresholded at $p \leq 0.05$, corrected for multiple comparisons using non-parametric permutation testing. The left side of the image corresponds to the right hemisphere of the brain. (See Appendix F for TBSS fill images).

Comparison of HPPCS and LPPCS groups on diffusion metrics

Next, we examined differences within the mTBI group, comparing individuals reporting higher levels of persistent post-concussion symptoms on the RPQ (HPPCS) compared to those who reports lower levels (LPPCS). The TBSS results are shown in Table 10, visualised in Figure 10 and TBSS Fill in the *(Appendix G).* Voxel-wise analysis demonstrated that the HPPCS

displayed significantly lower FA ($p < 0.05$), and significantly elevated RD compared to the LPPCS ($p < 0.05$) in. However, there were no differences in MD or AD between groups.

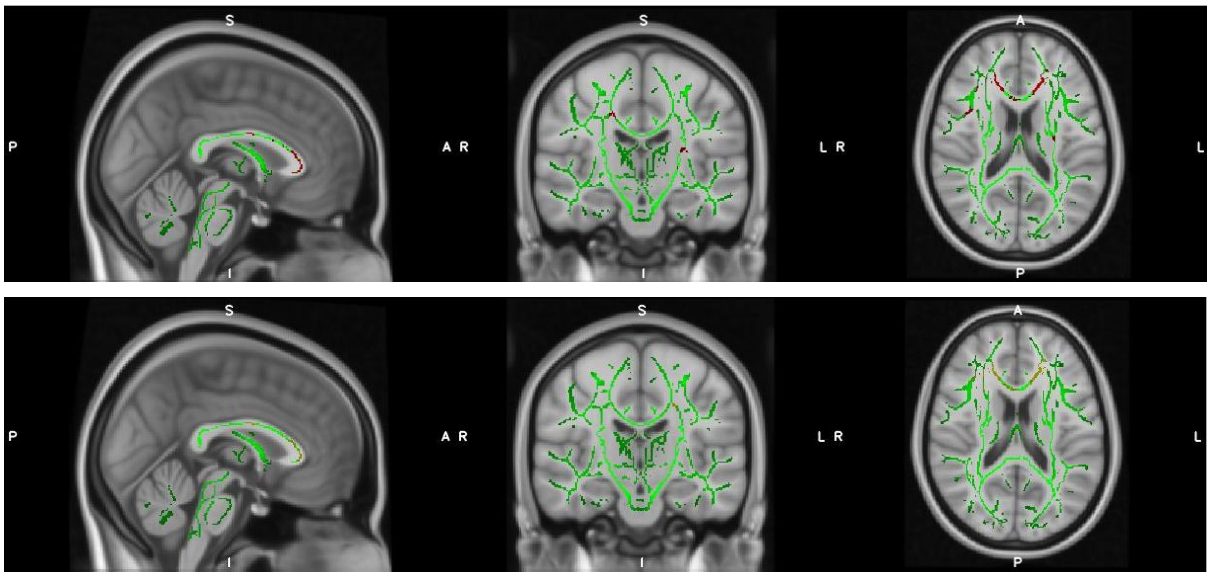
Table 10

DTI Comparisons for HPPCS Compared to LPPCS

Diffusion metric	Significant differences	Locations in the brain
FA	HPPCS group displayed significantly lower FA ↓($p < 0.05$) compared to the LPPCS group.	bCC, gCC, bilateral anterior and superior CR, left PTR (including optic radiation), and the left IC and EC.
RD	HPPCS displayed significantly higher RD↑ ($p < 0.05$) compared to LPPCS group.	bCC, sCC bilateral superior and posterior CR, right superior and ILF, right IFOF, bilateral IC, bilateral PTR, cingulum, left cerebral peduncle, inferior and middle cerebellar peduncle, and bilateral CST.

Note. bCC; body of corpus callosum, gCC; genu of corpus callosum ; sCC; splenium of corpus callosum; IFOF; inferior fronto-occipital fasciculus, ILF; inferior longitudinal fasciculus, IC; internal capsule, PTR; posterior thalamic radiation; CR; corona radiata, CST; corticospinal tract; external capsule.

Figure 10



TBSS Contrast Analysis Between HPPCS and LPPCS mTBI Groups on Measures of Fractional Anisotropy (FA) (Red) and Radial Diffusivity (RD) (Yellow). Areas in red are regions where FA was significantly lower in HPPCS compared to LPPCS (HPPCS < LPPCS FA). Areas in yellow are regions where RD was significantly higher in HPPCS compared to LPPCS (LPPCS < HPPCS). The contrasts are overlaid on a standard Montreal Neurological Institute 152 T11mm (MNI52-TI) template and the mean FA skeleton (in green) with display thresholds set form 0.2 to 0.7. The results are thresholded at $p \leq 0.05$, corrected for multiple comparisons. The left side of the image corresponds to the right hemisphere of the brain. (See Appendix G for more images).

Neuropsychological performance between and HPPCS and LPPCS groups

Chapter Three details the neuropsychological performance and analyses between both mTBI and controls and HPPCS and LPPCS groups. In this study, the variables on which there were significant differences between HPPCS and LPPCS groups were selected to be used as predictors in regression models of the DTI metrics for the total mTBI group. The relevant results are detailed in *Table 10.*

Table 11

Key Neuropsychological Differences Between the High PPCS and Lower PPCS mTBI Groups

Measure		
PASAT		Main effect of Group
Accuracy z-scores	HPPCS group performed worse overall compared to the LPPCS group.	$F_{(1,38)}$= 6.52, p = .02*.
Mean Time p/cr 4 trial	HPPCS group (n = 20) performed worse compared to the LPPCS group (n= 20)	Group differences $F_{(1,37)}$= 5.56, p = .02.
Mean Time p/cr 2 trial	HPPCS group (n = 23) performed more poorly compared to the LPPCS group (n=22).	Group differences $F_{(1,42)}$= 3.85, p = .06. *Approaching significance.*
CTIP	HPPCS group took significantly longer to perform the Semantic Trial only than the LPPCS group.	Group and Trial Condition interaction $F_{(1.54, 67.79)}$ = 4.54, p =.02.

Note. P/cr= per correct response.

The relationship between DTI metrics and cognitive function

To examine the relationship between white matter integrity and neuropsychological performance and to explore whether neural changes reflect function, we conducted a series of multiple linear regression models within the whole mTBI group on one measurement of the PASAT and the semantic trial on the CTIP. Linear regression models were run for all four DTI metrics, FA, MD, AD, RD.

The HPPCS group performed more poorly on both of the PASAT measures of mean time per correct response compared to the LPPCS group (four-trial, significant between group difference and two-trial approaching significance, 0 = .06). We selected the measure that included the largest number of mTBI participants, the PASAT mean time per correct response over the first two (pcr-2) trials (n = 45/46 mTBI participants compared to n= 40/46 for the four-trial measure).

We computed regression models to see whether performance on this PASAT measure, controlling for age, predicted the diffusion metrics (FA, MD, RD or AD). There was a significant negative association between PASAT mean time per correct response-2 trial and FA in the Corpus Callosum (genu, body, splenium), bilateral anterior CR, left superior CR, left superior longitudinal fasciculus, left IC and EC, left ILF, left IFOF, and bilateral PTR (see Figure 12 and Appendix H).

In other words slower performance on PASAT (higher mean time per correct response) was associated with lower FA. There was a significant positive association between PASAT mean time pcr-2 trials and MD in similar brain regions, including the CC (body and splenium), left ILF, left IFOF, bilateral anterior and posterior CR, right IC and left cingulum. In other words poorer performance on PASAT (slower performance) was associated with increased MD. There was also a significant positive relationship between RD and PASAT mean time pcr-2 in the CC (body, genu, splenium) bilateral CR, bilateral EC, bilateral PTR (see Figure 11) and for TBSS fill images see *(Appendix H)* However, there were no significant relationships between AD and PASAT mean time pcr-2.

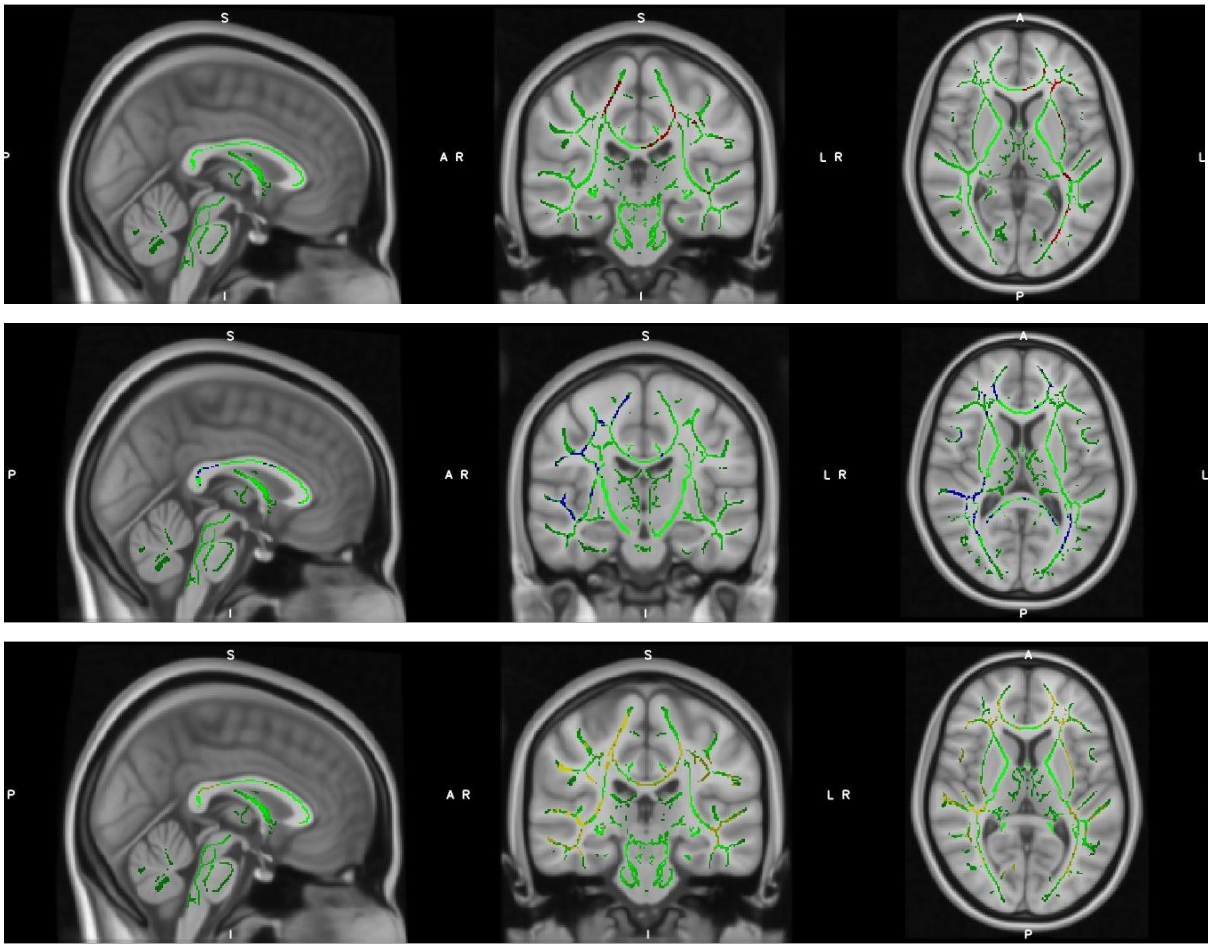


Figure 11

Regions Where Higher PASAT Mean Time per Correct Response over Two Trials (indicative of Poorer Performance) are Associated with Lower FA (Red), Higher MD (Blue), and Higher RD (Yellow), in the mTBI Group (n=45) $p < 0.05$, Corrected for Age and Multiple Comparisons. The left side of the image corresponds to the right hemisphere of the brain (See Appendix C for additional visualisation with TBSS fill)

Finally, a multiple regression model was run with the semantic trial on the CTIP as a predictor of the DTI metrics. None of the regression models revealed significant associations between performance on the semantic trial of the CTIP and FA, MD, RD, or AD.

Discussion

Information regarding the anatomical connectivity of the human brain can be gathered using diffusion tensor imaging (DTI). Fractional anisotropy is the most commonly derived value, and reflects how strongly directional diffusion is occurring in white matter tracts. Differences in FA (in addition to other diffusion metrics) are associated with differences in the underlying microstructure of the white matter. In this study, we examined between-group differences in white matter microstructure, and the relationship between diffusion metrics and cognitive performance on neuropsychological tests in individuals who had experienced a mTBI 3-6 months earlier. The study sought to address three questions. Firstly, to examine whether individuals 3-6 months after a mTBI display white matter disruption compared to heathy controls. Secondly, we explored whether there are differences in white matter microstructure between individuals who have experienced a mTBI and report high levels of persistent post-concussion symptoms (HPPCS) compared to those who report no or fewer symptoms (LPPCS). Finally, we investigated whether neuropsychological performance was associated with level of white matter disruption evidenced by diffusion metrics in the mTBI group.

Using TBSS to analyse diffusion-weighted data, our results show a number of significant white matter microstructural differences in individuals who have sustained a mTBI three to six months prior. Firstly, we found that mTBI participants had lower FA, higher MD and higher RD than healthy matched controls in a number of tracts in the brain. This finding supports previous suggestions that diffuse axonal injury (DAI) may result in microstructural changes in white matter following a mTBI, which can be evident for at least 3-6 months after the injury. Secondly, our TBI subgroup experiencing the highest levels of reported PPCS symptom had lower FA and increased RD compared to the mTBI subgroup with no or lower levels of PPCS symptoms. This suggests that microstructural changes in white matter may contribute to, or underlie, higher levels of PPCS. Finally, we found that in the TBI group, level of performance on the PASAT (mean time per correct response over two trials) was directly related to DTI metrics, with lower FA, higher MD and higher RD in a range of white matter tracts associated with poorer PASAT performance. These results demonstrate that individuals who have sustained a mTBI, have underlying ongoing disruption of structural connectivity, likely caused by diffuse axonal injury, and that poorer performance on the PASAT following TBI is related to these underlying changes..

Widespread white matter disruption following mTBI

The white matter differences in microstructure captured by DTI in the mTBI group suggest that there are fewer longitudinally-oriented elements that constrain diffusion and decrease directionality. Reduced FA, increased MD and RD have been attributed to axonal disruption and myelin degradation respectively (Wilde et al., 2008; Mayer et al., 2010). Therefore, this suggests some form of disruption to structural properties of white matter that could include axonal size and density, alignment of fibres and level of myelination, following mTBI. These results are consistent with the theory that diffuse axonal injury occurs as a direct result of the biomechanical forces of injury that place high strain on axons and microvasculature causing rotation, stretching and shearing (Bigler et al., 2016; Smith et al., 2003). Whilst axons and microvasculature can accommodate a degree of strain, their viscoelastic capacities are exceeded by the sudden and rapid application of force (Johnson et al., 2013; Smith, 2016) resulting in diffuse axonal injury (DAI). These findings were found at the group level in the whole mTBI group, which includes not only individuals experiencing high levels PPCS but those reporting none or lower levels PPCS. Our study supports previous studies, who displayed DTI metrics in the direction of reduced FA and increased MD at the chronic phase post-mTBI (Geary et al., 2010; Kraus et al., 2007; Lipton et al., 2008; Lo et al., 2009; Messé et al., 2010; Niogi et al., 2008; Rutgers et al., 2008; Veeramuthu et al., 2015).

The corpus callosum (CC) showed changes in all diffusion measures - FA, MD and RD, in the mTBI group. The CC is the most consistently reported white matter tract displaying disruption following mTBI (Cubon, Putukian, Boyer, & Dettwiler, 2011; Lo et al., 2009; Messé et al., 2010; Niogi et al., 2008, Rutgers et al., 2008; Sugiyama et al., 2009; Veeramuthu et al., 2015). The CC stretches across the midline of the brain connecting the left and right cerebral hemispheres and makes up the largest collection of axons in the brain (McDonald, Rushby, Dalton, Allen, & Parks, 2018). Damage to the CC following mTBI is significant, as the CC has an important role in integrating motor, sensory, and cognitive information across the two hemispheres, and damage to this area can lead to the behavioural, emotional, and cognitive impairments (Hofer, & Frahm, 2006; Kim, Choi, Yang, Cho, & Kang, 2015). Our study, identifies white matter disruption in a number of locations additional to the CC including the cingulum, inferior longitudinal fasciculus, the internal capsules, and the corona radiate, which have also been reported as areas of change in previous studies (Dean et al., 2015; Messé et al., 2010; Niogi & Mukherjee, 2010, Rutgers et al., 2008; Sugiyama et al., 2009; Veeramuthu et al., 2015). The cingulum is one of the largest neural tracts in the brain and has connections to the cerebral cortices, basal ganglia, medial temporal structure and limbic system (Wakana, Nagae-Poetscher, Van Zijl,

& Mori, 2004). Damage to the cingulum has been associated with impairments in attention, executive processing, learning and memory, and emotion formation, which are cognitive domains affected by mTBI (Devinsky, Morrell, & Vogt, 1995). The ILF is a long-range associative bundle that connects and transfers information between the occipital and temporal lobes (Herbert et al., 2018). Damage to the ILF is suggested to impair speed of visual and semantic processing and memory, and the integration of visual information with its emotional content (Fischer et al., 2016; Herbert et al., 2018; Shinoura et al., 2007). The anterior internal capsule runs from the thalamus to the frontal lobe, and connects the lenticular and caudate nuclei and the frontal cortex with the corpus striatum. Structural damage to these white matter projections can lead to inefficient processing and/or reduced regulation of arousal and awareness necessary for execution and completion of complex cognitive tasks (Bonelli, & Cummings, 2007; Doret al., 2013; Haber, & Knutson, 2010).

White matter damage present in PPCS

Comparisons of white matter diffusion-weighted data between HPPCS and LPPCS also supported our predictions, with the HPPCS group displaying lower FA and higher RD than the LPPCS group in a number of regions. These findings suggest those individuals reporting the highest levels of ongoing PPCS symptoms (HPPCS) also have greater reduction in the structural integrity of white matter, likely reflecting greater levels of DAI (Beaulieu, 2002) from the injury. This finding adds to a small literature which directly examining individuals with PPCS compared to individuals without PPCS. Our findings were consistent with the results of two studies that have directly compared individuals with PPCS with those without. Bartnik-Olson et al. (2014) found decreased FA and increased RD in the internal capsule in individuals with enduring cognitive symptoms (PPCS) following mTBI compared to those without enduring symptoms three to 12 months post-mTBI. Additionally, Messé et al. (2011) reported higher MD values in a number of tracts in individuals with PPCS (poor outcome) three months post-mTBI, compared to those with no PPCS (good outcome) and controls. These tracts comprised the corpus callosum, the right anterior thalamic radiations and the superior longitudinal fasciculus, the inferior longitudinal fasciculus and the fronto-occipital fasciculus bilaterally. The DTI changes in our HPPCS group included the same regions affected in these prior studies, but extended to further regions displaying diffusion changes, namely the corona radiata and cerebral and cerebellar peduncles. It is may be that we saw more extensive disruption to white tracts in our study compared to Bartnik-Olson et al. as we used TBSS, a whole brain analyses, whereas they use a ROI analysis and therefore were restricted by their prior hypothesis. Additionally, we may have seen more tracts in our study as our study investigated adults, whereas Bartnik-Olson et al. investigated adolescents.

It is possible that adolescent brains are more adaptive, resilient, and more likely to withstand, or recover from, injury.

The relationship between white matter structure and cognitive function

Finally we explored whether there was any relationship between DTI metrics and cognitive performance in the mTBI group. As predicted, reduced FA, increased MD and RD was associated with poorer performance on the PASAT mean time per correct response over two trials. These results provide support for an association between markers of altered white matter microstructure and poor performance on a measure of information processing speed, attention and working memory, an association that is present beyond three months since injury. A number of studies have explored the relationship between DTI metrics and cognitive performance in the acute and subacute phase post-mTBI, but this is one of the first studies that examined this relationship in the chronic phase post-mTBI. Our results are consistent with two previous findings that reported reduced FA correlated with measures of executive, attention and memory functions (Kraus et al., 2007) and reduced FA, increased MD and RD were associated with poorer performance on measures of attention, executive functioning and language (Veeramuthu et al., 2015). However, Grossman et al. (2013) found no significant relationship between DTI metrics and cognition. The common explanation for poor performance by individuals with PPCS on complex measures such as PASAT is that it reflects psychological factors, be it anxiety, illness beliefs or poor effort (Derakshan, & Eysenck, 2009; Larrabee, 2012). Yet our results show clearly that reduced performance can be associated with changes in DTI measures of white matter microstructure.

Contrary to our predictions, however, there was no significant relationship between DTI metrics and the performance on the PASAT mean time per correct response on four trials or the CTIP. On the 4-trial PASAT, five individuals did not complete the two trials of the PASAT. It is possible that the removal of this number individuals who struggle on this test removed too much of the variance to detect the relationship. With regards to the semantic trial of CTIP, it is possible that there was insufficient variation in performance on the CTIP, or that poorer performance reflects inefficient semantic processing at the cortical level.

Our results suggest that neural factors may play a role in the experience of PPCS. This study also demonstrates that mTBI-related neural alterations in white matter are an important component in understanding cognitive dysfunction on at least some measures, at the chronic stage. Furthermore, having demonstrated that *in vivo* markers of underlying neural changes are reliably associated with performance on one sensitive measure of cognitive function, these findings provide a basis for future research to investigate the extent to which structural neuropathology has

a causal relationship with cognitive dysfunction after mTBI, particularly in those individuals who do not follow the 'normal' recovery trajectory.

Strengths and Limitations

The majority of previous studies have typically explored changes in DTI metrics in a number of predefined brain locations known as regions of interest. While this approach is a sensitive method for identifying white matter damage, it is restricted to assessment of *a priori* defined regions and therefore may fail to identify changes that are occurring in other brain regions. In our study, we used TBSS, a whole-brain analysis technique, which resulted in identification of additional areas showing white matter changes. Additionally, the majority of research focuses on the use of FA and MD for investigating changes following mTBI. In our study were included the use of RD, which provides further insight into the nature of microstructural changes, as it is believed to reflect myelin integrity (Chu et al., 2010).

The primary criticism of the tensor model in DTI is that it can only estimate a single fibre orientation per voxel and cannot accurately determine the principal diffusion direction in voxels that contain multiple fibre orientations (Farquharson et al., 2013). This is known as the "crossing fibre problem". In voxels containing multiple fibre orientations, the information derived from the tensor model can be misleading and may misrepresent underlying tissue structure. In such regions, the graphical representation of the principal diffusion direction is non-ellipsoidal in shape and therefore does not accurately describe underlying tissue microstructure (Seunarine & Alexander, 2014; Tournier, Mori, & Leemans, 2011). This can sometimes lead to misinterpretation for example of increased RD. Despite this, the comparisons between the groups consistently found that the mTBI group and the HPPCS group showed lower FA, higher MD and RD, which are all indicators of white matter microstructural change. There were no occasions where the control group of LPPCS group showed such changes. Although weaknesses of the DTI method must be acknowledge, these weaknesses are unlikely to account for the pattern of results found in this study.

Our study used a cross sectional design to capture mTBI individuals in the chronic phase. Given the substantial differences shown in microstructure and cognition across the different phases following mTBI, it would be beneficial to measure mTBI participants across a series of time points. Longitudinal studies in which neurological and behavioural changes can be tracked over time would be helpful in order to better understand the progression after injury and therefore provide the best intervention strategies. Despite finding neural changes at the group level, for use in clinical practice, it is important to attempt to investigate changes at an individual level. Research would also benefit from measurements of specific tracts of white matter fibres. This

would provide understanding how changes in different aspects of white matter microstructure in specific tracts are related to cognitive function in the brain.

To conclude, our results represent support for a relationship between reduced white matter integrity in vivo for individuals at three months post-mTBI. Additionally, we found evidence that individuals reporting higher levels of persisting symptoms following mTBI displayed greater white matter disruption (reduced FA, increased MD and RD) compared to individuals who are reporting lower levels of persisting symptoms. These findings support the theory that DAI underlies PPCS following mTBI and challenges the argument that PPCS three months after mTBI can be explained by purely psychological and environmental factors rather than injury related factors (Silverberg, Gardner, Brubacher, Panenka, & Iverson, 2015). The current findings also demonstrate that we now have a reliable technique to examine the relationship between *in vivo* mTBI-related structural neuropathology and cognitive dysfunction following mTBI at a group level. These findings provide an avenue for substantial progress to be made in both research and clinical care for individuals with mTBI and PPCS.

Chapter Five

General Discussion

A sizeable minority of individuals fail to recover from mTBI and this can lead to detrimental effects on their health, wellbeing and quality of life. Understanding why some individuals experience enduring symptoms has been the topic of debate for a number of years. The tendency in research has been to attribute the aetiology of these enduring symptoms to psychological factors, as conventional imaging techniques have not supported a neural argument. The use of a relatively new MRI technique, DTI that can measure microstructural properties of white matter has produced promising results revealing microstructural changes *in vivo* following mTBI. This study specifically examined individuals with high levels of persisting post-concussion symptoms on the RPQ compared to fewer symptoms. We found poorer neuropsychological performance and greater self-reported mood difficulties were present in individuals with HPPCS. Our study was one of the first studies to use DTI to examine directly, and find, significant microstructural differences in individuals with high levels of enduring symptoms following mTBI compared to individuals reporting few symptoms 3-6 months after the injury. We also found that changes in the microstructure of the white matter were directly associated with clinical cognitive outcomes, as reduced white matter integrity was associated with poorer performance on a key cognitive test of processing speed in the mTBI group. Together these results contribute to support for the view that neural alterations may underlie, or contribute to, the development of PPCS.

Summary of Findings

Two studies contribute to this examination of the role of neural factors in PPCS. The first study is a clinical and neurobehavioural study (*Study 1*); and the second a neuroimaging study utilizing the technique of diffusion tensor imaging (*Study 2*). Both studies involved the same participants, a mTBI group who sustained their injury 3-6 month prior to the study and 20 healthy control participants who were matched for age and gender. The mTBI group was further divided into two groups, HPPCS and LPPCS, based on the mTBI individuals' self-report of currently experienced symptoms on the RPQ.

In *Study One,* we administered a selected battery of neuropsychological tests to explore cognitive differences in individuals who have sustained a mTBI compared to control individuals, followed by comparisons between individuals reporting high levels of persistent post-concussion symptoms compared to individuals reporting fewer symptoms. Overall, the mTBI group showed reduced performance on PASAT test (z-score over two trials) measuring psychomotor processing speed and visual scanning. Importantly we found that individuals with HPPCS performed more

poorly on measures of information processing speed, divided attention, working memory and reaction time compared to LPPCS. Notably these differences were shown on measures that incorporate multiple trials with increase in cognitive demand. These findings support the view that individuals reporting high levels of symptoms are experiencing difficulties, and that these may only be evident on measures that include conditions with high cognitive or processing speed demands

In *Study Two*, we used Diffusion Tensor Imaging to examine the presence of microstructural changes in individuals following a mTBI by comparing to white matter structure in individuals who have not had a mTBI. We also, more specifically, examined whether mTBI individuals with higher levels of PPCS symptoms display greater white matter disruption than individuals experiencing lower levels of PPCS symptoms. When we compared the whole mTBI group to the control group, we found striking results; significantly reduced FA and increased MD and RD was present in mTBI participants in extensive regions of white matter. These results suggest microstructural disruption is present and measureable in the mTBI group, likely caused by DAI at the time of injury that occurred 3-6 months previously. We also found that within the mTBI group, the higher symptom subgroup displayed significantly reduced FA and increased RD compared to the lower symptom subgroup in a number of white matter tracts. These findings suggest that underlying alterations in white matter contribute to the symptoms experienced in PPCS months after experiencing a mild TBI.

Cognitive symptoms are the most reported enduring symptom following mTBI and performance on neuropsychological measures are used as objective measures of cognitive functioning following mTBI. *In Study Two*, we examined whether level of cognitive performance on the PASAT and CTIP were associated with changes in DTI metrics following mTBI. A predictive relationship was found, namely that poorer performance on the PASAT, a measure of divided attention, working memory and processing speed, was associated with reduced FA, and increased MD and RD. These findings provide novel evidence of a systematic relationship between white matter structural disruption and enduring cognitive deficits at the chronic stage of recovery in *vivo*.

As the findings have already been discussed in detail throughout the proceeding two chapters, in the next sections I will discuss the context of our study and future directions of mTBI research. First, I will discuss the contribution of this research to understanding the basis of PPCS. This will be followed by discussion of some of the limitations of the study of PPCS, which are influencing the progression of this area. I will highlight points of further research needed in both of these sections. Finally, I will comment on the clinical implications of these findings and suggest possible interventions for management of mTBI.

The Use of DTI to Examine Contribution of White Matter Disruption to PPCS

Over the recent years, DTI has become a popular method to examine microstructural features of white following mTBI. DTI has proven sensitive as a method to localise and quantify the changes in white matter tracts *in vivo* in the brain of individuals who have sustained a mTBI, which previously have remained undetected on conventional imaging tools. However, there are limited studies investigating microstructural changes in the chronic stage post-mTBI. In our study, DTI was successful in identifying changes in white matter in the chronic stage of recovery, with greater change evident in individuals reporting high levels of enduring symptoms. To our knowledge, this study is one of a very small number of studies that have specifically compared individuals with enduring symptoms compared to those without. Until recently, the DAI theory has failed to receive support, particularly in the clinical management of mTBI, given conventional imaging does not identify positive findings in the vast majority of individuals experiencing a mTBI. The use of DTI, however, has challenged the view that PPCS is purely psychological in origin (Hellstrøm et al., 2017; Massey et al., 2015; Ponsford, 2012; van der Naalt et al., 2017). Our results indicated that alterations in white matter microstructure in this sample of mTBI participants were associated with poorer cognitive performance on a task with demands on processing speed and working memory. Specifically, individuals with higher levels of PPCS displayed poorer cognitive performance on the PASAT. These results provide support for the theory that DAI occurs at the point of injury, which affects information processing speed and therefore higher cognitive functions. This provides a second form of objective evidence linking underlying neural changes and the difficulties and symptoms experienced by individuals with PPCS.

The use of longitudinal studies is one way to increase the power of findings utilising DTI for research in PPCS. This would mean measuring within individual in white matter structure across the recovery phases (acute, subacute and chronic) following mTBI. This would provide further insight into the course of recovery and could help predict later clinical outcome from earlier characteristics. Additionally, this study utilises a group design to detect differences. The ability to integrate this technique into clinical management will depend on the ability to identify individual markers that reliably predict clinical outcome.

Our Results within the PPCS picture

A major contribution of this research is that it provides objective support for a neural basis of PPCS, which for a number of years has been frequently denied, including in the New Zealand context. Our study has also has provided evidence that neural changes, cognitive changes and mood changes 3-6 months post-TBI are present in individuals with higher levels of PPCS post-

mTBI. We argue that our data suggests mood disruption in PPCS may be a consequence of the severity of the effects of the initial mTBI and later of unresolved persisting symptoms, rather than being an indicator of pre-morbid psychological difficulties causing PPCS. Typically, no injury, or individual experience of PPCS and recovery is the same. It is not surprising therefore that in clinical practice and research, it has been difficult to predict the rate at which a person will improve and recover following a mTBI. We propose conducting a comprehensive longitudinal study, including measures of neural, cognitive, psychological, and cognitive factors, in order to capture the full experience of recovery for individuals and to tackle current challenges in studying PPCS. Such designs would allow stratified subgroup analyses to identify patients at risk for developing persistent symptoms, and might help to advance early and personalised treatment.

Challenges in PPCS Research

PPCS itself has been a controversial area of neuropsychology for many years and there are a number of controversies, which remain unresolved. These include: the classification of the mTBI itself, the diagnostic criteria for PPCS, the varied terminology used for both mTBI and PPCS, the aetiology of PPCS and even the validity of the actual existence of the syndrome (Pollinder et al, 2018). These controversies, have led to a number of difficulties when comparing studies and drawing conclusions and ultimately hinders the broader understanding of mTBI and PPCS. These controversies have resulted in many clinicians accepting the view any prolonged symptoms reflect psychological factors. Consequently individuals who sustain a mTBI may not have the understanding they need and continue to struggle with prolonged symptoms. A number of methodological changes need to be addressed in order to improve consistency in research.

Firstly, there are numerous measures used to measure and diagnose PPCS mTBI, with little consistency in the diagnostic cut offs. This impacts research as different groups of individuals are compared based on different diagnostic criteria. For example, despite, the DSM-IV and ICD-10 having similar criteria with good concordance between the symptoms involved (Boake et al., 2004), they have significantly different rates of classifications between the two criteria. Boake et al. (2004) assessed 178 individuals with persisting symptoms at three months post-mTBI and reported 104 individuals met criteria for post-concussive syndrome according to the ICD-10, but only 19 were classified as having post-concussive disorder under the DSM-IV criteria. The differences were accounted for by the DSM- IV requirement of significant cognitive deficits. As indicated, there is a significant difference in classification. As mentioned in previous chapters, our method of dividing the mTBI group into high and low PPCS by a median split turned out to be conservative because of the number of people in the low PPCS group who would have met criteria for PPCS by the ICD-10 and DSM-IV. Despite this, however, we found significant

differences between groups. Defining a universally accepted diagnostic tool with cut-offs for PPCS would facilitate consistency in studies evaluating the experience of individuals with PPCS and associated with underlying causes. Our study had a large proportion of individuals reporting high numbers of enduring symptoms. Unfortunately, the number of individuals with HPPCS cannot contribute to the literature pertaining to the frequency of PPCS because although there was an original invitation to all participants who sustained a mTBI at the Emergency Department, there was self-selection bias in those who agreed to participant 3-6 months later. Consequently, we are not able to identify whether the distribution of severity of reported PPCS out of the 46 mTBI participants is reflective of the original 120 who expressed interest, or whether the mTBI participant's response was biased towards those with ongoing difficulties.

The argument supporting a psychological basis for PPCS has dominated the aetiology debate. Indeed, as mentioned above one reason for support for the psychological argument is based on inconsistencies in the literature regarding neurobehavioral performance and neuroimaging of the PPCS population, therefore reducing support for the neural argument. We propose that the inconsistent findings might, in part, be due to the fact that most studies have investigated long-term consequences of mTBI by studying a cohort of mTBI participants without taking the status of PPCS specifically into account. Most studies report that only a subgroup (25%) of mTBI individuals report PPCS symptoms in the chronic phase of an injury (although it was higher in the sample in our study). Hence characterising the sample using a measure assessing the severity of their symptoms is needed to identify these individuals. Additionally, almost all studies that have measured PPCS have compared these participants to healthy controls. Given the controversy about the specificity of the symptoms of PPCS and the reporting of these in the normal population, our view is that a tighter design involves assessment of mTBI patients with and without sustained PPCS. This means the two groups have in common the experience of having an mTBI and will enable more targeted investigations into why some individuals have prolonged PPCS. Albeit sparse, there are a few studies that have made this direct comparison, for neurobehavioral studies (Bohnen, Jolles, & Twijnstra, 1992; Messé et al., 2012, Sterr et al., 2006) and neuroimaging (Bartnik-Olson et al., 2014; Messé et al., 2012), a number of which report significant results. Future studies should therefore incorporate these comparisons.

Another limiting factor in PPCS research, is the neuropsychological tests typically chosen to evaluate cognitive difficulties are insufficiently sensitive to measure the subtle difficulties reported by individuals with PPCS (Allen, Wu, & Bigler, 2011; Bigler, 2013). Individuals with PPCS typically report difficulty in situations with require complex cognitive processing. For example, attending to a conversation at a party, when there is background music, background chatting, and flashing lights. This situation requires complex cognitive processes such as

complex, sustained and divided attention. Simple cognitive tests will not assess for this difficulty, nor will tasks focussed on a number of cognitive domains. In future studies including targeted tests requiring complex cognitive skills that place greater demands on cognitive systems (including processing speed measures) will increase the sensitivity of detecting the subtle, yet impactful, changes experienced by individuals with PPCS (Allen, Wu, & Bigler, 2011).

Cognitive rehabilitation

Our study has revealed an understanding of underlying white matter microstructural changes 3-6 months after a mTBI, changes that are more marked in those experienced more severe PPCS symptoms. It has also shown a predictive relation between complex processing speed and white matter disruption following mTBI. This clearly indicates that there are symptoms and cognitive difficulties that relate to the mTBI and associated changes in white matter. This suggests that rehabilitation specifically targeted on increasing cognitive functioning may be useful. Cognitive rehabilitation involves activities intended to improve cognitive functioning via compensatory and restorative mechanisms. Compensatory activities rely on external compensatory mechanisms or environmental supports to re-establish previously learned patterns of behaviour and establish new patterns of cognitive activity. Compensatory approaches seek to enable persons to adapt to their cognitive disability in order to improve their overall level of functioning and quality of life. Restorative cognitive rehabilitation seeks to re-establish previously learned patterns of cognitive activity and reduce neurological impairments through training. A number of studies have used cognitive rehabilitation targeted to improve cognitive function for individuals and have shown cognitive improvement following TBI (Caplan et al, 2017; Chen et al., 2011; Nelson, MacDonald, Stall, & Pazdan, 2013; Novakovic-Agopian et al., 2011; Tiersky et al., 2005).

Two studies specifically have incorporated both compensatory and restorative mechanisms (Chen et al., 2011; Novakovic-Agopian et al., 2011) in interventions for individuals with PPCS six month post-mTBI. Participants undertook a training intervention for improving goal-directed attention regulation that takes into account the links connecting attention, working memory and goal-based direction of behaviour in daily life. In contrast to training via practice on isolated tasks, this training protocol involved application of attention regulation skills, problem solving skills, and mindfulness strategies. Individuals who completed the training protocol significantly improved on neuropsychological measures of attention and executive control, whilst participation in a brief educational activity resulted in no such improvements. The training also transferred to improvement in cognitive in complex real-world settings that the individuals were not directly trained (Chen et al., 2011; Novakovic-Agopian et al., 2011). These forms of

rehabilitation are effective for individuals with PPCS, as they target real-life situations, which individuals with PPCS struggle with.

In line with all PPCS research, a number of views and meta-analyses conclude that the evidence for the effectiveness of cognitive rehabilitation specifically for these patients is inconclusive (Rohling, Faust, Beverly, & Demakis 2009; Snell, Surgenor, Hay-Smith, & Siegert, 2009). Thus, although promising, there remains significant controversy regarding the efficacy of cognitive rehabilitation for mTBI patients.

Acceptance Commitment Therapy

Considering all the unresolved controversies surrounding PPCS, individuals with PPCS can find themselves left with enduring symptoms and with few answers. Enduring symptoms affecting individuals' everyday life can significantly influence individuals' psychological wellbeing and quality of life. In our study, the HPPCS group reported higher levels of anxiety and depression and we argued that this occurred as a consequence of the mTBI. Anxiety is a commonly reported psychological complaint following mTBI (Ponsford et al., 2019). Neural damage, physical and psychological adjustment, coping styles, feelings of grief, loss, and uncertainty regarding the future are all considered to contribute to the aetiology of anxiety following mTBI (Williams, Evans & Fleminger, 2003). Additionally, some individuals struggle to adjust to the changes in their functional abilities post-mTBI.

With this in mind, we propose that individuals with PPCS would benefit from a "third wave" mindfulness-based behavioural intervention termed Acceptance Commitment Therapy (ACT), which focuses on making value-based behavioural changes (Hayes, Strosahl & Wilson, 2009). ACT is an intervention that focuses of individuals' living purposeful, meaningful lives, whilst accepting the co-occurring pain/suffering that might occur when people move towards their values. From an ACT perspective, psychological suffering occurs when individuals become attached ("fused") with their unwanted thoughts, along with the tendency to try to avoid, control, or suppress unwanted thoughts, emotions, and sensations (Hayes et al.). ACT attempts to increase psychological flexibility, mainly by targeting experiential avoidance (Hayes et al.)

We propose that ACT may be suited for individuals with PPCS who may be struggling to adjust to and accept their reduced functional deficits, particularly as the intervention emphasises the pursuit of valued goals in spite of obstacles. Additionally, due to the transdiagnostic nature of ACT, it can target both the emotional and physical symptoms of PPCS (e.g. tinnitus).

General Conclusion

The use of Diffusion Tensor Imaging has been shown as a sensitive measure for measuring the microstructural changes following in individuals with PPCS following a mTBI Changes in white matter structure in mTBI have been associated with poorer performance on cognitive tests. These changes considered to reflect diffuse axonal injury that occurs at the point of injury. These results provide evidence supporting a neural explanation in PPCS, which is a novel finding in this area of research. Despite this, this area of research is highly controversial with many incompletely answered questions and requires further research.

Appendices

Appendix A: Participant Screening Form

Participant Screening Form

The first thing I would like to do is ask you some brief questions about you and your background. These are standard questions that we ask everyone in the study. The first part is personal information and the second part is information related to the mild traumatic brain injury.

1. Personal information

Identifier				
Name				
DOB				
Gender	Male		Female	
Ethnicity				
Date of Injury				
Age at Injury				
Hx of Learning Difficulties or ADHD				
Years of Secondary Education				
Secondary Qualifications	SchoolC NCEA 1	6FormC NCEA 2	Bursary NCEA 3	
Years of Tertiary Education				
Tertiary Qualifications	Degree	Postgrad	Other	Nil
Employment Type				
Employment Hours	Fulltime (>35 hours)	Part-time (<35 hours)	Unemployed	Retired
Study	Fulltime	Parttime	Other	
Previous mTBI	Yes		No	
If yes, date(s) of Injury Mechanism Effects				
Psychiatric History What? When? Treatment? Have you had a time in your life where you				

experienced problems with your mental health, for instance depression, anxiety, schizophrenia or similar? Have you ever required treatment for any emotional, nervous, or psychiatric illness?	
Current alcohol intake (average previous week)	
Prior Alcohol History	
Current Drug Intake (average previous week) Has there been a time in your life when a prescription medication, or a non-prescription drug (e.g., recreational drugs), has been a problem for you? For example, you may have had difficulty stopping a medication that you were on (e.g., sleeping tablets).	
Prior Drug History	
Any medical conditions?	
Current Medication Regime (dosages)	
Current Support System	

2. Injury information

Mechanism of Injury	MVA	Fall	Assault	Sport	Other
Point of Impact					
GCS at ED	13	14	15	Not Avail.	
PTA Length					
Scans	CT	MRI	Nil		
Scan Results					
Time between injury and presentation to medical specialist					
Medical Specialist	GP	A&E	Other		
Other injuries sustained					

Diagnosis Given (if known by participant)	
Treatment Advice Given (if known by participant)	
Other Important Information	

Thank you for taking the time to answer these questions. We would like to contact you in about three months to undertake the rest of the study. We will contact you closer to that time to make an appointment for the MRI scanning and the neuropsychological assessment.

Appendix B: Participant Information Sheet and Consent form

SCHOOL OF PSYCHOLOGY
Faculty of Science
The University of Auckland
Private Bag 92019
Auckland 1142, New Zealand

Participant Information Sheet

Study title:	***Investigating Recovery from Mild Traumatic Brain Injury***	
Locality:	**School of Psychology,**	Ethics committee
	University of Auckland,	ref.:**13/STH/177**
Lead investigator:	**Eleanor Krol**	
	PhD candidate	

INVESTIGATORS

Eleanor Krol a PhD candidate in the School of Psychology at the University of Auckland is carrying out this study. Study co-investigators include Associate Professor Lynette J. Tippett (ph. 09 373 7599 Ex 88551) and Dr Gjurgjica Badzakova-Trajkov, who are both senior researchers and registered clinical psychologists.

OVERVIEW OF THIS PARTICIPANT INFORMATION SHEET

You are invited to take part in a study on mild traumatic brain injury. Whether or not you take part is your choice. If you do not want to take part, you do not have to give a reason, and it will not affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you would like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether you will participate in this study. Before you decide, you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is **6** pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to understand factors that affect recovery from mild traumatic brain injury. Mild traumatic brain injury (mTBI) results from a jolt or blow to the head causing the brain

to move rapidly in the skull. MTBIs are very common and recovery is often rapid, but sometimes it takes longer. In this study, we aim to identify the key things, which contribute to slower recovery. We hope that findings from the study will improve understanding about mTBI in the general public and in rehabilitation services, and that findings from this study may be useful in developing effective early screening and rehabilitation methods.

This study has received ethical approval from the Health and Disabilities Ethics Committee on 24/12/2013 (Reference number: 13/STH/177).

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You have been invited to take part in this study because you are a healthy control, are fluent in English and aged between 18-64 years. You will be asked a few questions to ensure you are eligible for the study.

If you are eligible, you will be invited to complete the study procedures. These includes having a brain scan, performing some thinking tasks, and filling out some questionnaires about your current mood and your beliefs about yourself.

All participants will be asked a few questions to ensure they are eligible to have a brain scan. If eligible, you will be asked to come to the Centre for Advanced MRI (CAMRI) located in the Faculty of Medical and Health Sciences, 85 Park Road, Grafton around 3 months post-injury. You will be provided with directions to CAMRI and parking.

At CAMRI, you will undergo an MRI brain scan. The scan will take approximately 45 minutes. For the scan, you will change into a gown, removing all metallic objects and jewellery. You will then be asked to lie on your back on a bed, and lightweight equipment will be placed around your head. Because the scanning is noisy, you will be provided with protective headphones. You will then be slid into the scanner tunnel on the bed. You will be asked to remain as still as possible so that the images are movement fee. You will be able to communicate with the MRI operator via voice or the emergency buzzer at all times, and can request to be slid out of the scanner at any time.

Following the scan, you will be asked to complete a range of thinking tasks, either then, or on another occasion within 1-2 weeks. These thinking tasks measure how fast you are able to process information, how well you can attend to information and your speed of reactions. Some of these tasks require you to listen to and process information. Other tasks are pencil and paper tests. During one of the tasks where you are required to read aloud a list of words, it will be preferable to audio record your responses. The task will be administered without the audio recording if you do not consent to it.

In addition, you will be asked to fill in questionnaires about any symptoms you may be experiencing post-injury, your current mood, and your beliefs about yourself and recovery.

The thinking tasks and questionnaires will take approximately 110 minutes to complete.

During one of the thinking tasks you will be asked to wear a heart rate monitor for approximately 20 minutes. This is a belt that clips around your upper chest and records your heart rate. It can be attached and removed by you easily.

If you would prefer, the thinking tasks and questionnaires can be completed at your home, or a more convenient location. This would need to be completed as soon after the MRI scan as possible.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

There are no medical or health risks associated with any of the procedures used in this study. There are no known side effects or risks associated with MRI scanning. It is painless, and involves

no radiation exposure, needles or injections. However, 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 a safety checklist to make sure this is not the case for you.

Some individuals may find the MRI scanner noisy but you will be provided with headphones to minimise this. People who are prone to claustrophobia can find lying in the narrow tunnel of the MRI scanner difficult. Therefore, we do not recommend that they participate. Very rarely, people can find the scanner makes them feel warm or can feel a tickling or twitching sensation. These are harmless. However, if you feel uncomfortable for this or any reason whilst in the scanner you should let the MRI operator know via the communication system or the emergency buzzer. It is always your right to request that scanning be discontinued and that you be removed from the scanner.

Your MRI scan is for research purposes only and is not a medical examination. Images are not routinely reviewed by a radiologist. In the event that a clinical abnormality is detected (although unlikely) through performing the scan, you will be informed of this as per CAMRI policy. You will also receive an electronic copy of the anatomical scan of your brain. You will be advised to consult your general practitioner or other health professional of your choice. You should be aware that once you have been informed about the clinical abnormality, this could affect your ability to obtain insurance or your ability to work in certain professions, whether or not you take the matter further. If you would not want to know, you should not participate.

Some people may find the testing session a little tiring, but you will be able to stop at any time to have a break.

There are no particular benefits to taking part in this study. However, your participation will contribute towards our understanding of factors influencing rate of recovery from mTBI and may be useful in devising better rehabilitation strategies.

WHO PAYS FOR THE STUDY?

Taking part in this study will not cost you anything. All costs, for example scanning costs, will be covered by the research team. You will receive a $20 supermarket/petrol voucher in recognition of your contribution to the research, your time, and travel expenses.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You will have to lodge a claim with ACC through your GP and this would be assessed by ACC as per their protocols. If your ACC claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study will not affect your cover.

WHAT ARE MY RIGHTS?

Taking part in this study is voluntary. If you choose to participate, you can change your mind at any time without giving a reason and without any negative consequences. You also have the right to withdraw during the period of time between consent is given and the test procedures commence. Whether or not you participate will not affect your access to health care related to the mild traumatic brain injury. After your participation is completed, you have the right to request access to your data. You will also have the right to withdraw your data from the study for up to three months. You will receive a copy of this document to keep.

To protect your privacy, your name will only appear on the attached Consent Form and your name will not appear on any other data gathered in this study. No material that could personally identify you will be used in any of the reports relating to this study. Only the principle investigators, or study staff that have signed a confidentiality agreement, will have access to your information.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

Following completion of the study, all information will be stored securely at The University of Auckland for 10 years. Health data derived from the study must be stored for a minimum of 10 years according to the Health (Retention of Health Information) Regulations 1996. With your permission, information collected from you during this study may also be used in future studies. All stored information will be destroyed 10 years after the completion of the study.

Once the study is complete, a summary of the main finding can be provided to you if you would like this. The results of the study will be reported in scientific publications and presentations. No personal information that could personally identify you will be included. Results from the study may also be reported to health care providers and ACC.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Eleanor Krol: ekro816@aucklanduni.ac.nz (PhD candidate)

Associate Professor Lynette Tippett (Co-investigator)

Email: l.tippett@auckland.ac.nz

If you want to talk to someone who is not 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

Maori health support:

If you require Māori cultural support, talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 2324

If you have any questions or complaints about the study you may contact the Auckland and Waitematā District Health Boards Maori Research Committee or Maori Research Advisor by telephoning 09 4868920 ext 3204

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone:	0800 4 ETHICS
Email:	hdecs@moh.govt.nz

SCHOOL OF PSYCHOLOGY
Faculty of Science
The University of Auckland
Private Bag 92019
Auckland 1142, New Zealand

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND
Te Whare Wānanga o Tāmaki Makaurau
Ph. 64 9 3737599 ext 88557
Facsimile 64 9 373 7450
www.psych.auckland.ac.nz

Consent Form

Please tick to indicate your consent to the following

I have read and I understand the Participant Information Sheet which explains this research project and my role as a participant.	Yes ☐	No ☐
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	No ☐
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.	Yes ☐	No ☐
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.	Yes ☐	No ☐
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	Yes ☐	No ☐
I understand that I will be invited to participate in an MRI brain scan that will take approximately 45 minutes. • In the unlikely event that a clinically significant abnormality is accidentally found in my brain, the researchers will be obliged to inform me. I will also receive an electronic copy of the anatomical scan of my brain.	Yes ☐	No ☐
I understand that I will be invited to complete some thinking tasks, fill out some questionnaires about mood and my view of myself, and wear a heart monitor briefly during the cognitive assessment. I understand that this part of the study will take approximately 110 minutes.	Yes ☐	No ☐
I consent to the research staff audio recording my responses during one of the cognitive tasks as explained in the participant information sheet.	Yes ☐	No ☐

I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	No ☐
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
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. The data from this research will be stored confidentially to allow for publication and future analyses coded by number to de-identify me.	Yes ☐	No ☐
I understand that health data derived from the study must be stored for a minimum of 10 years according to the Health (Retention of Health Information) Regulations 1996.	Yes ☐	No ☐
I understand the compensation provisions in case of injury during the study.	Yes ☐	No ☐
I know who to contact if I have any questions about the study in general.	Yes ☐	No ☐
I understand my responsibilities as a study participant.	Yes ☐	No ☐
I wish to receive a summary of the results from the study.	Yes ☐	No ☐
I consent to research staff contacting me regarding the possibility of taking part in a new research project/s on mild traumatic brain injury (concussion). By ticking yes, I agree to only being provided with the relevant participant information sheet related to the new research project/s.	Yes ☐	No ☐

Declaration by participant:

I hereby consent to take part in this study.

Participant's name: _____

Signature: _____ Date: _____

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name: _____

Signature: _____ Date: _____

Appendix C: MRI Consent Form

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND
Te Whare Wānanga o Tāmaki Makaurau

uniservices

Centre for Advanced MRI

MRI SAFETY AND CONSENT FORM

Name _____ _____

Date of Birth ___/___/___ NHI _____

Weight _____ kg Height _____ cm

Magnetic Resonance Imaging involves the use of an extremely powerful magnet.
For your **safety** please answer the following questions

Have you had a previous MRI scan?	☐yes ☐no
Do you have **or** have you **ever** had a cardiac pacemaker?	☐yes ☐no
Do you have a brain aneurysm clip?	☐yes ☐no
Have you **ever** had an injury to the **eye** with a metallic object or fragment?	☐yes ☐no
Have you had any previous surgery?	☐yes ☐no
Please list _____	
Do you have any allergies to medications?	☐yes ☐no
Please list _____	
Do you have any of the following:	
Anaemia, blood disorders, kidney disease or seizures?	☐yes ☐no

FEMALE PATIENTS

Is there any chance that you could be pregnant?	☐yes ☐no
Are you currently breastfeeding?	☐yes ☐no

PLEASE ANSWER THE QUESTIONS ON THE BACK OF THIS SHEET

DO YOU HAVE ANY OF THE FOLLOWING?

Implanted cardiac defibrillator	☐yes	☐no
Implanted electronic or magnetic device	☐yes	☐no
Metallic stent, filter or coil	☐yes	☐no
Cochlear implant or other ear implant	☐yes	☐no
Heart valve prosthesis	☐yes	☐no
Any type of prosthesis (eye, limb etc)	☐yes	☐no
Joint replacement	☐yes	☐no
Screws, plates or wires in bones or joints	☐yes	☐no
Shunt (spinal, intraventricular, or heart)	☐yes	☐no
Vascular or drug access port or catheter	☐yes	☐no
Radiation seeds or implants	☐yes	☐no
Medication patches (Nicotine or hormone)	☐yes	☐no
Tattoo or permanent makeup	☐yes	☐no
Dentures or partial plate	☐yes	☐no
Hearing aid	☐yes	☐no
Shrapnel, bullets or other metal	☐yes	☐no

BEFORE ENTERING THE MR SCAN ROOM

You must remove all metallic objects, including jewellery, watches, keys, coins, credit cards, pens, cell phones, hearing aids, clothing with metallic zips and fasteners, metallic threads, or glitter finishes. You may be asked to change into a gown.

Owing to the loud noises emitted by the MR system, you will be given headphones or ear plugs to protect your hearing.

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

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

I confirm that the above information is correct to the best of my knowledge.

Signature _____ Date___/___/___

Screening form checked by _____

Appendix D: Rivermead Post-Concussions Symptoms Questionnaire

The Rivermead Post-Concussion Symptoms Questionnaire*

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

0 = Not experienced at all
1 = No more of a problem
2 = A mild problem
3 = A moderate problem
4 = A severe problem

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

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

Are you experiencing any other difficulties?

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

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

06/23/08

Appendix E: Irritability Depression Anxiety Scale

Appendix I:

nferNelson
understanding potential

Irritability-Depression-Anxiety Scale (IDAS)

Name:_____ **Date:**_____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies. Your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

D

I feel cheerful:
0 Yes, definitely
1 Yes, sometimes
2 No, not much
3 No, not at all

A

I can sit down and relax quite easily:
0 Yes, definitely
1 Yes, sometimes
2 No, not much
3 No, not at all

D

My appetite is:
3 Very poor
2 Fairly poor
1 Quite good
0 Very good

I

I lose my temper and shout or snap at others:
3 Yes definitely
2 Yes, sometimes
1 No, not much
0 No, not at all

D

I can laugh and feel amused:
0 Yes, definitely
1 Yes, sometimes
2 No, not much
3 No, not at all

I

I feel I might lose control and hit or hurt someone:
3 Sometimes
2 Occasionally
1 Rarely
0 Never

A

I have an uncomfortable feeling like butterflies in the stomach:
3 Yes, definitely
2 Yes, sometimes
1 Not very often
0 Not at all

I'm awake before I need to get up:
3 For 2 hours or more
2 For about 1 hour
1 For less than an hour
0 Not at all. I sleep until it is time to get up

I feel tense or 'wound up':
3 Yes, definitely
2 Yes, sometimes
1 No, not much
0 No, not at all

I have kept up my old interests:
0 Yes, most of them
1 Yes, some of them
2 No, not many of them
3 No, none of them

I am patient with other people:
0 All the time
1 Most of the time
2 Some of the time
3 Hardly ever

I get scared or panicky for no very good reason:
3 Yes, definitely
2 Yes, sometimes
1 No, not much
0 No, not at all

People upset me so that I feel like slamming doors or banging about:
3 Yes, often
2 Yes, sometimes
1 Only occasionally
0 Not at all

I can go out on my own without feeling anxious:
0 Yes, always
1 Yes, sometimes
2 No, not often
3 No, I never can

FOLD HERE

I	D	A

TOTAL

10

Appendix F: TBSS Fill Images mTBI and Control Group Comparison

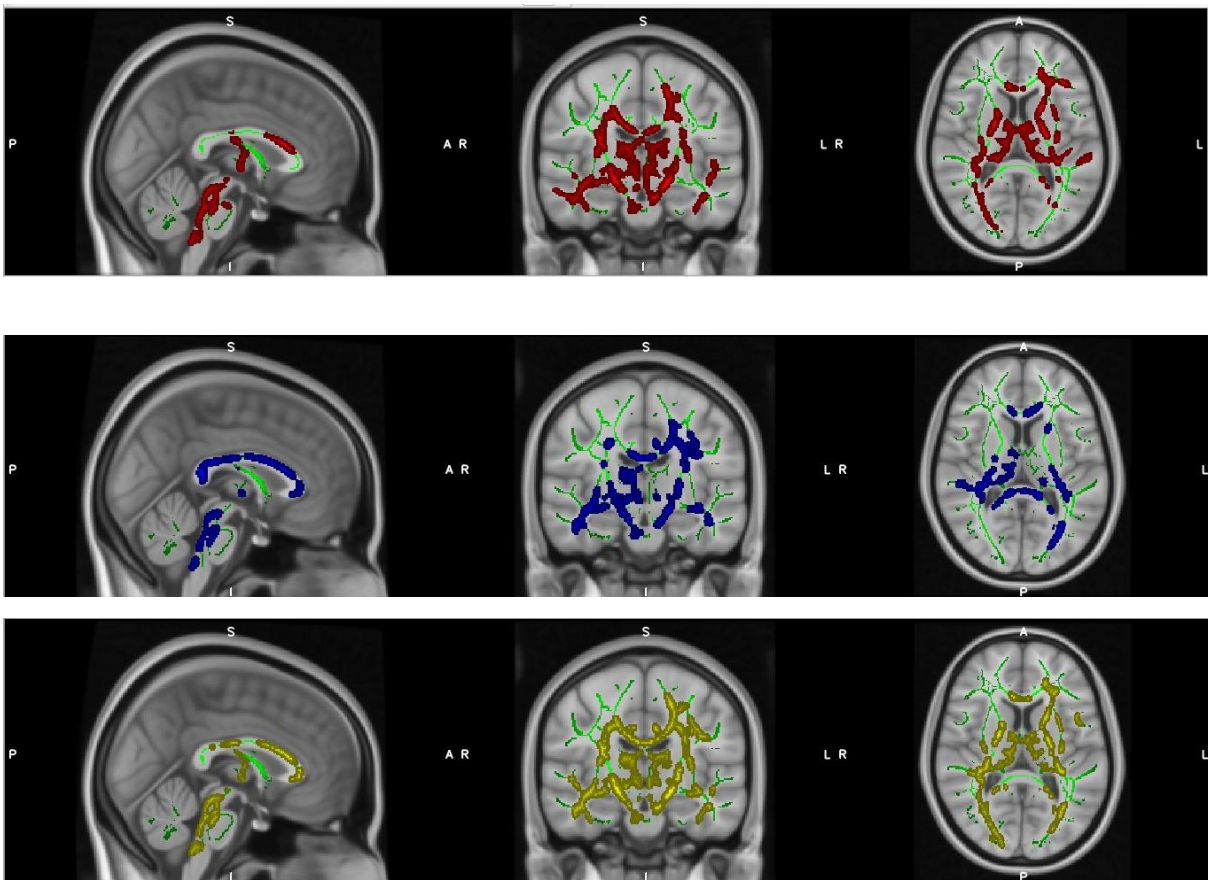


Figure A1. TBSS fill contrast analysis between controls and mTBI groups on measures of fractional anisotropy (FA) (red), mean diffusivity (MD) (blue) and radial diffusivity (RD) (yellow) in mTBI and control groups. Areas in red are regions where FA was significantly lower in mTBI compared to controls. Areas in blue are regions were MD was significantly higher in the mTBI group compared to the controls group. Areas in yellow are regions where RD was higher in the mTBI group compared to controls. The contrasts are overlaid on a standard Montreal Neurological Institute 152 T11mm (MNI52-TI) template and the mean FA skeleton (in green) with display thresholds set from 0.2 to 0.7. The results are thresholded at $p \leq 0.05$, corrected for multiple comparisons using non-parametric permutation testing. The left side of the image corresponds to the right hemisphere of the brain.

Appendix G: TBSS fill images HPPCS vs LPPCS group comparison

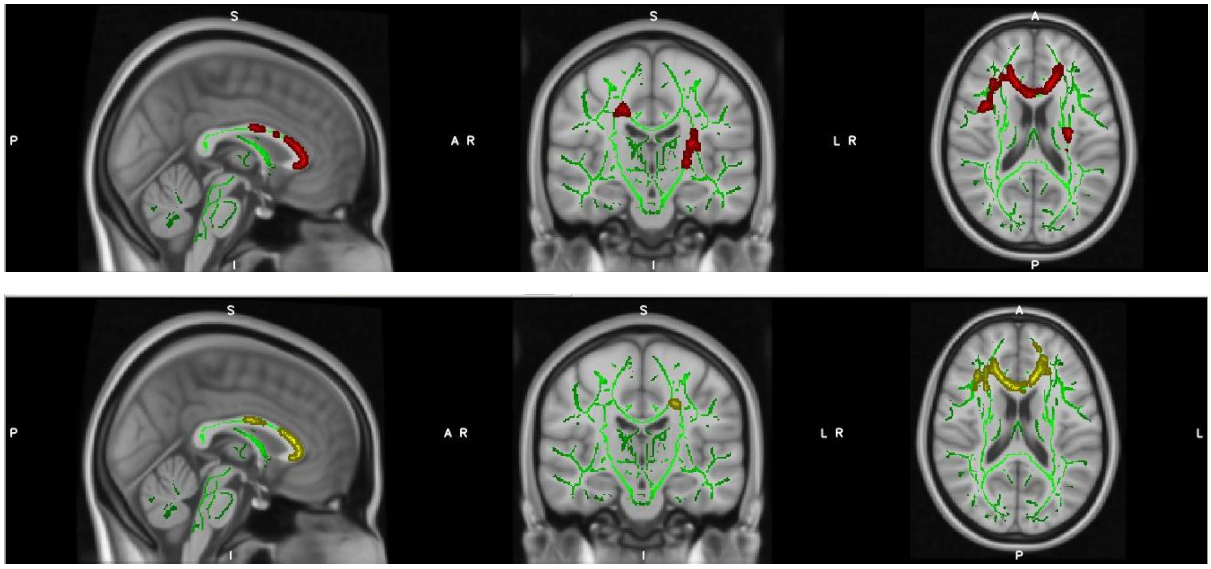


Figure B1. TBSS fill contrast analysis between HPPCS and LPPCS mTBI groups on measures of fractional anisotropy (FA) (red) and radial diffusivity (RD) (yellow). Areas in red are regions where FA was significantly *lower* in HPPCS compared to LPPCS (HPPCS < LPPCS FA). Areas in yellow are regions where RD was significantly *higher* in HPPCS compared to LPPCS (LPPCS < HPPCS). The contrasts are overlaid on a standard Montreal Neurological Institute 152 T11mm (MNI52-TI) template and the mean FA skeleton (in green) with display thresholds set form 0.2 to 0.7. The results are thresholded at $p \leq 0.05$, corrected for multiple comparisons. The left side of the image corresponds to the right hemisphere of the brain.

Appendix H: TBSS Fill Images Whole mTBI group and PASAT-2

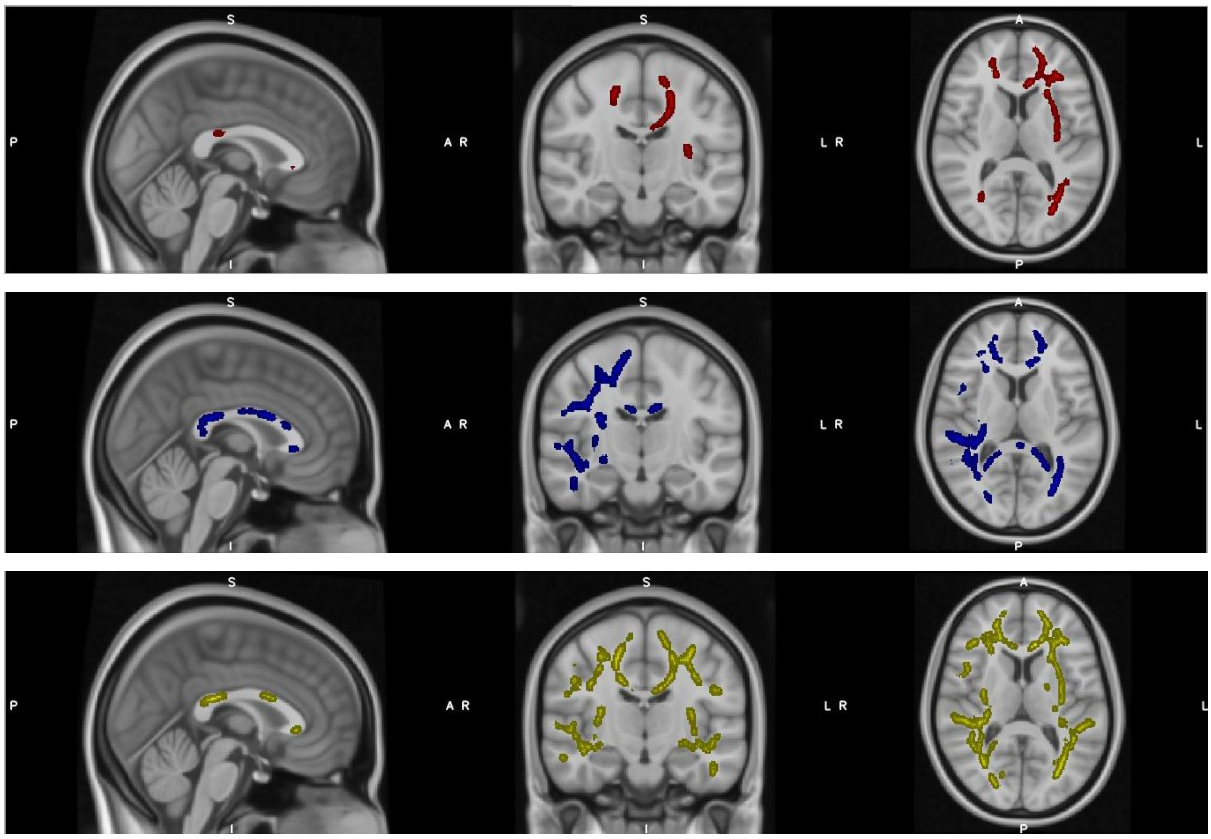


Figure C1. TBSS fill used to display regions where higher PASAT mean time per correct response over two trials (indicative of poorer performance) are associated with lower FA (red), higher MD (blue), and higher RD (yellow), in the mTBI group (n=45) $p < 0.05$, corrected for age and multiple comparisons. The contrasts are overlaid on a standard Montreal Neurological Institute 152 T11mm (MNI52-TI). The results are thresholded at $p \leq 0.05$, corrected for multiple comparisons. The left side of the image corresponds to the right hemisphere of the brain

References

Adams, J. H., Doyle, D., Ford, I., Gennarelli, T. A., Graham, D. I., & McLellan, D. R. (1989). Diffuse axonal injury in head injury: definition, diagnosis and grading. *Histopathology*, *15*(1), 49-59.

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