Changes to white matter and cognition following adult traumatic brain injury

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List of Abbreviations

ADC	Apparent diffusion coefficient
ANTs	Advanced Normalisation Tools
CC	Corpus callosum
CI	Confidence interval
CMA	Comprehensive Meta-Analysis
COWA	Controlled Oral Word Association Test
CT	Computed tomography
DAI	Diffuse axonal injury
DTI	Diffusion tensor imaging
DW	Diffusion-weighted
FA	Fractional anisotropy
FBA	Fixel-based analysis
FC	Fibre-bundle cross-section
FD	Fibre density
FDC	Fibre density & fibre-bundle cross-section
FOD	Fibre orientation distribution
g	Hedges' *g* effect sizes
GAMMA	Graphical model-based multivariate analysis
GCS	Glasgow Coma Scale
HARDI	High angular resolution diffusion-weighted imaging

JHU	John Hopkins University
LM-I	Logical Memory immediate trial (Wechsler Memory Scale – Third Edition)
LM-II	Logical Memory delayed trial (Wechsler Memory Scale – Third Edition)
LOC	Loss of consciousness
MD	Mean diffusivity
MRI	Magnetic resonance imaging
N/A	Not applicable
$N_{control}$	Number of control participants
N_{fs}	Failsafe N statistic
$N_{healthy}$	Number of healthy control participants
N_{mild}	Number of mild traumatic brain injury participants
$N_{moderate}$	Number of moderate traumatic brain injury participants
$N_{orthopaedic}$	Number of orthopaedic control participants
$N_{participants}$	Number of participants
N_{severe}	Number of severe traumatic brain injury participants
$N_{studies}$	Number of studies
N_{TBI}	Number of traumatic brain injury participants
PCS	Post-concussion syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTA	Post-traumatic amnesia
ROI	Region of interest
RT	Reaction time

SD	Standard deviation
SLF	Superior longitudinal fasciculus
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T	Tesla
TBI	Traumatic brain injury
TBSS	Tract-based spatial statistics
US	United States
VBA	Voxel-based analysis
VR-I	Visual Reproduction immediate trial (Wechsler Memory Scale – Third Edition)
VR-II	Visual Reproduction delayed trial (Wechsler Memory Scale – Third Edition)
WM	White matter
WMS	Wechsler Memory Scale

ABSTRACT

The cognitive impairments that frequently occur following a traumatic brain injury (TBI) are thought to be primarily caused by diffuse white matter (WM) injury. Computed tomography and magnetic resonance imaging have traditionally been used to determine the location and extent of this WM damage, however they better detect macroscopic damage, while underestimating the amount of microstructural damage to WM. Diffusion tensor imaging (DTI), on the other hand, better detects microstructural WM changes by measuring the diffusion of water molecules. DTI has been used to examine WM changes following TBI, however findings are mixed, with the location and magnitude of the changes varying between studies. Similarly, disparate findings concerning the relationship between DTI findings and cognitive outcomes have been reported. Finally, the traditional methods used to analyse DTI data are limited in areas of the brain that contain more than one WM tract.

The overarching aim of this thesis was therefore to examine WM changes and cognitive outcomes following adult TBI. Four studies were completed to address these aims. Specifically, two meta-analyses were performed to synthesise the findings from studies that 1) used DTI to examine the location and extent of WM changes following adult TBI; and, 2) examined the relationship between DTI findings and cognitive outcomes following adult TBI. The third study aimed to determine whether the findings from the meta-analyses — which were primarily based on small samples (most studies had fewer than 30 participants) — were replicated in large TBI and control samples. Finally, the same diffusion data were analysed using a recently developed method of analysis, known as fixel-based analysis (FBA), in order to determine whether it detected micro- and macro-structural WM changes in individual WM tracts following TBI.

The first study (Chapter 3) meta-analysed the findings from 44 studies that used DTI to examine adult TBI to determine the location and extent of WM changes. The findings indicated that WM changes, reflected in lower fractional anisotropy (FA) and higher mean diffusivity (MD),

were evident in a very large number of brain regions following both mild and moderate to severe TBI, with more severe injuries leading to more prominent WM changes. These regions included the corpus callosum, fornix, superior longitudinal fasciculus, internal capsule, occipital white matter, centrum semiovale, and thalamic radiations. The second study (Chapter 4) meta-analysed 20 studies that examined the relationship between DTI findings and cognition following adult TBI. It was found that lower FA and higher MD from a number of brain regions were related to poorer cognitive functioning, particularly in the domains of memory and attention. These regions were similar to those that were identified in the first meta-analysis and included the corpus callosum, fornix and superior longitudinal fasciculus. However, most findings were based on single studies with relatively small samples (60% of studies from the two meta-analyses had fewer than 30 participants), limiting the conclusions that could be drawn.

Thus, in the third study (Chapter 5), a large sample of adults with mild to severe TBIs (N=165) and a healthy and orthopaedic control group (N=106) underwent DTI and cognitive testing. Based on the findings from the meta-analyses, FA and MD were calculated using a region of interest approach for the corpus callosum (genu, body, splenium), fornix and superior longitudinal fasciculus and participants completed tests of memory, attention and executive functioning. Although mild TBI was not associated with significant WM or cognitive changes, people with moderate to severe TBI displayed large WM alterations (all regions) and poorer cognitive performance.

The final study (Chapter 6) analysed the same diffusion data examined in Study 3 using a novel method of analysis known as FBA. This emerging methodology is designed to overcome the main limitation of traditional DTI methods of analysis: that these methods are inaccurate in regions containing crossing fibres. Again, the mild group did not show evidence of WM changes, but the moderate to severe group displayed considerable changes in widespread WM tracts, reflecting fewer axons (reduced fibre density) and a reduction in cross-sectional area. Similarly,

the mild group did not show slower reaction times, but the moderate to severe group did, although the fixel findings were not associated with reaction times/processing speed.

This thesis showed that WM changes are widespread following moderate to severe TBI and can be detected using DTI and FBA. Findings following mild TBI, however, are less clear and warrant further research. TBI is a complex and multifaceted injury that does not have a typical pattern of damage that is readily captured using a single neuroimaging analysis technique. Research is now needed to determine whether DTI and/or FBA can predict long-term cognitive outcomes.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Erica Jane Wallace

Signed: Date: 29/04/2020

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PREFACE

BACKGROUND

Traumatic brain injury (TBI) is a major cause of death and disability, affecting an estimated 27.08 million people each year, globally (James et al., 2019). Cognitive impairments are among the most common and debilitating consequences of TBI, with memory, attention and executive functioning frequently being affected (Cristofori & Levin, 2015; Dikmen et al., 2009; Rabinowitz & Levin, 2014). TBIs often also result in a wide range of psychological, behavioural and functional problems that vary in severity and duration (Bigler & Stern, 2015; Cristofori & Levin, 2015; Griffen & Hanks, 2014). These problems are all thought to be largely due to diffuse axonal injury (DAI), a shearing injury that affects the white matter (WM) and, consequently, the ability of axons to effectively transfer information (Arfanakis et al., 2002; Huisman et al., 2004; Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013).

DAI is common after TBIs of all severities, even in the absence of the focal injuries that frequently occur following moderate to severe injuries (Shenton et al., 2012). Unfortunately, most DAI is microstructural and cannot be accurately identified using conventional neuroimaging techniques (e.g., computed tomography [CT], magnetic resonance imaging [MRI]), which better detect macrostructural damage following moderate to severe TBI (Shenton et al., 2012; Voelbel, Genova, Chiaravalotti, & Hoptman, 2012).

In contrast, an advanced MRI sequence known as diffusion tensor imaging (DTI), can now identify microstructural WM damage through the measurement of water diffusion in the brain (Niogi & Mukherjee, 2010). In healthy tissue, diffusion is restricted by the microstructural organisation of the WM (Niogi & Mukherjee, 2010; Shenton et al., 2012); however diffuse damage resulting from TBI leads to altered diffusion properties that can be measured using DTI.

PROBLEM STATEMENT

DTI has been used increasingly to assess WM changes following adult TBI with disparate findings reported regarding the location and extent of such changes. Paediatric populations have also been examined using DTI, however, paediatric TBI is associated with a range of issues concerning the developing brain (Pinto, Poretti, Meoded, Tekes, & Huisman, 2012); thus, the current thesis focusses solely on adult TBI. Although a number of reviews and meta-analyses have synthesised the literature regarding WM changes detected using DTI following TBI (e.g., Aoki, Inokuchi, Gunshin, Yahagi, & Suwa, 2012; Oehr & Anderson, 2017; Zhu, Ling, & Ding, 2019), most focus solely on mild TBI. Thus, the extent and location of WM alterations across the full spectrum of injury remain unclear. In addition, a range of findings have been reported regarding the relationship between DTI findings and cognitive outcomes following adult TBI and, moreover, many studies examining these associations have been limited by small samples (e.g., fewer than 30 participants).

The traditional methods that have been used to analyse DTI data, such as region of interest (ROI) analyses, calculate measures (e.g., fractional anisotropy, mean diffusivity) that are averaged across all fibre populations within each voxel (Raffelt et al., 2015). However, recent evidence suggests that voxel-averaged measures may lead to spurious conclusions in voxels containing multiple fibre tracts (i.e., crossing fibres) (Mori & Tournier, 2014; Raffelt et al., 2015). Further, crossing fibres may be present in up to 90% of all voxels (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2013). New methods have recently been developed to analyse diffusion data that attempt to overcome this limitation. One such method, known as fixel-based analysis (FBA), can differentiate between individual fibre tracts, enabling the detection of both microstructural and macrostructural changes in specific WM tracts where there are multiple fibre tracts or they cross one another (Raffelt et al., 2015; Raffelt et al., 2017). However, it is not currently known whether FBA can detect changes to specific WM tracts resulting from TBI.

AIMS

The overarching aim of this thesis was therefore to examine WM changes and cognitive outcomes following adult TBI. Two meta-analyses of existing research and two cross-sectional, quantitative studies were completed in order to:

1. determine the location of the greatest WM changes following adult mild, moderate and severe TBI (Meta-analysis 1/Study 1);
2. investigate the relationship between these WM changes and cognitive outcomes following adult mild, moderate and severe TBI (Meta-analysis 2/Study 2);
3. determine whether these relationships were replicated in a larger sample of adult TBI participants (Study 3); and
4. investigate whether WM alterations were detected following TBI using a novel method of analysis capable of examining individual fibre tracts (i.e., FBA) (Study 4)

SIGNIFICANCE

The current thesis was designed to extend existing research about the utility of DTI in identifying WM changes, and the relationship of these with cognitive outcomes, following adult mild, moderate and severe TBI. The identification of brain regions that are both commonly affected by TBI and related to cognitive outcomes may lead to improvements in the way we predict, and ultimately treat, cognitive problems following TBI. Importantly, this research may help to identify individuals who are most likely to exhibit cognitive problems and, therefore, those who require early intervention and rehabilitation in order to optimise their outcomes and decrease the levels of TBI-related disability in the community. In addition, determining the utility of a novel method of analysis in the examination of TBI may provide a viable alternative to DTI that could potentially be useful in clinical settings.

OVERVIEW OF THESIS STRUCTURE

This thesis comprises seven chapters. Chapters 1 and 2 review the relevant literature to provide context for the studies presented in Chapters 3 to 6. Chapter 1 reviews the literature on TBI; specifically, TBI is defined, and the types, incidence and prevalence, and causes and risk factors of TBI, severity of injury, assessment of TBI, and outcome following TBI will be outlined, with a particular focus on cognitive outcomes. Chapter 2 reviews the literature focussing on conventional neuroimaging (CT, MRI), followed by DTI, including how it works, methods of analysis, the use of DTI in TBI, and issues involved in the use of DTI. The aims of the thesis are included at the end of this chapter.

Chapters 3 to 6 contain four journal articles summarising four studies. A preamble is provided before each article, explaining the rationale for the study and highlighting the relevance to the overarching research goals. These papers were submitted for publication and two have been published, one has been accepted for publication, and the remaining paper is currently under review:

1. Wallace, E. J., Mathias, J. L., & Ward, L. (2018a). Diffusion tensor imaging changes following mild, moderate and severe adult traumatic brain injury: a meta-analysis. *Brain Imaging and Behavior*. *12*(6), 1607-1621. doi:10.1007/s11682-018-9823-2
2. Wallace, E. J., Mathias, J. L., & Ward, L. (2018b). The relationship between diffusion tensor imaging findings and cognitive outcomes following adult traumatic brain injury: A meta-analysis. *Neuroscience & Biobehavioral Reviews*, 92, 93-103. doi:10.1016/j.neubiorev.2018.05.023
3. Wallace, E. J., Mathias, J. L., Ward, L., Pannek, K., Fripp, J., & Rose, S. (2020a). *Chronic white matter changes detected using diffusion tensor imaging following adult traumatic brain injury and their relationship to cognition.* Under review.

4. Wallace, E. J., Mathias, J. L., Ward, L., Fripp, J., Rose, S., & Pannek, K. (2020b). A fixel-based analysis of micro- and macro-structural changes following adult traumatic brain injury. *Human Brain Mapping.* Advance online publication (31 January 2020). doi:10.1002/hbm.24939

Chapter 3 outlines a meta-analysis of studies that have examined adult TBI using DTI in order to determine which brain regions show the greatest WM alterations following injury, relative to controls. Separate findings are presented for mild and moderate to severe TBI. Chapter 4 extends this by meta-analysing studies that have examined the relationship between DTI findings and cognitive outcomes following injury. A list of the studies included in each meta-analysis is provided at the end of Chapters 3 and 4 and the superscript number corresponds to the reference number used in the tables.

Chapter 5 outlines the first cross-sectional study that examined the findings of the two preceding meta-analyses in a much larger sample of people with mild, moderate and severe TBI, as well as a control group comprising both healthy persons and those with orthopaedic injuries. DTI data were analysed using a ROI approach, with fractional anisotropy and mean diffusivity calculated for the CC (genu, body, splenium), fornix and SLF. Memory, attention and executive functioning performance were also assessed.

Chapter 6 presents the final study, in which a novel method known as FBA was used to analyse the diffusion data for the same TBI and control groups. FBA is used to evaluate the individual fibre tracts that are present within a single voxel (i.e., crossing fibres) and can therefore overcome one of the main limitations of traditional DTI methods of analysis (e.g., ROI). The aim of this study was to determine whether microstructural and macrostructural WM alterations could be detected in a large sample of people with mild, moderate and severe TBI using FBA.

These articles were each submitted to different journals and were prepared to adhere to the guidelines for each of these journals. Slightly different terminology has been used in different papers, at the request of reviewers. Throughout these chapters, the American Psychological

Association (Sixth edition) has been used, alongside British English spelling, for consistency. Thus, the published/submitted versions of these studies may differ slightly to the chapters. A combined reference list can be found at the end of the thesis. Tables and figures are embedded within the chapters and supplementary material is provided at the end of each chapter.

Finally, Chapter 7 examines the key findings from the four studies and their contribution to the broader TBI and DTI literature. The implications and limitations of this research are identified, and directions for future research are outlined.

CHAPTER 1: TRAUMATIC BRAIN INJURY

1.1 Definition and types of traumatic brain injury

1.1.1 Definition

Traumatic brain injury (TBI) is defined as "an alteration in brain function or other evidence of brain pathology, caused by an external force" (Menon, Schwab, Wright, & Maas, 2010, p 1638). Altered brain function encompasses decreased levels or loss of consciousness, amnesia/memory loss, neurological issues (e.g., dizziness, impaired vision), confusion, disorientation or other changes in mental state. Additionally, there may be structural alterations identified using neuroimaging (e.g., positive findings on magnetic resonance imaging [MRI]) or other methods (e.g., biomarkers of injury) that indicate a TBI. Finally, there are various mechanisms of injury that may lead to a TBI, including the head hitting, or being hit by, a blunt object; the head being penetrated by a foreign object; the sudden acceleration/deceleration/rotation of the head; or blast/pressure waves resulting from an explosion (Langlois Orman, Kraus, Zaloshnja, & Miller, 2011; Menon et al., 2010).

1.1.2 Types of traumatic brain injury

There are three main types of TBI — penetrating, non-penetrating and blast injuries — which differ in terms of their causes and pathophysiology (Arbour, 2013; Santiago, Oh, Dash, Holcomb, & Wade, 2012). Penetrating TBIs occur when a foreign object (e.g., a bullet or shrapnel) penetrates the scalp, dura matter and brain tissue, exposing the brain to the external environment (Arbour, 2013; Santiago et al., 2012). This type of injury is relatively uncommon in civilian populations, accounting for approximately 5% to 12% of all TBIs, but is often associated with a poor prognosis and high mortality rate (Santiago et al., 2012).

The most common TBIs are non-penetrating, which are caused by the head hitting or being hit by a blunt object, or the rapid acceleration/deceleration/rotation of the head (McKee & Daneshvar, 2015; Santiago et al., 2012; WHO, 2006). Non-penetrating TBIs can lead to focal and/or diffuse brain injuries. Focal injuries include contusions (bruises), lacerations (torn, jagged wounds), skull fractures, haematomas (localised collection of blood), and haemorrhages (bleeding), which are especially common at the frontal and temporal regions of the brain due to protrusions on the inside of the skull (Bigler, 2007; Dikmen et al., 2009; McKee & Daneshvar, 2015). Focal injuries are common following more serious injuries and are generally visible using conventional neuroimaging (i.e., computed tomography [CT] and MRI) (Shenton et al., 2012).

Diffuse injuries, on the other hand, affect widespread regions of the brain and include DAI (shearing injury to axons), hypoxic-ischemic injury (deprivation of oxygen to tissue) and microvascular injury (damage to small blood vessels) (McKee & Daneshvar, 2015). Often occurring with or without focal injury (McKee & Daneshvar, 2015), diffuse injury is typically microscopic, making it difficult to identify using conventional neuroimaging techniques (CT and MRI) (Douglas, Muldermans, & Wintermark, 2018; Koerte, Hufschmidt, Muehlmann, Lin, & Shenton, 2016). One type of diffuse injury, known as DAI (also termed traumatic axonal injury), is caused by sudden acceleration, deceleration or rotational forces, which result in axons stretching, swelling, shearing, disconnecting and degenerating (Hill, Coleman, & Menon, 2016; Johnson, Stewart, & Smith, 2013). This, in turn, affects the ability of axons to relay information (Raffelt et al., 2017). DAI can be extremely widespread, affecting commissural WM tracts that connect the left and right hemispheres (e.g., CC), association fibres that connect two regions within the same hemisphere (e.g., superior and inferior longitudinal fasciculi, uncinate fasciculi), and projection fibres connecting cortical and subcortical regions (e.g., fornix, internal capsule) (Aralasmak et al., 2006). It was originally thought that DAI only occurred in the acute[1] and subacute periods

[1] Definitions of the terms 'acute' and 'subacute' vary considerably. 'Acute' generally encompasses the period of time from the injury to approximately one-week post-injury. 'Subacute' refers to approximately one week to three months post-injury (Amyot et al., 2015).

following TBI, however, axonal swelling and degeneration have been found to continue for years post-injury (Chen, Johnson, Uryu, Trojanowski, & Smith, 2009; Hill et al., 2016). DAI is thought to underpin many of the cognitive impairments that occur after a TBI (Arfanakis et al., 2002; Huisman et al., 2004; Hulkower et al., 2013).

The third type of TBI is blast TBI, which is a particular type of non-penetrating injury caused by pressure waves resulting from an explosion (Dixon, 2017). The pathophysiology of these injuries is unique (Hawryluk & Manley, 2015); the blast wave produces energy that may cause the brain to rotate/accelerate, leading to DAI which can be far more widespread than the DAI caused by non-blast injuries (Dixon, 2017; Filley & Kelly, 2018). Furthermore, blast injuries often lead to oedema (swelling) and vasospasm (narrowing of arteries). The explosion may also damage tissue by causing shock waves in the cerebrospinal fluid and/or blood (Dixon, 2017). In addition, blast TBIs are often polytraumatic, also occurring with penetrating and non-penetrating injuries (e.g., being hit by debris from the explosion) and/or injuries from the person being thrown by the blast wind (e.g., head hitting the ground) (Dixon, 2017; Filley & Kelly, 2018).

Blast TBIs are uncommon in civilians, but frequently occur in military populations (Faul & Coronado, 2015). These injuries are often accompanied by post-traumatic stress disorder (Hendrickson, Schindler, & Pagulayan, 2018a), substance abuse and depression (Wilde et al., 2015). Blast TBI and these psychological issues have very similar symptoms, including problems with sleep, irritability, negative emotional states and difficulties concentrating, making them difficult to disentangle (Hendrickson, Schindler, & Pagulayan, 2018b; Menon et al., 2010). The current thesis focussed solely on non-penetrating TBI due to the differences in aetiology, pathophysiology, clinical course and outcomes, and the fact that both penetrating and blast TBIs rarely occur in civilian populations.

1.1.3 Primary and secondary damage

In addition to the different types of TBI, the brain damage that results from TBI can be further categorised into primary and secondary damage. Primary damage is sustained at the time of the injury when external mechanical forces directly or indirectly damage brain tissue (McKee & Daneshvar, 2015). Different mechanisms of injury can lead to different types of primary damage; acceleration/deceleration forces commonly result in diffuse injury and subdural haematomas, while contact injuries frequently lead to contusions and epidural haematomas (Hawryluk & Manley, 2015). Primary injuries are not amenable to treatment or intervention (Hawryluk & Bullock, 2016; McKee & Daneshvar, 2015), but can be prevented through the implementation of education programs and legislation (Chua et al., 2007). For example, the use of helmets when riding bicycles and seatbelts in motor vehicles, adhering to workplace health and safety regulations, and balance training for elderly people, are all designed to reduce the number of accidents and prevent TBIs (Chua et al., 2007).

Secondary damage, on the other hand, occurs in the days and weeks, or even years, following an injury (Hill et al., 2016). This type of damage is an indirect result of the primary injury, and involves delayed, progressive damage that may include bleeding, excitotoxicity (neuronal death resulting from excessive release of excitatory neurotransmitters), and axonal degeneration (Hawryluk & Bullock, 2016; Hill et al., 2016; McKee & Daneshvar, 2015). Secondary injuries are not immediate and therefore have the potential to be managed or reversed through therapeutic or neurosurgical interventions (Hawryluk & Bullock, 2016; Hawryluk & Manley, 2015; McKee & Daneshvar, 2015). Thus, it is possible that the progressive WM damage associated with significant cognitive impairments could be substantially minimised by appropriate clinical care (Menon & Ercole, 2017).

1.2 Incidence of traumatic brain injury

TBI is a leading cause of death and disability worldwide. A systematic analysis of global TBI burden in 2016 reported age-standardised incidence rates of 275 (230-327) per 100,000 population in Australia (James et al., 2019). The incidence of TBI was slightly higher in the United States (333 [280-396] per 100,000 population) and highest in Central Europe, with 857 (750-988) per 100,000 population (James et al., 2019). Regardless of country, the rates are significantly higher amongst males (Faul & Coronado, 2015; James et al., 2019).

Overall, the incidence of TBI is on the rise, with most of this data obtained via hospital records. In 2007, approximately 10 million people were affected annually (i.e., new cases) (Hyder, Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007), but this increased to 27.08 million new cases of TBI in 2016 (James et al., 2019). Indeed, the incidence of TBI increased by 3.6% between 1990 and 2016 (age-standardised incidence rates) (James et al., 2019). The rising incidence of TBI, worldwide, is thought to be due to the ageing population in higher income countries, with more elderly people sustaining TBIs as a consequence of falls (Brazinova et al., 2015). In addition, a greater awareness of the potential negative outcomes that may occur after even a single mild TBI has led to more individuals seeking medical help (Faul, Xu, Wald, & Coronado, 2010). Despite this, many people with mild TBI still do not go to hospital, instead seeking treatment in an outpatient clinic or from a general practitioner, or not seeking any medical help (Bruns & Hauser, 2003; Langlois Orman et al., 2011; Ruff, Iverson, Barth, Bush, & Broshek, 2009). Given that the majority of data is based on hospital records, mild TBIs remain underreported.

In addition, developing countries often lack sophisticated record keeping and reporting systems, making it particularly difficult to determine the incidence rates from these countries (Kinyanjui, 2016). In military settings, TBIs often occur with other injuries and therefore, in many

cases, the injury is not reported as a TBI (Hyder et al., 2007). As a result, the overall reported incidence rates of TBI are likely to be underestimates (Shenton et al., 2012).

The current thesis focusses solely on adult TBI because damage to the developing brain (i.e., paediatric TBI) is associated with a range of specific and complex issues (see Pinto, Poretti, et al., 2012). However, these incidence rates are for entire populations; paediatric TBI is inevitably captured in these data.

1.3 Causes and risk factors

TBIs are most frequently caused by motor vehicle accidents, falls, violence/assaults and sport (Khan, Baguley, & Cameron, 2003; Marshman, Jakabek, Hennessy, Quirk, & Guazzo, 2013; WHO, 2006). They are more common during early childhood (0-4 years of age), late adolescence/early adulthood (15-24 years of age) and older adulthood (over 75 years of age) (Langlois Orman et al., 2011). The primary cause of injury varies depending on the age group; falls occur more frequently in early childhood and the elderly, while motor vehicle accidents are more common in late adolescence/early adulthood (Bruns & Hauser, 2003; Faul & Coronado, 2015; Hyder et al., 2007).

The main risk factor for a TBI is sex, with males approximately 1.4 to 3 times more likely than women to be injured, regardless of age, severity or cause of injury (Faul et al., 2010; Langlois, Rutland-Brown, & Wald, 2006; WHO, 2006). The disparity between males and females peaks in adolescence, but the rates are almost equal by the age of 75 (Faul et al., 2010). This sex difference has been attributed to males' tendency toward risk-taking behaviours (e.g., violence) and their greater participation in 'risky' leisure activities (e.g., contact sports) and occupations (e.g., military, construction) (Corrigan, Selassie, & Orman, 2010; Khan et al., 2003).

A number of other factors directly or indirectly increase the risk of sustaining a TBI. These include alcohol and substance use (Hesdorffer, Rauch, & Tamminga, 2009; Tagliaferri, Compagnone, Korsic, Servadei, & Kraus, 2006; Weil, Corrigan, & Karelina, 2016), previous TBI

(Langlois Orman et al., 2011), low levels of education, low socioeconomic status and/or poverty (Basso, Previgliano, Duarte, & Ferrari, 2001; Liao et al., 2012; Nordstrom, Edin, Lindstrom, & Nordstrom, 2013), and seizures (WHO, 2006).

1.4 Classification of traumatic brain injury severity

The severity of a non-penetrating TBI is often determined by Glasgow Coma Scale (GCS) scores, the duration of post-traumatic amnesia (PTA) and/or the duration of loss of consciousness (LOC) (Saatman et al., 2008). GCS (Teasdale & Jennett, 1974) scores are the most common method of classifying TBI severity, with three separate scores (verbal, motor, eye opening) combined to give a total score ranging from 3 to 15. A GCS of 13-15, 9-12, and 3-8 indicate mild, moderate and severe TBIs, respectively (Teasdale & Jennett, 1974; WHO, 2006). The GCS is commonly used before a patient is admitted to hospital (e.g., when attended by paramedics), in emergency departments to monitor status soon after an injury, and for longer periods of time following more severe injuries (Chua, Ng, Yap, & Bok, 2007; Faul & Coronado, 2015). However, the GCS is inaccurate when a patient is sedated, intubated, intoxicated or paralysed because they may not be able to make the verbal, motor or eye responses for reasons other than the TBI (Saatman et al., 2008; Whitaker-Lea & Valadka, 2017; Zhu, Wang, & Liu, 2009). In addition, the GCS does not always accurately differentiate between mild and moderate TBI; some researchers categorise a GCS of 13 as a 'moderate' rather than a 'mild' TBI (Einarsen et al., 2018; Mena et al., 2011).

PTA refers to a period of confusion, agitation and amnesia following a TBI (Marshman et al., 2013) and is also used to classify TBI severity. PTA of less than 24 hours, between one and seven days, and more than seven days indicate mild, moderate and severe TBIs, respectively (Amyot et al., 2015; Cristofori & Grafman, 2017; Russell & Smith, 1961). PTA duration is generally measured from the time of an injury until a patient becomes orientated and able to form and retain new memories (Langhorn, Sorensen, & Pedersen, 2010). Longer PTA duration is associated

with poorer cognitive and functional outcomes (Ahmed, Bierley, Sheikh, & Date, 2000; Khan et al., 2003; Langhorn et al., 2010; Marshman et al., 2013).

LOC refers to the length of time that a person is unconscious following a TBI. Mild, moderate and severe TBIs are indicated by a LOC of less than 30 minutes, 30 minutes to 24 hours, and more than 24 hours, respectively (Amyot et al., 2015; Cristofori & Grafman, 2017). However, some cases of mild TBI do not experience any LOC (Iverson et al., 2017; Ruff et al., 2009); thus it does not measure the full spectrum of injury severity. Additionally, the duration of LOC is difficult to determine unless trained medical professionals are present from the outset (Menon et al., 2010). Self-reports often overestimate the duration and witnesses may have difficulty determining whether someone is unconscious or not (Faul & Coronado, 2015; Menon et al., 2010; Sherer et al., 2015), reducing the accuracy of LOC.

Overall, there is no consensus regarding which measure of severity should be used. Each has been found to predict outcome, with a recent meta-analysis reporting that GCS, PTA duration and LOC duration each moderately to strongly predicted cognition following TBI (Konigs, Engenhorst, & Oosterlaan, 2016).

Mild TBI

Mild TBIs are indicated by a GCS of 13-15, PTA of less than 24 hours and LOC of less than 30 minutes (Amyot et al., 2015). A distinction is sometimes made between complicated and uncomplicated mild TBIs; the former involves a GCS of 13-15 in conjunction with brain pathology identified using neuroimaging, while the latter has comparable GCS scores, but no neuroimaging abnormalities (Cristofori & Levin, 2015; Filley & Kelly, 2018). A subset of mild TBIs, known as concussions, are predominantly sustained in sport, however, many researchers use the terms mild TBI and concussion interchangeably (see Bigler, 2008; Dwyer & Katz, 2018; Filley & Kelly, 2018; Guenette, Shenton, & Koerte, 2018; Sussman, Pendharkar, Ho, & Ghajar, 2018). Mild TBIs are the most common, making up 70% to 90% of all TBIs (Holm, Cassidy, Carroll, & Borg, 2005), however

this percentage is likely to be higher, given that many people with mild TBIs do not seek medical help (Ruff et al., 2009).

Compared to more severe injuries, mild TBIs are harder to diagnose, primarily because the acute symptoms (e.g., PTA, confusion) generally resolve quickly and conventional neuroimaging (e.g., CT/MRI) rarely shows any abnormalities (Ruff et al., 2009; Shenton et al., 2012; Strauss et al., 2015). It was originally thought that mild TBIs only led to transient symptoms and that most people recover rapidly and entirely (i.e., within minutes to days following injury), however there is evidence to suggest that even a single mild TBI may lead to long-term cognitive and functional problems (Bigler, 2008; McInnes, Friesen, MacKenzie, Westwood, & Boe, 2017; McKee & Daneshvar, 2015). Persistent symptoms — such as memory and attention problems, headache, fatigue, irritability, depression and anxiety — that last longer than three months are referred to as persistent post-concussion symptoms or post-concussion syndrome (PCS) (Bigler, 2008), however PCS is controversial (see Arciniegas, Anderson, Topkoff, & McAllister, 2005). Approximately 15% to 30% of people who sustain a mild TBI are affected by persistent post-concussion symptoms (Bigler, 2008; McKee & Daneshvar, 2015; Shenton et al., 2012). This number may be even higher, with a recent review suggesting that approximately 50% of people with mild TBI have long-term issues (McInnes et al., 2017). The contribution of neurological damage and psychological or psychiatric factors to these symptoms continues to be debated (see Arciniegas et al., 2005; Dwyer & Katz, 2018) and some researchers argue that these symptoms are psychogenic (psychological rather than physical) in nature (see Snell, Macleod, & Anderson, 2016). Furthermore, litigation associated with mild TBI is a considerable confound that can lead to malingering and symptom invalidity (Goeke, 2017; Snell et al., 2016); however this issue varies between countries, due to different medical and litigation systems.

Moderate to severe TBI

Moderate and severe TBIs are less common than mild, each making up approximately 10% of all TBIs (Cristofori & Levin, 2015; Whitaker-Lea & Valadka, 2017). Consequently, moderate

and severe TBIs are frequently studied together, despite prognoses being better for moderate injuries (Einarsen et al., 2018). Moderate TBIs are indicated by a GCS of 9-12, PTA between one and seven days and LOC of 30 minutes to 24 hours, and severe TBIs are indicated by a GCS of 3-8, PTA of more than seven days and LOC of more than 24 hours (Amyot et al., 2015). Secondary brain injury is common following severe TBI and includes brain swelling, hypotension (low blood pressure), and hypoxaemia (low levels of oxygen in blood) (McKee & Daneshvar, 2015). Severe TBIs more frequently lead to poor outcomes, such as coma, vegetative state, disability and death, than moderate injuries (McKee & Daneshvar, 2015).

A recent large-scale study found that, 12 months after a moderate TBI, 6% of people had died, 8% were severely disabled and 44% had moderate disability, assessed using the extended Glasgow Outcome Scale (Einarsen et al., 2018). Poorer outcomes were associated with a number of variables, including lower GCS scores, older age, subdural haematomas, no alcohol intoxication on the day of injury, and preinjury disability (Einarsen et al., 2018). Another large-scale study of severe TBI reported that 38% of people who had survived a year post-injury were severely disabled, 43% had moderate disability and only 19% had recovered well (Jourdan et al., 2013). Poorer outcomes were related to older age, lower education and longer stays in intensive care (Jourdan et al., 2013). The findings of these two studies suggest that outcomes tend to be better following moderate than severe TBI.

Focal injuries are common following both moderate and severe TBIs, which can be identified using conventional neuroimaging (e.g., CT, MRI) (Shenton et al., 2012). These more serious injuries also frequently result in diffuse damage, the full extent of which cannot be visualised using conventional scans (Amyot et al., 2015). Finally, impairments (e.g., cognitive, behavioural, functional) tend to be worse and last longer following more severe injuries (Cristofori & Levin, 2015; Filley & Kelly, 2018).

1.5 Assessment and treatment of TBI

The main aim of neuroimaging and neuropsychological assessment following a TBI is to determine the extent of structural brain changes and the level of cognitive and behavioural impairment, in order to provide appropriate clinical care following a TBI (Niogi & Mukherjee, 2010). Treatment, on the other hand, is administered with the main aim of preventing and/or minimising secondary damage resulting from bleeding, inflammation and increased intracranial pressure, and reduced oxygen to the brain (Chua et al., 2007; Whitaker-Lea & Valadka, 2017).

Individuals often undergo neuroimaging in the acute post-injury period, with CT and conventional MRI scans frequently used to assess the location and extent of any brain damage, and to determine whether neurosurgical intervention is necessary (Amyot et al., 2015; Wilde, Hunter, & Bigler, 2014). Neurosurgery may be required, particularly following severe TBI, to stop intracranial bleeding, repair skull fractures and remove haematomas (blood clots), which may increase intra-cranial pressure and cause further damage. A decompressive craniectomy, in which a portion of the skull is temporarily removed to accommodate brain swelling, may also be performed to reduce intra-cranial pressure (Menon & Ercole, 2017; Whitaker-Lea & Valadka, 2017). In some cases, medications are additionally used to minimise secondary damage; including anti-convulsants to reduce the risk of brain injury caused by post-injury seizures, diuretics to reduce intracranial pressure, and sedatives to control pain and agitation (Menon & Ercole, 2017; Whitaker-Lea & Valadka, 2017).

Individuals may also undergo neuropsychological evaluations to assess the cognitive, behavioural, functional and emotional sequelae of TBI, generally in the post-acute period (Soble, Critchfield, & O'Rourke, 2017). Neuropsychological tests are used to identify cognitive deficits, allowing for prognosis and the development and evaluation of individual rehabilitation strategies (Prigatano & Borgaro, 2006; Soble et al., 2017). Where deficits are identified, people may require rehabilitation with input from a multidisciplinary team to assist their recovery (Chua et al., 2007).

These teams may comprise clinical psychologists, neuropsychologists, speech pathologists, physiotherapists, occupational therapists, vocational counsellors and social workers (Chua et al., 2007).

1.6 Outcome following traumatic brain injury: mortality, disability and impairments

There is enormous variability in outcomes following TBI, with some people returning to pre-injury levels of functioning, others living with long-term impairments, and others dying as a result of their injuries (Bigler & Stern, 2015). Mortality rates following TBI have decreased significantly over the years, with the Centers for Disease Control and Prevention reporting a 13.7% decrease in mortality from 1995 to 2010 (National, Vital, Statistics, & System, 2009), largely due to medical advances and improved intensive care and clinical interventions (Faul & Coronado, 2015; Khan et al., 2003). In 2015, a systematic review of TBI epidemiology in Europe reported that mortality rates from TBI ranged from 3 to 28 per 100,000 population per year (Brazinova et al., 2015). The number of TBI-related deaths vary depending on injury severity: mortality rates were estimated to be <1% following mild TBI (WHO, 2006), 0.9% to 8% following moderate injuries (Einarsen et al., 2018), and as low as 20% following severe TBI in well-resourced hospitals (Hawryluk & Bullock, 2016). Despite an overall decrease in mortality rates, the number of deaths from TBI remains higher in developing than developed countries, with the former less able to treat TBIs because of poorer facilities and limited resources (Hyder et al., 2007).

As mortality rates decrease, more people are living with TBI-related medical, physical, psychological, behavioural and/or cognitive impairments that impact on their daily lives. The severity and duration of these impairments varies considerably, even for those who sustain injuries of similar severities (Bigler & Stern, 2015). It is estimated that 55 million people are living with a TBI-related disability (James et al., 2019).

1.6.1 Medical and physical outcomes

The medical and physical sequelae of TBI include headaches (Lew et al., 2006; Lucas, Hoffman, Bell, Walker, & Dikmen, 2012); sleep disturbances (Castriotta & Murthy, 2011; Singh, Morse, Tkachenko, & Kothare, 2016); chronic pain (Lahz & Bryant, 1996; Moshourab, Schafer, & Al-Chaer, 2015); balance issues, dizziness and vertigo (Fife & Giza, 2013; Szczupak, Hoffer, Murphy, & Balaban, 2016); and gait problems (Williams, Morris, Schache, & McCrory, 2009). Additionally, TBIs may increase the risk of long-term neurological disorders, such as Alzheimer's disease (Bazarian, Cernak, Noble-Haeusslein, Potolicchio, & Temkin, 2009), dementia (Plassman & Grafman, 2015), post-traumatic epilepsy (Christensen, 2015; Frey, 2003), chronic traumatic encephalopathy, which is a degenerative disorder caused by multiple concussions (Filley & Kelly, 2018; Montenigro, Corp, Stein, Cantu, & Stern, 2015), and stroke (Albrecht et al., 2015). A link between TBI and Parkinson's disease has also been found (Crane et al., 2016; Dick et al., 2007).

The rates of people affected by medical and physical issues following a TBI vary significantly between studies. For example, 30% to 90% of people suffer from post-traumatic headaches (Lew et al., 2006) and 30% to 70% of people reportedly have sleep disturbances (Singh et al., 2016). Differences in the definition, diagnostic and inclusion criteria used by researchers may account for these variable estimates (Singh et al., 2016). The association between TBI and other disorders (e.g., Alzheimer's disease) is also contentious. For example, multiple studies have reported that Alzheimer's disease is associated with a prior TBI (for reviews, see Bazarian et al., 2009; Filley & Kelly, 2018), but a recent meta-analysis found insufficient evidence to link the two (Julien et al., 2017).

1.6.2 Psychological and behavioural outcomes

Psychological problems, including depression and anxiety, are common following TBI. A recent meta-analysis reported that 27% of people are diagnosed with major depressive disorder or dysthymia and 38% self-report clinically significant levels of depression following a TBI (Osborn,

Mathias, & Fairweather-Schmidt, 2014). In addition, 11% of people are diagnosed with generalised anxiety disorder, with clinically-significant levels of anxiety being reported by 37% of persons after their TBI (Osborn, Mathias, & Fairweather-Schmidt, 2016). However, the prevalence of depression and anxiety vary considerably depending on injury severity, diagnostic criteria, the measure used to assess symptoms, and the time post-injury at which a person is assessed (Osborn et al., 2014, 2016).

TBI has also been associated with post-traumatic stress disorder (Gill, Mullin, & Simpson, 2014; Hendrickson et al., 2018b; Motzkin & Koenigs, 2015), substance abuse (Weil et al., 2016), emotional dysregulation (Ashman, Gordon, Cantor, & Hibbard, 2006), and suicidal thoughts and attempts (Fisher et al., 2016). Behavioural changes are also common following TBI and include increased aggression (Hesdorffer et al., 2009); apathy, which may manifest as reduced goal-directed behaviour (fewer interests, decreased effort and/or productivity), indifference, or a lack of emotional response to events (Starkstein & Pahissa, 2014); or irritability and impatience (Trevena & Cameron, 2011), all of which can negatively affect rehabilitation.

1.6.3 Cognitive outcomes

Cognitive impairments are common following TBIs, with enormous heterogeneity in the severity and duration of these impairments (Bigler & Stern, 2015). In general, the severity and chronicity of cognitive impairments is related to TBI severity (Cristofori & Levin, 2015; Dikmen et al., 2009; Filley & Kelly, 2018). The most commonly affected cognitive domains are memory, attention, executive functioning (including planning, self-monitoring and problem solving) and processing speed (Bigler, 2007; Cristofori & Levin, 2015; Dikmen et al., 2009; Mathias & Wheaton, 2007; Rabinowitz & Levin, 2014), with deficits in general intelligence, reasoning, verbal and language skills, awareness, and visuospatial reasoning also reported (Konigs et al., 2016; Rabinowitz & Levin, 2014). Cognitive impairments may lead to lower life satisfaction and health-related quality of life (Gorgoraptis et al., 2019).

Memory

Memory impairments affect 69% to 80% of people with TBI and frequently persist for longer than other cognitive problems (Barker-Collo & Feigin, 2008). In particular, people with TBI tend to show deficits in episodic and verbal memory (Dikmen et al., 2009; Filley & Kelly, 2018), however prospective memory can also be affected (Mathias & Mansfield, 2005). These impairments are largely thought to be due to damage to the hippocampus and temporal lobe caused by non-penetrating TBIs (Cristofori & Levin, 2015).

Memory impairments can occur after TBIs of all severities, however the literature relating to mild TBI is mixed. Although everyday memory problems are frequently reported by people with mild injuries, some studies have failed to find evidence of these problems (e.g., Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Wammes, Good, & Fernandes, 2017). In contrast, other researchers have found evidence of memory problems in veterans who sustained mild TBIs, even after controlling for the psychiatric problems (e.g., post-traumatic stress disorder) that are frequently comorbid with TBI, particularly in military populations (Vanderploeg, Belanger, & Curtiss, 2009; Vanderploeg, Curtiss, Luis, & Salazar, 2007). In another study, a mild TBI group tested five years post-injury displayed deficits in episodic and autobiographical, but not semantic memory, in the absence of more general cognitive decline (Wammes et al., 2017).

On the other hand, more severe injuries lead to longer-term memory problems, which have been detected 10 years following moderate to severe injury (Ponsford, Downing, et al., 2014). These impairments can affect many aspects of a person's life, leading to difficulties interacting with others, completing simple everyday tasks, living independently, and maintaining a job (Barker-Collo & Feigin, 2008; Cristofori & Levin, 2015).

Attention

Attention enables an individual to select relevant information from the environment for further cognitive processing (Cohen, 2014). Attention encompasses a range of cognitive and

behavioural processes that involve broad neural networks and include focused, selective, divided, sustained, directed, controlled, voluntary and automatic attention (Cohen, 2014). Due to the diffuse nature of TBI, these injuries can lead to problems in many different types of attention (Ponsford, Downing, et al., 2014) and attentional deficits have been associated with damage to various brain regions, including the frontal and parietal regions (i.e., frontoparietal attentional network), precentral gyrus, bilateral cingulate, medial frontal, middle frontal and superior frontal gyri (Cristofori & Levin, 2015).

Overall, attentional impairments tend to be worse for those with more severe injuries, with up to 60% of people who sustain moderate to severe TBIs experiencing long-term problems (Draper & Ponsford, 2008; Ponsford, Bayley, et al., 2014; Ponsford, Downing, et al., 2014). Attentional problems have also been reported following mild TBI (e.g., Bigler & Snyder, 1995; Mathias, Beall, & Bigler, 2004; Owens, Spitz, Ponsford, Dymowski, & Willmott, 2018), however these largely recover between one week and six months post-injury (Cristofori & Levin, 2015). Impairments to attention have been associated with difficulty concentrating, fatigue, confusion and lack of intention (Cohen, 2014). These impairments can affect almost every activity, especially those requiring concentration over time (e.g., work, school/study, maintaining social relationships) (Ponsford, Downing, et al., 2014).

Divided attention is frequently affected by TBI. For instance, people with mild to severe TBIs were slower than controls to complete tests of divided attention, selective attention, working memory and processing speed, but were not less accurate, indicating that the TBI group may have sacrificed speed for accuracy (Owens et al., 2018). Attention is strongly associated with processing speed (Park, Moscovitch, & Robertson, 1999; Ponsford & Kinsella, 1992) and these abilities are challenging to assess in isolation. Indeed, some researchers have suggested that deficits in attention may be the result of slowed processing speed (see Azouvi, Arnould, Dromer, & Vallat-Azouvi, 2017; Mathias & Wheaton, 2007; Owens et al., 2018; Ponsford & Kinsella, 1992).

Executive functioning

Executive functioning is an 'umbrella term' (Chan, Shum, Toulopoulou, & Chen, 2008; Jewsbury, Bowden, & Strauss, 2016) that is used to refer to a range of cognitive processes, including planning, working memory, problem solving, monitoring, metacognition (thinking about thinking), mental flexibility and inhibition (Cristofori & Levin, 2015; Kennedy et al., 2008). Executive functions also help to facilitate and coordinate other cognitive functions, including memory and attention (Cristofori & Grafman, 2017). However, unlike other cognitive functions, executive functioning is not well defined or understood, making it challenging to assess (Chan et al., 2008; Jewsbury et al., 2016).

Executive functions are thought to be controlled by the prefrontal cortex, which is extremely vulnerable to damage following TBI because of its proximity to bony protrusions on the inside of the skull (Cristofori & Levin, 2015). Many TBI patients with frontal lobe damage experience impairments in one or more types of executive function (Cristofori & Grafman, 2017; Miyake et al., 2000). These impairments can lead to issues with other cognitive domains (e.g., memory and attention) and can affect emotion and behaviour, social functioning, overall independence, and quality of life (Cristofori & Grafman, 2017; Cristofori & Levin, 2015; Rabinowitz & Levin, 2014).

Studies have found impairments in executive functioning, after both mild (e.g., Erez, Rothschild, Katz, Tuchner, & Hartman-Maeir, 2009; Frencham, Fox, & Maybery, 2005) and moderate to severe TBI (Demery, Larson, Dixit, Bauer, & Perlstein, 2010). One study found that people with moderate to severe TBI performed worse than controls on a number of tests (Trail Making Test A and B; Stroop Interference; Paced Auditory Serial Addition Test; Digit Symbol), but people with mild TBI only performed worse than controls on the Trail Making Test B. Further, the Digit Span Backward Test was most accurate in differentiating TBI, suggesting the utility of this test following TBI (Demery et al., 2010).

Recovery of cognitive impairments

Over time, cognitive functioning can recover, depending on the severity of the injury (Cristofori & Levin, 2015; Filley & Kelly, 2018; Schretlen & Shapiro, 2003). Approximately 85% to 95% of people with mild TBI recover to their pre-injury levels of cognitive functioning (Cristofori & Levin, 2015). Most of this recovery takes place within the first few weeks and, for the majority who sustain a mild TBI, cognitive impairments resolve within one to six months post-injury (Belanger et al., 2005; Cristofori & Levin, 2015; Schretlen & Shapiro, 2003). Indeed, a meta-analysis found that memory, working memory and attention, executive functioning, and processing speed may all be affected in the acute period following mild TBI, however by three months post-injury, cognitive performance was comparable to that of healthy controls (Frencham et al., 2005).

These findings are not supported by other studies, which report that 15% to 30% of those with mild TBI experience long-term cognitive and functional deficits (McKee & Daneshvar, 2015; Shenton et al., 2012). In fact, this number may be even higher, with a recent review reporting that approximately 50% of people who sustain a single mild TBI exhibit long-term cognitive problems (McInnes et al., 2017). As noted, however, whether mild TBI leads to long-term impairment remains contentious, with some researchers believing these symptoms may be the result of psychological factors, rather than neurological damage (Snell et al., 2016).

Individuals who sustain moderate to severe injuries, on the other hand, tend to experience more serious cognitive problems that recover more slowly than those with mild TBIs (Dikmen et al., 2009). Indeed, people with moderate to severe TBI may have deficits in memory, executive functioning and processing speed ten years post-injury (Draper & Ponsford, 2008). It is estimated that 60% of people with moderate TBI, but only 15% to 20% of people with severe injuries, return to pre-injury cognitive levels (Cristofori & Levin, 2015; Filley & Kelly, 2018).

Although long-term deficits have been found, some cognitive domains recover, at least partially. For instance, memory performance improved significantly in a sample of moderate to

severe TBI patients who were examined every month between six and 12 months following injury (Novack, Alderson, Bush, Meythaler, & Canupp, 2000). Improvements were also seen in processing speed, language and construction, but to a lesser extent (Novack et al., 2000). Similarly, patients with moderate to severe TBI who were examined three, six and 12 months after their injury showed improvements in executive functioning and verbal learning at each assessment (Rabinowitz, Hart, Whyte, & Kim, 2017). In contrast, processing speed initially improved, then declined (older participants) or plateaued (younger participants) (Rabinowitz et al., 2017).

Studies have also shown that most recovery occurs soon after the injury (after regaining consciousness). For instance, moderate to severe TBI patients tested at three time points (two, five and 12 months post-injury) showed improvements to every cognitive domain that was assessed — memory, executive functioning, attention, processing speed, verbal skill and visuospatial reasoning — but there was greater recovery between two and five months, compared to five and 12 months (Christensen et al., 2008). However, at 12 months, cognitive performance in all domains was still below the normative average (Christensen et al., 2008). Recovery can also take place more than 12 months post-injury, but few studies have examined longer-term cognitive outcomes (e.g., years to decades; Filley & Kelly, 2018).

Although recovery of cognitive functioning is associated with the severity of injury, it is also dependent on a range of other variables. These include the location and extent of damage, age, educational attainment, premorbid functioning, psychiatric comorbidities, social support, and recovery mechanisms (e.g., brain plasticity) (Bigler & Stern, 2015; Cristofori & Levin, 2015). It has been suggested that these factors contribute to a person's level of 'cognitive reserve' — a theory that was developed as a possible explanation for the discrepancy between brain pathology and the clinical manifestation of that damage (Bigler & Stern, 2015; Stern, 2009). The cognitive reserve hypothesis/theory posits that reserve accumulates throughout life through educational and occupational attainment, and by engaging in mentally, socially and physically stimulating

leisure activities, which interact to provide a buffer against damage (Stern, 2009). Theoretically, a person with more cognitive reserve can withstand more damage before showing symptoms of that damage (e.g., cognitive, behavioural, functional impairments) (Bigler & Stern, 2015; Stern, 2002, 2009), however research into cognitive reserve and TBI is limited (see Mathias & Wheaton, 2015 for a meta-analysis).

1.6.4 Daily living activities, work/study participation, interpersonal relationships

Physical, psychological, behavioural and cognitive sequelae can lead to difficulties with activities of daily living, work or study, and interpersonal relationships. For example, the ability to perform daily activities — including shopping, driving, using public transport, cooking, cleaning, and caring for children — may be diminished and/or people may require assistance to complete these tasks (Goverover, Genova, Smith, Chiaravalloti, & Lengenfelder, 2017; Griffen & Hanks, 2014). A person's capacity to work or study may also be affected; indeed, rates of unemployment are high following a TBI, ranging from 60% to 80%, with more severe injuries being associated with higher rates of unemployment (Griffen & Hanks, 2014).

In addition, relationships with partners or spouses, children, parents and friends are sometimes affected by TBI due to mood disorders; reduced independence, confidence and sense of identity; and/or changes to behaviour and personality (Bay, Blow, & Yan, 2012). Changes in leisure and social activities are also common, with individuals unable to participate in, or no longer enjoying, the same activities that they previously did (Goverover et al., 2017; Wise et al., 2010). For instance, people with moderate to severe TBIs were more likely to engage in sedentary and less social activities (e.g., watching television, spending time on the computer) compared to the social and active hobbies they engaged in prior to their injuries (e.g., participating in sport, partying, consuming alcohol) (Wise et al., 2010). Overall, these changes in day-to-day activities can lead to decreased life satisfaction and quality of life (Goverover et al., 2017; Williams, Rapport, Millis, & Hanks, 2014).

1.6.5 Impaired self-awareness

Many people who sustain a TBI are unaware of the deficits and impairments they experience as a consequence of their injury (Geytenbeek, Fleming, Doig, & Ownsworth, 2017). This lack of awareness has been linked with lesions in the parietal and frontal lobes (Cristofori & Levin, 2015) and is frequently worse in those with more severe injures (Geytenbeek et al., 2017). For instance, one study found that people with mild to moderate TBI had impaired self-awareness at hospital discharge, and one, three and six months after discharge (38%, 50%, 25% and 25% of mild-moderate participants, respectively) (Geytenbeek et al., 2017). Rates of impaired self-awareness were higher for people with severe injuries (62—79% of people with severe TBI) (Geytenbeek et al., 2017). Other studies have reported that self-awareness is impaired in 28% to 97% of people with TBI (e.g., Engel, Chui, Goverover, & Dawson, 2019; Evans, Sherer, Nick, Nakase-Richardson, & Yablon, 2005). Although it is more common for people to be unaware of the problems associated with their injury in the acute phase, underestimation of their long-term cognitive, behavioural and functional impairments is also common (Geytenbeek et al., 2017), and may persist for more than five years following moderate to severe TBIs (Kelley et al., 2014).

People with impaired self-awareness may not understand their need for rehabilitation and/or support with tasks and may therefore be less likely to engage with rehabilitation programs (Geytenbeek et al., 2017). Additionally, they may set unrealistic goals or exhibit low motivation (Evans et al., 2005). Impaired self-awareness has also been associated with decreased independence and community integration, poor social relationships, and poor employment outcomes (Geytenbeek et al., 2017; Kelley et al., 2014; Sherer et al., 1998). Conversely, increased self-awareness is associated with decreased life satisfaction (Evans et al., 2005) and emotional distress, suggesting that a lack of awareness may protect against emotional distress (Geytenbeek et al., 2017).

1.7 Summary

TBI is a significant public health problem that affects approximately 30 million people each year (James et al., 2019). These injuries are predominantly caused by motor vehicle accidents, falls, assaults and sports (Marshman et al., 2013; WHO, 2006), and males are more likely than females to sustain a TBI (Langlois Orman et al., 2011). Non-penetrating TBIs are the most common and can result in focal and/or diffuse damage (McKee & Daneshvar, 2015). This damage is further classified as primary (sustained at the time of injury) or secondary (can persist for years post-injury) in nature; primary damage cannot be reversed but it is possible that secondary damage may be prevented, managed or reversed (Hawryluk & Bullock, 2016). In particular, secondary WM degeneration resulting from DAI can continue for years post-injury and is thought to be a primary contributor to the physical, psychological, behavioural and cognitive impairments that frequently occur after TBIs (Hill et al., 2016; Hulkower et al., 2013).

These impairments may lead to issues with daily activities, work, school or community involvement, and interpersonal relationships (Goverover et al., 2017; Wise et al., 2010). As a result, TBIs can lead to decreased life satisfaction and quality of life (Williams et al., 2014). Impairments may be short- or long-term, potentially leading to lifelong disabilities, and tend to be worse for more severe injuries (Cristofori & Levin, 2015).

In order to evaluate the damage resulting from a TBI, people frequently undergo neuroimaging to determine the location and extent of any damage (Amyot et al., 2015). However, traditional neuroimaging modalities are limited in the assessment of mild TBI, which make up the majority of all TBIs, and also underestimate the WM damage that is a primary contributor to impairments following TBI (Ruff et al., 2009; Strauss et al., 2015). Advanced neuroimaging techniques, such as diffusion tensor imaging (DTI), are now able to identify this microstructural WM damage (Suri & Lipton, 2018), which may lead to the identification of

individuals likely to exhibit long-term impairment, possibly allowing for early intervention and rehabilitation.

CHAPTER 2: DIFFUSION TENSOR IMAGING

The following chapter reviews the literature on neuroimaging and its use in the assessment of TBI. Conventional neuroimaging techniques (CT and MRI) will be introduced first, focussing on issues associated with their use. DTI will then be reviewed, including how it works, methods of analysis, use in TBI, and issues associated with its use. Finally, a novel method used to analyse diffusion-weighted imaging data, known as fixel-based analysis (FBA), will be introduced.

2.1 Conventional neuroimaging

When an individual sustains a TBI, they frequently undergo neuroimaging in the acute phase after injury (Amyot et al., 2015; Douglas et al., 2018). Neuroimaging is used to identify the location and extent of damage, and to determine whether immediate medical and/or surgical interventions are required (Niogi & Mukherjee, 2010). Additionally, acute neuroimaging can provide information regarding the severity of an injury and may help to predict functional and cognitive outcomes (Amyot et al., 2015).

2.1.1 Computed tomography

Neuroimaging has advanced rapidly since CT first became available in the 1970s (Amyot et al., 2015; Shenton et al., 2012), but this imaging modality remains the most commonly used to assess acute TBI (Douglas et al., 2018). Images are generated using narrow x-ray beams that rotate around the body; signals are then used to generate 'slices' (i.e., cross-sectional, two-dimensional images), which can be grouped together digitally to create three-dimensional representations of the head (Amyot et al., 2015). CT scans are fast to complete and can identify focal injuries (e.g., skull fracture, haemorrhage, oedema) to determine whether immediate surgical interventions are required (Amyot et al., 2015; Bigler & Maxwell, 2011; Wilde et al., 2014), making them particularly useful for moderate to severe TBIs. For instance, CT

abnormalities have been found in 90% of people with severe TBI (Wilde et al., 2014). Importantly, life-support machinery and monitoring equipment can be accommodated during CT scanning (Shenton et al., 2012).

Although CT is useful in cases of moderate to severe TBI, it is not sensitive enough to identify subtle pathology or microstructural alterations, such as those seen in DAI (Bigler & Maxwell, 2011; Douglas et al., 2018; Koerte et al., 2016). CT therefore has limited utility in the assessment of mild TBI, with less than 10% of mild TBIs showing CT abnormalities (Smits et al., 2008). Further, CT scans do not detect any damage in up to 20% of cases of moderate to severe TBI, with scans at admission appearing normal or near normal (Amyot et al., 2015). Furthermore, CT scans are not very useful for predicting outcomes (Niogi & Mukherjee, 2010; Strauss et al., 2015). Additional disadvantages of CT include the risks associated with moving the patient, including exacerbating neck or back injuries, and exposing the patient to radiation, which can lead to an increased risk of cancer (Brody et al., 2007; Kutanzi, Lumen, Koturbash, & Miousse, 2016).

2.1.2 Magnetic resonance imaging

MRI is also used regularly in the acute period following TBI, 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). First used in the mid-1980s, MRI uses magnetic fields and radiofrequency pulses to alter the alignment of hydrogen protons in water molecules in the body, generating a spatially encoded signal that is used to create images (Amyot et al., 2015; Shenton et al., 2012). The strength of the magnetic field is measured using Tesla (T); initially, low-field magnets were used (0.5T), with stronger magnets used in clinical practice today (generally 1.5 or 3T) and research settings (up to 7T) (Moenninghoff et al., 2015; Wardlaw et al., 2012).

MRI is considerably more sensitive than CT (Bigler et al., 2016; Guenette et al., 2018), with MRI abnormalities identified in 30% of people with TBI who had normal CT scans (Niogi &

Mukherjee, 2010). MRI is safer than CT because it does not use radiation (Shenton et al., 2012). In addition to identifying macroscopic damage in the acute phase, MRI can also be used in the subacute and chronic phases following TBI to monitor the progress of structural damage and identify the long-term effects of TBI (Bigler & Maxwell, 2011; Koerte et al., 2016). Different types of images can be produced during MRI acquisition; the contrast between grey and white matter can be seen, allowing for the visualisation of large WM tracts and some WM changes resulting from moderate to severe TBI (Niogi & Mukherjee, 2010).

Although more sensitive, MRI underestimates microstructural damage (e.g., DAI) and is therefore limited in the assessment of mild TBI (Koerte et al., 2016; Strauss et al., 2015). MRI scans also take longer to complete than CT and are contraindicated in individuals with claustrophobia or metallic objects in their bodies (Shenton et al., 2012). These scans are also quite poor at predicting cognitive and functional outcomes (see Niogi & Mukherjee, 2010; Strauss et al., 2015), potentially due to their inability to identify the microstructural changes that frequently cause impairments following TBI (Arfanakis et al., 2002; Huisman et al., 2004; Hulkower et al., 2013). The development of more sensitive scans, such as diffusion-weighted imaging and DTI, has allowed for the investigation of microstructural damage, such as that occurring in mild TBI and DAI.

2.2 Diffusion-weighted imaging and diffusion tensor imaging

Diffusion-weighted imaging is an advanced MRI sequence that is based on the principle of Brownian motion: that the diffusion of water molecules is random when there are no cellular structures to inhibit it (Shenton et al., 2012). First used with humans in 1991 (Le Bihan, 1991), diffusion-weighted imaging measures the diffusion of water molecules within the brain. The diffusion profile varies depending on the cellular structure of the tissue being investigated (i.e., cerebrospinal fluid, WM, grey matter) and is altered when cellular structures are damaged due to injury or disease (Huisman, 2010; Shenton et al., 2012).

DTI (Basser, Mattiello, & LeBihan, 1994) is an extension of diffusion-weighted imaging and involves the calculation of a 'diffusion tensor' from diffusion-weighted scans measured in a single direction. At least six non-collinear directions are required to calculate the 'tensor', in addition to one scan with no diffusion-weighting (Basser et al., 1994; Newcombe, Das, & Cross, 2013; Niogi & Mukherjee, 2010; Strauss et al., 2015). Different measures can be calculated from the diffusion tensor, with fractional anisotropy (FA) and mean diffusivity (MD; also known as apparent diffusion coefficient; ADC) being the most common of these (Douglas et al., 2018; Koerte et al., 2016). Unlike CT and conventional MRI, DTI can be used to assess the microstructural properties of WM (Strauss et al., 2015).

Diffusion occurs in 'ellipsoids' and, 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 symmetric diffusion ellipsoid and is known as 'isotropic' diffusion (Amyot et al., 2015; Huisman, 2010). In WM regions, diffusion is restricted by microstructural elements, such as axonal membranes, myelin sheaths, neurofilaments and microtubules (Koerte et al., 2016; Strauss et al., 2015). Diffusion occurs freely parallel to axons when these structures are intact (i.e., healthy brains), but is restricted in other directions. 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). The DTI metric used to quantify the directional dependence of diffusion is FA, which is measured on a scale of 0 (reflecting isotropic/spherical diffusion) to 1 (indicating anisotropic/directional diffusion) (Newcombe et al., 2013; Suri & Lipton, 2018). In adult WM, higher values may indicate WM integrity, while lower values may reflect WM damage (Koerte et al., 2016; Voelbel et al., 2012).

In contrast, MD or ADC provide an average of the rate or magnitude of diffusion (Amyot et al., 2015; Douglas et al., 2018; Voelbel et al., 2012). The microstructural organisation of WM restricts MD and, therefore, low MD values are thought to indicate healthy WM, with high MD values reflecting WM damage (Niogi & Mukherjee, 2010).

2.2.1 Methods of analysis

There are a number of methods that are used to analyse DTI data and to calculate various DTI measures (e.g., FA, MD), each of which has its own strengths and limitations (Strauss et al., 2015). These methods can be broadly grouped into two categories: regional analyses (e.g., region of interest: ROI, tractography) and whole brain approaches (e.g., histogram, voxel-based analysis) (Hulkower et al., 2013; Niogi & Mukherjee, 2010). There is no one method that is optimal under all circumstances, with the most appropriate method dependent on the aims of the DTI examination (Newcombe et al., 2013; Van Hecke & Emsell, 2016).

One of the most popular regional methods used to analyse DTI data is ROI analysis, in which mean or median diffusion metrics (e.g., FA, MD) are extracted from pre-defined brain regions (Hulkower et al., 2013; Jones & Cercignani, 2010; Van Hecke & Emsell, 2016). ROI analysis is relatively easy to perform and, due to the regionally-specific information it provides, is particularly useful in studies that have a-priori hypotheses about which regions of the brain will be affected, or the location of differences between groups (e.g., patients and controls) (Hulkower et al., 2013; Niogi & Mukherjee, 2010). ROIs can be identified manually or automatically. Manual identification is subjective, time-consuming and can be affected by both inter- and intra-rater variability, although training may help to minimise these issues. Alternatively, automated or semi-automated ROI placement algorithms may be implemented in which individual brains are registered to a template, but these can be inaccurate when pathology is present (Van Hecke & Emsell, 2016). ROI analysis cannot be used to investigate the whole brain because it uses pre-determined specific locations (Newcombe et al., 2013). When multiple ROIs are selected, more

statistical tests are conducted and corrections for multiple comparisons are required (Van Hecke & Emsell, 2016). ROI analysis may also underestimate individual differences in the extent and location of any damage, instead providing an overview of the most typically damaged regions within a group (Hulkower et al., 2013; Niogi & Mukherjee, 2010). Despite this, ROI analyses continue to provide a popular and simple method for investigating region-specific hypotheses (Van Hecke & Emsell, 2016).

Tractography, or fibre tracking, is a newer type of regional analysis that was developed to investigate entire WM tracts (Niogi & Mukherjee, 2010). Seed ROIs — selected ROIs used as a starting point for the tractography — are identified manually or automatically and, using the directional diffusion information from the DTI data, WM tracts are reconstructed by following the long, principle axis of the diffusion ellipsoid (Van Hecke & Emsell, 2016). Mean or median DTI metrics (e.g., FA, MD) can then be calculated for the entire WM pathway (Niogi & Mukherjee, 2010; Van Hecke & Emsell, 2016). The main strength of tractography is that it provides information about connectivity; researchers can determine how connections between different brain regions relate to functional outcomes (Shenton et al., 2012). Tractography is also more reproducible than ROI analysis because, in general, few ROIs are required to reconstruct WM tracts (Van Hecke & Emsell, 2016). However, these reconstructions are simplistic and are not directly related to underlying anatomy or pathology; instead they are virtual, mathematical representations of the WM tract that reflect water diffusion (Strauss et al., 2015; Van Hecke & Emsell, 2016). Although the water diffusion tends to suggest the underlying anatomy, the reconstructions are particularly affected by multiple WM tracts (i.e., crossing fibres) and/or different tissue types (i.e., partial volume effects) contained within single voxels[2] (Jones, Knosche, & Turner, 2013; Strauss et al., 2015; Van Hecke & Emsell, 2016).

[2] A voxel is a unit of a three-dimensional image; comparable to a pixel in a two-dimensional image

Tractography provides regionally-specific information, and may underestimate microstructural, localised damage because it averages measures across the whole tract. In addition, this method requires a-priori hypotheses about where differences will be found, because specific tracts are reconstructed and, as with regional analyses, the whole brain is not investigated (Smith et al., 2006). Like ROI analysis, there are issues associated with manual and automatic placement of ROIs: manual placement is operator dependent and automatic placement can be inaccurate when pathology is present (Van Hecke & Emsell, 2016). Multiple comparison corrections are also required if multiple tracts are examined (i.e., more statistical tests are performed) (Van Hecke & Emsell, 2016).

Whole brain approaches, on the other hand, provide quantitative DTI information for the entire brain. One method, known as histogram analysis, involves the extraction of DTI measures (e.g., FA, MD) from all voxels of interest (e.g., all WM voxels) within the brain (Van Hecke & Emsell, 2016). These measures are then summarised in a histogram, providing a frequency distribution of voxels with a particular value of the parameter of interest (e.g., FA, MD) (Van Hecke & Emsell, 2016). Mean or median values of the diffusion measures (e.g., FA, MD) are then extracted from these data and compared between groups in order to identify global changes to the WM (Van Hecke & Emsell, 2016). Histogram analysis is reasonably simple and fast, is not labour-intensive (e.g., compared to ROI/tractography) and can be used for exploratory studies; hypotheses about the location of differences are not required (Jones & Cercignani, 2010; Van Hecke & Emsell, 2016). In addition, fewer statistical tests are completed, thus the problem of multiple comparisons is minimised (Van Hecke & Emsell, 2016). However, because DTI measures are averaged across all WM voxels in the brain, global changes are identified and specific regions cannot be investigated (Niogi & Mukherjee, 2010; Van Hecke & Emsell, 2016). Partial volume effects, which occur when there is more than one type of tissue present in a single voxel (e.g., WM, grey matter), are particularly problematic for this type of analysis and can lead to inaccurate measures at the edge of WM structures (Van Hecke & Emsell, 2016).

Another whole-brain approach is known as voxel-based analysis. DTI measures (e.g., FA) are calculated for every individual voxel within the brain, providing overall information about whole-brain changes in addition to changes at the individual voxel level — the smallest scale possible (Van Hecke & Emsell, 2016). Voxel-based analysis is fully automated, thus, there is no risk of inter- or intra-rater variability (Strauss et al., 2015). Thousands of statistical analyses are completed during a voxel-based analysis (i.e., in each voxel) and it is crucial that multiple comparisons corrections are applied (Van Hecke & Emsell, 2016). A-priori hypotheses and specification of regions of interest are not required when using voxel-based analysis, making it appropriate for exploratory studies (Niogi & Mukherjee, 2010; Smith et al., 2006). Voxel-based analysis is, however, technically demanding and there are several sources of potential error that can arise using this method, including issues with image alignment, spatial normalisation, which is a registration step that is performed to ensure that voxels correspond across different people, and the interpretation of results (Strauss et al., 2015; Van Hecke & Emsell, 2016).

2.2.2 Diffusion tensor imaging in traumatic brain injury

DTI is more sensitive to microstructural WM changes than CT and conventional MRI and has therefore been used to investigate WM integrity following TBI (e.g., Aoki et al., 2012; Hulkower et al., 2013; Roberts, Mathias, & Rose, 2014). The majority of studies have found lower FA and higher MD following adult TBI, especially in the subacute and chronic phases post-injury, which may reflect demyelination, gliosis, or more permanent axonal degeneration (see Amyot et al., 2015; Niogi & Mukherjee, 2010; Shenton et al., 2012 for reviews). However, DTI performed in the acute stages after injury has revealed some conflicting findings. For example, several studies have found that FA was higher and MD was lower when DTI was performed soon after injury (e.g., within 72 hours, 1 week and 12 days post-injury; Bazarian et al., 2007; Huisman et al., 2004; Mayer et al., 2010). These discrepant findings may be attributable to axonal swelling. Further complicating the matter is the fact that there is little consensus regarding what constitutes 'acute'

and/or 'short-term', which may include one (Huisman et al., 2004; Zhu et al., 2014) or two weeks after injury (Hulkower et al., 2013), or not be clearly defined (Niogi & Mukherjee, 2010; Strauss et al., 2015).

WM changes have been consistently identified using DTI in a number of brain regions, particularly in the subacute and chronic post-injury periods. The most commonly examined regions are large WM tracts that are known to be susceptible to TBI, most notably the CC. This region is particularly vulnerable to DAI given its anatomical shape and location (Shiramizu et al., 2008; Uchino, Takase, Nomiyama, Egashira, & Kudo, 2006) and has displayed alterations in both FA and MD in many studies (Amyot et al., 2015; Hulkower et al., 2013). Additionally, regions such as the corona radiata, uncinate fasciculus, superior and inferior longitudinal fasciculus, internal and external capsule, fornix, cingulum, and centrum semiovale frequently show WM alterations, most typically lower FA/higher MD, following TBI (see Amyot et al., 2015; Filley & Kelly, 2018; Hulkower et al., 2013; Niogi & Mukherjee, 2010 for reviews). However, examination of other brain regions has led to conflicting findings and the extent of damage varies between studies (Shenton et al., 2012). Furthermore, there are considerable methodological differences between the studies: research has been conducted into different severities of injury, with varied intervals between injury and examination, and a wide range of brain regions has been examined (Hulkower et al., 2013; Shenton et al., 2012). There has yet to be a meta-analysis synthesising the findings from different studies to determine the location and extent of WM changes following TBIs of all severities.

There is some evidence to suggest that DTI findings from various brain regions are related to functional outcomes (e.g., Castano-Leon et al., 2018; Newcombe et al., 2011) and cognitive impairments following TBI (e.g., Arenth, Russell, Scanlon, Kessler, & Ricker, 2014; Gu et al., 2013; Palacios et al., 2011). Studies have found that compromised WM (lower FA, higher MD) is associated with cognitive impairment, most notably in the domains of memory, attention,

executive functioning and processing speed (see Filley & Kelly, 2018; Shenton et al., 2012 for reviews). However, the strength and direction of the relationship between cognition and the DTI findings vary between studies, and may be dependent on the brain region/cognitive domain examined, the timing of the examination, scanning parameters (e.g., voxel size, magnet strength, number of diffusion-weighted images) and the test/outcome measure used (Hulkower et al., 2013). Many studies have also used small samples. Thus, conclusions regarding the relationship between DTI findings and cognition have been limited.

2.3 Limitations of diffusion tensor imaging

Despite the advantages of DTI, there are numerous pitfalls concerning the acquisition, analysis and interpretation of DTI data (Jones et al., 2013) that may be barriers to using DTI in clinical settings. Firstly, there is currently insufficient evidence that DTI can detect WM changes in individuals following a TBI (see review by Douglas et al., 2018). Rather, most methods of analysis utilise group comparisons (e.g., comparing TBI patients with controls), which are useful for highlighting regions that are commonly affected by TBI, however they underestimate individual differences in the magnitude and location of this damage. This is a significant issue given that TBI is extremely heterogeneous (Douglas et al., 2018; Hulkower et al., 2013; Koerte et al., 2016; Lepage et al., 2018). For DTI to have clinical utility, it must accurately and reliably identify damage resulting from TBI in individual patients (Strauss et al., 2015). Subject-specific analyses are starting to be used (e.g., Guenette et al., 2018; Lepage et al., 2018). Particularly promising is the development of normative databases to which individuals can be compared (Guenette et al., 2018; Koerte et al., 2016; Strauss et al., 2015), although more research is needed to determine whether DTI is appropriate for clinical practice.

Secondly, there are a number of scanner variables and acquisition parameters that may affect DTI findings. Different scanners (e.g., different brands, models, magnet strength) can produce disparate findings, even if all other acquisition parameters (e.g., b-values that measure

the strength and timing of the diffusion-weighting, voxel size, number of diffusion-weighted images) are identical; these issues can be mitigated by using the same scanner for all participants when conducting research (Strauss et al., 2015). Further, the strength of the magnet may affect the findings, with 3T magnets having shorter acquisition times and clearer, less grainy images (i.e., better signal to noise ratio) than 1.5T magnets (Strauss et al., 2015; Wardlaw et al., 2012). Additionally, there are a range of data acquisition parameters that must be chosen, including the b-values, voxel size, and the number of diffusion-weighted images (Amyot et al., 2015). In a review of DTI studies, the number of diffusion-weighted images was found to be associated with differences in FA; at least six diffusion-weighted images are needed to calculate the tensor, and the studies reviewed used between six and 64 diffusion-weighted images (Dodd, Epstein, Ling, & Mayer, 2014). Interestingly, higher FA was found for studies that used 30 or more diffusion-weighted images, while lower FA was found for studies that used 25 or less (Dodd et al., 2014). Thus, differences in the magnet strength, the number of diffusion-weighted images and other data acquisition variables may contribute to discrepant findings.

Thirdly, the method used to analyse the DTI data — including ROI, tractography, histogram and voxel-based analysis — can affect the findings. Each of these methods have specific strengths and limitations; the most appropriate method is largely dependent on the aims of the DTI examination (Van Hecke & Emsell, 2016). For example, ROI and tractography are more suited to hypothesis-driven studies, while histogram and voxel-based analysis are useful in exploratory studies. The identification of ROIs (i.e., manual or automated) in ROI and tractography analyses can also be a source of variability; manual identification tends to be more accurate, but can be affected by both inter- and intra-rater variability (Van Hecke & Emsell, 2016). A range of software is also available for the pre- and post-processing of DTI data. Although much of this software is simple to use (sometimes referred to as ‘push-button’ software; Jones et al., 2013), it has been suggested that the same DTI data could lead to different results when analysed using different software, or even different versions of the same software (Van Hecke & Emsell,

2016), highlighting the importance of using the same software and version for each participant in a study, especially in longitudinal studies.

Finally, traditional methods of analysis cannot evaluate crossing fibres[3] within a single voxel (Douglas et al., 2018; Mori & Tournier, 2014; Raffelt et al., 2015). Traditional metrics, such as FA and MD, provide voxel-averaged information; thus, information cannot be attributed to specific fibre tracts (Jones et al., 2013). Therefore, the degeneration of a primary fibre tract and preservation of a secondary tract in a single voxel may cause FA to increase, which may be incorrectly attributed to more directional diffusion (i.e., recovery/resolution of damage) (Mori & Tournier, 2014). Several novel methods have recently been developed in an attempt to overcome this limitation, including FBA, which may provide tract-specific information about WM changes following TBI (Raffelt et al., 2017).

As highlighted by Jones and colleagues (see Jones, 2010; Jones & Cercignani, 2010; Jones et al., 2013), these limitations do not lessen the usefulness of DTI. Rather, they must be taken into consideration to increase the robustness and reliability of DTI studies.

2.4 Fixel-based Analysis

FBA is a statistical method that is used to analyse high angular resolution diffusion-weighted imaging (HARDI) data (Pannek et al., 2018). HARDI is a higher-order acquisition protocol that is an extension of DTI; a higher b-value (e.g., 3000 rather than 1000) and as many diffusion-weighted images as time allows are typically used, which enables accurate orientation information to be obtained (Mori & Tournier, 2014). Using FBA, individual fibre tracts within a single voxel (known as a 'fixel'; (Raffelt et al., 2015) are identified. FBA provides information about the microstructural and macrostructural properties of the WM by attributing WM

[3] The term 'crossing fibres' refers to a voxel where a single fibre population changes orientation/direction (e.g., bend, converges, diverges), or a voxel that contains more than one fibre population/tract (Mori & Tournier, 2014).

integrity/damage to individual fibre tracts in voxels that contain more than one (Raffelt et al., 2017).

FBA evaluates tissue microstructure and macrostructure via three measures: fibre density (FD), fibre-bundle cross-section (FC), and a combined measure of fibre density and cross-section (FDC) (Raffelt et al., 2017). *FD* measures tissue microstructure and decreases in cases of WM damage where there are fewer axons contained within a fibre bundle (i.e., less densely packed), but the area that the bundle occupies does not change (Pannek et al., 2018; Raffelt et al., 2015; Raffelt et al., 2017). *FC* measures tissue macrostructure and decreases in cases of damage where the fibre bundle cross-sectional area is reduced (i.e., the fibre bundle occupies less voxels), however the density of axons remains unchanged. Following disease or damage, both tissue microstructure (FD) and macrostructure (FC) may be altered, leading to a change in the combined measure of *FDC*. A decrease in FDC would therefore reflect fewer, less densely packed axons within a fibre bundle that has a decreased cross-sectional area (Pannek et al., 2018; Raffelt et al., 2017).

Recent studies have used FBA to detect tract-specific micro- and/or macro-structural changes to the WM in a range of neurological conditions, including temporal lobe epilepsy (Vaughan et al., 2017), preterm infants (Pannek et al., 2018), Alzheimer's disease (Mito et al., 2018), and multiple sclerosis (Gajamange et al., 2018). Although TBI leads to WM damage, which has been detected using DTI (for reviews, see Amyot et al., 2015; Hulkower et al., 2013; Niogi & Mukherjee, 2010; Shenton et al., 2012), adult TBI has yet to be examined using FBA. Thus, the limitations of DTI (i.e., crossing fibres) have not been addressed in this sample.

2.5 Summary

Neuroimaging is crucial in the detection of damage following a TBI (Douglas et al., 2018). Despite significant advances in neuroimaging techniques, CT and MRI are still commonly used to

assess TBI (Amyot et al., 2015; Shenton et al., 2012). Although these scans are able to identify macroscopic damage following moderate and severe TBIs, and determine whether immediate surgical intervention is required, they underestimate the WM damage (Koerte et al., 2016; Ruff et al., 2009; Strauss et al., 2015) that is associated with significant post-injury cognitive impairments.

DTI is a relatively new imaging modality that provides a more sensitive evaluation of WM damage than CT and conventional MRI, making it particularly useful in the examination of TBI. This advanced MRI sequence has been used to examine WM integrity via the calculation of various metrics, with FA and MD used most commonly (Koerte et al., 2016). Higher FA, reflecting more directional diffusion, and lower MD, indicating a slower rate of diffusion, are generally interpreted as reflecting WM integrity (Shenton et al., 2012). Following TBI, most studies have reported lower FA and higher MD, especially in the subacute and chronic post-injury intervals. These changes are thought to reflect demyelination, gliosis, or axonal degeneration (Amyot et al., 2015; Niogi & Mukherjee, 2010; Shenton et al., 2012). However, existing studies have reported disparate findings in the location and extent of WM changes (Douglas et al., 2018; Niogi & Mukherjee, 2010; Shenton et al., 2012). In addition, some studies have found the reverse (higher FA, lower MD) following TBI, particularly when examined in the acute post-injury period, which has been attributed to early axonal swelling (Amyot et al., 2015; Bazarian et al., 2007; Huisman et al., 2004). The relationship between DTI findings and cognitive outcomes following TBI has also been examined by individual studies, but inconsistent findings have been reported (e.g., Arenth et al., 2014; Gu et al., 2013; Palacios et al., 2011). Differences between studies in the TBI samples that were examined; the brain regions investigated; the measures that were used; the interval between injury and assessment; and data acquisition and methods of analysis used may have contributed to the variable findings. These discrepancies limit the conclusions that can be drawn from this body of literature and the usefulness of DTI in the examination of TBI.

In addition, the very recent development of a novel method known as FBA appears promising in the investigation of WM changes and may provide an alternative to both traditional neuroimaging techniques (CT, MRI) and DTI (Raffelt et al., 2015; Raffelt et al., 2017). Importantly, this method is able to overcome one of the main limitations of DTI: that it lacks specificity in voxels that contain more than one WM tract (Mori & Tournier, 2014; Raffelt et al., 2015). FBA provides tract-specific information in addition to providing information about the way in which a tract may be altered, providing micro- and macro-structural information about WM (Mito et al., 2018; Raffelt et al., 2017). Despite promising findings from studies that have used FBA to examine other neurological conditions (e.g., Gajamange et al., 2018; Mito et al., 2018; Pannek et al., 2018; Vaughan et al., 2017), it is not known whether FBA can detect WM changes following TBI and, if so, whether the findings are largely similar to those obtained using DTI.

2.6 Aims of thesis

The main aim of the current thesis was to examine WM changes and cognitive outcomes following adult mild, moderate and severe TBI. Specifically, four studies were completed to determine the location and extent of WM changes following TBI; the relationship between these changes and cognitive outcomes; and to determine whether a novel method of analysis (i.e., FBA) could identify WM alterations following adult TBI.

The first study involved a meta-analysis of research that has used DTI to examine WM microstructure following adult TBI to determine where and to what extent WM was altered following mild, moderate and severe non-penetrating TBI. The impact of specific methodological variables on the DTI findings was examined (severity of injury, the timing of the DTI, magnet strength, brand of scanner, differences in b-values, number of diffusion weighted images).

A second meta-analysis was then conducted to investigate the relationship between WM changes and cognitive outcomes following adult TBI. The findings from studies that examined the

relationship between DTI findings (FA, MD/ADC) for individual ROIs and cognitive outcomes were synthesised. Again, the impact of a number of methodological variables was evaluated to determine whether they affected the relationship between DTI findings and cognitive outcomes, namely: the severity of injury, the timing of the DTI, the timing of the DTI relative the cognitive testing, or scanner or acquisition parameters (e.g., magnet strength, brand of scanner, differences in b-values, number of diffusion weighted images).

The third study used a ROI approach to examine the relationship between the DTI findings (FA, MD) and cognitive outcomes following adult TBI in order to determine whether the findings from meta-analysis two were replicated in a considerably larger sample. Adults who had sustained a mild, moderate or severe non-penetrating TBI (N = 169) and a combined group of healthy and orthopaedic controls (N = 106) underwent DTI and cognitive testing. The genu, body and splenium of the CC, fornix and SLF were chosen as the ROIs because they displayed large and consistent FA/MD changes compared to controls, as found in meta-analysis one, and were also strongly related to cognitive outcomes in the second meta-analysis. Memory, attention and executive functioning were examined because these cognitive domains were strongly related to the DTI findings in meta-analysis two. This study was designed to determine whether: (1) TBI led to WM alterations in these five regions and whether the alterations were more prominent following more severe injuries; (2) people with TBI performed more poorly than controls on the cognitive tests, and whether cognitive performance was worse following more severe injury; and (3) cognitive performance was associated with WM integrity following TBI, and whether any relationships were equivalent to those seen in the control group.

Finally, the fourth study utilised an emerging methodology, known as FBA, to examine diffusion-weighted data obtained from the same sample of TBI and control participants. FBA assesses tissue microstructure and macrostructure and, importantly, is able to overcome one limitation of traditional methods of analyses: that these methods are unable to resolve crossing

fibres. This study was designed to determine whether WM alterations were detected using FBA following adult TBI and, if so, which areas of the brain differed in terms of tissue microstructure and macrostructure.

CHAPTER 3: META-ANALYSIS – DIFFUSION TENSOR IMAGING FOLLOWING TRAUMATIC BRAIN INJURY

3.1 Preamble

This chapter consists of a paper entitled "Diffusion tensor imaging changes following mild, moderate and severe adult traumatic brain injury: A meta-analysis", which has been published in Brain Imaging and Behavior (2018).

As highlighted in the preceding review, a number of studies have examined adult TBI using DTI, however the results have been mixed. Therefore, this study meta-analysed existing studies that have used DTI to determine the location and extent of WM alterations in adults who have sustained mild, moderate or severe non-penetrating TBIs.

Tables and Figures have been provided within the text to make it easier to read. Supplementary material for this paper is provided at the end of the chapter (pages 70-82), comprising:

- Logic grids for each database (Appendix A)
- Summary details for the studies included in the meta-analysis (Table S1)
- Mild TBI: Hedges' g effect sizes for FA data for individual ROIs, rank-ordered by effect sizes (Table S2)
- Moderate-severe TBI: Hedges' g effect sizes for FA data for individual ROIs, rank-ordered by effect sizes (Table S3)
- Mild TBI: Hedges' g effect sizes for MD/ADC data for individual ROIs, rank-ordered by effect sizes (Table S4)

- Moderate-severe TBI: Hedges' g effect sizes for MD/ADC data for individual ROIs, rank-ordered by effect sizes (Table S5)

- Subgroup analyses (Table S6)

At the end of the chapter, there is a list of the studies that were included in this meta-analysis, with the superscript number (1-44) corresponding to the reference number used in the tables. A complete list of all references for the thesis, including those for this paper, is provided at the end of the thesis (pages 216-236).

CHAPTER 3: PAPER 1

Diffusion tensor imaging changes following mild, moderate and severe adult traumatic brain injury: A meta-analysis

Authors: E.J. Wallace, J.L. Mathias, L. Ward

Statement of authorship is on the following page

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Contribution to the Paper	Conducted literature searches, coded articles, analysed and interpreted data, and wrote manuscript		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/4/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Jane Mathias		
Contribution to the Paper	Supervised and contributed to the study design, analysis and data interpretation, and manuscript preparation, and acted as corresponding author		
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Contribution to the Paper	Assisted in analysing and interpreting data, and evaluating and editing the manuscript		
Signature		Date	29-4-20

3.2 Paper one

Abstract

Diffusion tensor imaging quantifies the asymmetry (fractional anisotropy; FA) and amount of water diffusion (mean diffusivity/apparent diffusion coefficient; MD/ADC) and has been used to assess white matter damage following traumatic brain injury (TBI). In healthy brains, diffusion is constrained by the organization of axons, resulting in high FA and low MD/ADC. Following a TBI, diffusion may be altered; however the exact nature of these changes has yet to be determined. A meta-analysis was therefore conducted to determine the location and extent of changes in DTI following adult TBI. The data from 44 studies that compared the FA and/or MD/ADC data from TBI and Control participants in different regions of interest (ROIs) were analysed. The impact of injury severity, post-injury interval (acute: ≤ 1 week, subacute: 1 week-3 months, chronic: > 3 months), scanner details and acquisition parameters were investigated in subgroup analyses, with the findings indicating that mild TBI should be examined separately to that of moderate to severe injuries. Lower FA values were found in 88% of brain regions following mild TBI and 92% following moderate-severe TBI, compared to Controls. MD/ADC was higher in 95% and 100% of brain regions following mild and moderate-severe TBI, respectively. Moderate to severe TBI resulted in larger changes in FA and MD/ADC than mild TBI. Overall, changes to FA and MD/ADC were widespread, reflecting more symmetric and a higher amount of diffusion, indicative of white matter damage.

Diffusion tensor imaging changes following mild, moderate and severe adult traumatic brain injury: A meta-analysis

Introduction

Traumatic brain injuries (TBI) can lead to heterogeneous outcomes, ranging from transient symptoms to persistent cognitive, emotional, behavioural and physical problems that cause long-term disability (Cristofori & Levin, 2015). Diffuse axonal injury (DAI), resulting from a shearing injury in which the white matter (WM) of the brain is damaged, is common following TBI and is thought to underpin many of these impairments (Hulkower et al., 2013). However, DAI is often microscopic and, consequently, small amounts may not be visible on computed tomography (CT) and magnetic resonance imaging (MRI), which better detect more macroscopic damage (Shenton et al., 2012). In contrast, diffusion tensor imaging (DTI) is able to detect microstructural changes to WM, enabling DAI to be more easily identified (Niogi & Mukherjee, 2010).

DTI has been used to measure WM integrity by quantifying changes to the diffusion of water molecules within these fibre tracts (Shenton et al., 2012). In organized/healthy WM, diffusion is constrained by its microstructural organization, with water diffusing freely parallel to axons, but restricted in other directions (Douglas et al., 2015; Huisman, 2010; Mueller, Lim, Hemmy, & Camchong, 2015). This asymmetry is referred to as anisotropic diffusion (Niogi & Mukherjee, 2010). When WM is damaged following a TBI, diffusion becomes more symmetric and, consequently, anisotropy decreases (Shenton et al., 2012; Strauss et al., 2015). At the extreme, when diffusion is not constrained, it occurs equally (symmetrically) in all directions; which is known as isotropic diffusion (Huisman, 2010; Mueller et al., 2015). Alterations to the symmetry of diffusion are quantified using a measure known as fractional anisotropy (FA), which can range in value from 0 (symmetric/isotropic diffusion, indicating WM damage) to 1

(asymmetric/anisotropic diffusion, indicative of healthy/myelinated/intact WM) (Niogi & Mukherjee, 2010).

Alternatively, mean diffusivity (MD), also known as the apparent diffusion coefficient (ADC) (Niogi & Mukherjee, 2010), refers to the average distance over which water diffuses (Dodd et al., 2014; Strauss et al., 2015); providing a measure of the *amount* of diffusion. In healthy brains, the amount of diffusion is limited by the microstructural organization of WM tracts (Niogi & Mukherjee, 2010); resulting in low MD/ADC values. However, this can increase following a TBI due to damage/alterations to the WM microstructure, which previously restricted diffusion (Shenton et al., 2012). In general, low MD/ADC is thought to be indicative of healthy/intact axons, with higher MD/ADC values suggesting WM damage (Niogi & Mukherjee, 2010).

DTI has increasingly been used by researchers to investigate WM damage following TBI. Many different regions of interest (ROIs) have been investigated, with the greatest focus being on large WM tracts that are known to be susceptible to damage following TBI (Hulkower et al., 2013), such as the corpus callosum (e.g., Chang & Jang, 2010; Kasahara, Hashimoto, Abo, & Senoo, 2012; Kumar, Gupta, et al., 2009). To date, most studies have reported lower FA and higher MD/ADC following TBI, reflecting more symmetric and increased diffusion, which are indicative of WM damage. For example, Arfanakis et al. (2002) found lower FA in the corpus callosum, and the internal and external capsules in the early stages (< 24 hours) after a mild TBI, compared to non-injured controls. Similarly, Inglese et al. (2005) reported significantly lower FA and higher MD in the corpus callosum and internal capsule, in both the early (< 10 days) and late (mean = 5.7 years) stages after a mild TBI. In addition, Kennedy et al., (2009) found long-term (mean = 7 years) reductions in FA and increased MD in the centrum semiovale, and the superior and inferior frontal WM following severe TBI. A dose-response relationship has also been reported, with Kraus et al. (2007) and Matsushita et al. (2011) both reporting lower FA values following more severe injuries.

DTI performed in the early stages after injury has, however, also revealed some conflicting findings. For example, Bazarian et al. (2007) found that within 72 hours of a mild TBI, their sample had higher FA and lower MD than orthopaedic controls; a finding attributed to early axonal swelling caused by DAI. Huisman et al. (2004) also found lower ADC in the splenium of the corpus callosum within 1 week of a TBI. Thus, whether there are differences in the FA and MD/ADC values seen in short- and long-term after TBI remains unresolved.

Much of the available research has thus far focused on mild TBI, which has been examined in a number of recent reviews and meta-analyses (see Aoki et al., 2012; Dodd et al., 2014; Gardner et al., 2012; Shenton et al., 2012). These reviews consistently report lower FA and higher MD/ADC following a TBI, with some mention of studies that report the reverse (higher FA and lower MD/ADC), however none examine the full spectrum of injury severity to determine whether there is a dose-response relationship. Severe TBIs result in greater physical damage, which should be reflected in greater changes to FA and MD/ADC (Kraus et al., 2007; Matsushita, Hosoda, Naitoh, Yamashita, & Kohmura, 2011). Moreover, few studies have examined the influence of injury severity on DTI findings by comparing TBIs of different severities, with many focusing on one category — most commonly mild TBI — or combining findings from different severities. Consequently, the relationship between DTI and injury severity has yet to be adequately examined; hence the current focus on the full range of injuries.

The current meta-analysis was designed to identify the location and extent of WM changes following mild, moderate and severe TBI in adults. To this end, TBI and Control groups were compared in terms of their FA and MD/ADC values for individual ROIs, and the effects of injury severity and post-injury interval (timing of scan) were investigated in order to determine what areas of the brain are most commonly affected by TBI, the extent of damage associated with different injury severities, and whether changes differ depending on the timing of scan following a TBI.

Method

Literature Search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff, & Altman, 2009) were followed throughout. A comprehensive search of five electronic databases (PubMed, Embase, PsychINFO, Web of Science, Scopus) was conducted to identify research that used DTI with adult TBI samples (see Supplementary Material; Appendix A for logic grids for each database) prior to March 2016. The reference lists of all included studies were additionally searched to identify any other potentially relevant studies.

Eligibility for inclusion was based on the following criteria: (1) the study examined adults aged 18 years and over who had sustained a mild, moderate or severe non-penetrating TBI, (2) a control group comprising healthy or trauma/orthopaedic/medical participants was additionally examined, (3) participants were scanned using DTI, and FA and/or MD/ADC values were reported for both the TBI and Control groups, (4) studies were published in English in a peer-reviewed journal (peer-review status checked via Scopus), and (5) all information needed to calculate effect sizes (group differences: Hedges' *g*) was provided (means and standard deviations, exact *t*-test or one-way ANOVA statistics, exact *p*-values, or raw data for the FA and/or MD/ADC data for TBI and Control groups).

The current meta-analysis focused solely on non-penetrating/blunt-trauma, with penetrating and blast injuries (military samples) being excluded due to differences in the pathophysiology of these injuries (Bandak, Ling, Bandak, & De Lanerolle, 2015; Santiago et al., 2012). Case studies and studies with very small samples ($N \leq 5$) were also excluded. Studies of concussion were eligible, provided the participants did not have a history indicating multiple concussions.

As seen in Figure 1, the initial search identified 13,922 potentially relevant articles, which reduced to 9,845 when duplicates were removed. The titles and abstracts of these papers underwent preliminary screening using the aforementioned inclusion criteria, further reducing the number to 427. Full-text versions of these articles were retrieved and re-screened, resulting in 89 potentially eligible studies.

Of these, 24 studies were otherwise eligible, but did not provide adequate data for the calculation of effect sizes. The corresponding authors for these studies were contacted; four of whom provided the requisite data and were included in the final sample (Bazarian et al., 2007; Kasahara et al., 2012; Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010; Yuh et al., 2014). In addition, the authors of three other studies were contacted because they did not specify the minimum age of participants; one provided this information, however the minimum age was < 18, rendering it ineligible (Haberg et al., 2015). In the absence of a response, the remaining two studies were not included because the mean age of their TBI sample minus one standard deviation was < 18.

Next, all studies were checked to ensure that their samples were independent; when this was not the case (text indicated that the same sample was used in multiple papers or the sample characteristics and authors overlapped) the studies were combined and treated as one. To this end, 14 studies were combined to form 6 independent studies (see Figure 1 for details), resulting in a final sample of 58 studies, from which data were extracted.

Data Extraction & Preparation

Demographic (age, gender, education, handedness), study (sample size, control group type, recruitment source), injury (injury severity: category and Glasgow Coma Scale [GCS] score; length of post-traumatic amnesia [PTA]; loss of consciousness [LOC]; time post-injury), scanner

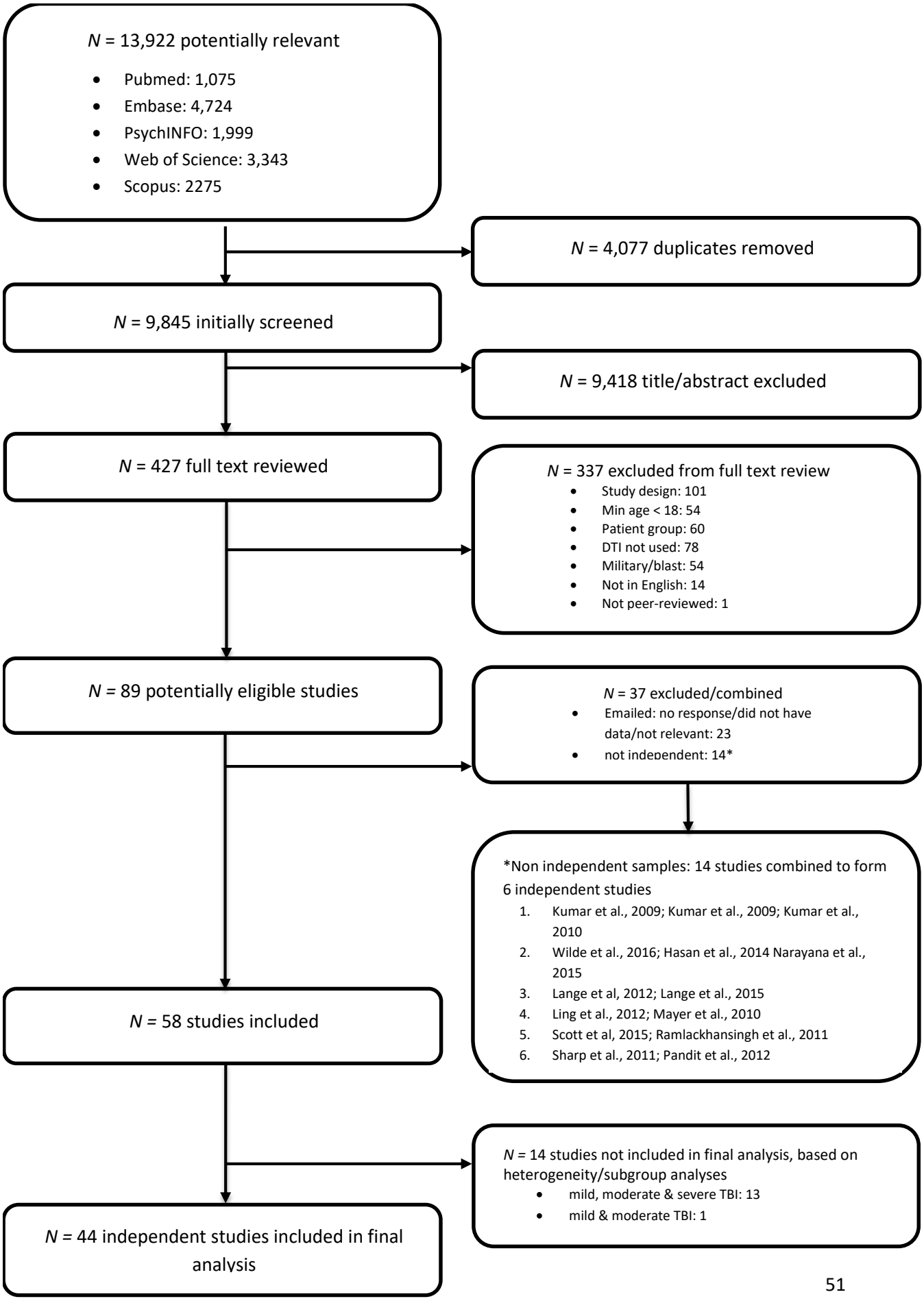


Figure 1: Literature search flow chart

(brand, strength/tesla), and acquisition/DTI (*b*-values, number of diffusion weighted images, method of analysis) details were extracted from each study, as were the FA and/or MD/ADC data for each ROI (TBI and Control group means, standard deviations; exact *t*-test or one-way ANOVA statistics or exact *p*-values; or raw data).

If a study reported data for more than one post-injury interval (e.g., Sidaros et al., 2008), only the last was analysed because this was thought to better reflect final levels of damage/recovery. Consistent with this, a recent systematic review reported that most TBI research is conducted more than one year after injury (Brazinova et al., 2015).

Finally, five studies (Chang & Jang, 2010; Chang, Kim, Kim, Bai, & Jang, 2010; Hong et al., 2012; Jang et al., 2013; Seo et al., 2012) classified participants on the basis of their DAI grading (Adams et al., 1989), rather than categorizing them as mild, moderate or severe injuries (or providing GCS scores). Three were subsequently classified as severe TBI (Hong et al., 2012; Jang et al., 2013; Seo et al., 2012) because participants' LOC scores exceeded the 24 hour criterion used to define severe injuries (Blyth & Bazarian, 2010). The remaining two studies included participants with all levels of DAI, consequently they were classified as mild to severe TBIs (Chang & Jang, 2010; Chang et al., 2010).

Data Analysis

All analyses were completed using Comprehensive Meta-Analysis Version 3.3 (CMA; 2014, Biostat, Inc., Engelwood, NJ, USA) and all plots generated using Meta Data Viewer (Boyles, Harris, Rooney, & Thayer, 2011). The standardized mean difference — Hedges' *g* — was used to assess the differences between the FA or MD/ADC values of the TBI and Control groups for individual ROIs. Hedges' *g* corrects for bias that may arise from using small samples (Hedges & Olkin, 1985; Lakens, 2013; Lipsey & Wilson, 2001), resulting in a more conservative estimate. All effect sizes were calculated so that a negative *g* indicated lower FA or higher MD/ADC values (indicative of WM damage) and a positive *g* indicated higher FA or lower MD values in the TBI samples, relative

to controls. Hedges' *g* values of 0.2, 0.5, 0.8 and 1.3 correspond to a small, medium, large and very large effects, respectively (Cohen, 1992; Rosenthal, 1996).

A number of additional statistics were computed, namely: *p*-values, ninety-five percent confidence intervals (*95%CIs*) and fail-safe N statistics (N_{fs}). Probability (*p*) values less than .05 indicate a statistically significant difference in the FA or MD/ADC values for the TBI and Control groups, and *95%CIs* provide a range within which there is a 95% chance that the population effect lies (Ellis, 2010; Lipsey & Wilson, 2001). Finally, N_{fs} statistics were calculated using Orwin's method to assess the potential impact of publication bias (Orwin, 1983; Rothstein, Sutton, & Borenstein, 2006). The N_{fs} statistic is a hypothetical value that indicates the number of unpublished studies with non-significant findings (g = .2; small difference in FA or MD/ADC between the TBI & Control groups) that would need to exist in order to reduce the finding for a specific ROI to a small/negligible effect (Lipsey & Wilson, 2001).

WM integrity was considered to be reduced in a ROI following TBI if Hedges' *g* was negative and at least medium to large in size ($g \leq -.5$), statistically significant ($p < .05$) and the *Nfs* statistic was greater than the number of studies examining that ROI (i.e., unlikely to be sufficient unpublished studies, with non-significant results, that could negate the finding).

In addition, it was intended that heterogeneity in the effect sizes for different studies be examined using *Q* (a measure of between-study heterogeneity) and I^2. The latter measures the proportion of observed variance that is attributable to between-study variability ('true' heterogeneity), rather than random or sampling error within studies (Borenstein, Hedges, Higgins, & Rothstein, 2009; Higgins, Thompson, Deeks, & Altman, 2003; Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). However, it was not possible to calculate *Q* and I^2 for individual ROIs because these statistics are under-powered when there is a small number of studies ($N_{studies} < 20$), as was the case for all ROIs, and/or the samples are small ($N_{participants} < 80$; (Huedo-Medina et al., 2006), which was also often the case. Therefore, between-study heterogeneity in the effect

sizes reported for specific ROIs was dealt with in two ways. First, we used a random-effects model — which assumes that effect sizes from different studies vary due to random or sampling error — to calculate all mean effects (Borenstein, Hedges, Higgins, & Rothstein, 2010). Second, we performed subgroup analyses to determine whether specific methodological variables were associated with significantly different effect sizes and, consequently, whether the data should be analysed separately for these subgroups. The variables of interest were: the timing of the DTI (acute: ≤ 1 week; subacute: >1 week to ≤ 3months; chronic: > 3 months), injury severity (mild, moderate, severe), scanner details (magnet strength [1.5 Tesla, 3 Tesla], brand of scanner [General Electric, Philips, Siemens), and scan acquisition parameters (differences in b-values [<1000, ≥1000], number of diffusion weighted images[<30, ≥30]) (see Supplementary material Table S6 for details of these subgroup analyses). Unfortunately, very few studies examined moderate TBI alone ($N_{studies}$ = 4), consequently the injury severity subgroup analysis was constrained to comparing the findings for mild TBI with those of moderate to severe TBI.

Heterogeneity and Subgroup Analyses

Significant heterogeneity was found between the mean effect sizes obtained from individual studies, both for FA (Q[52] = 1278.56, p < .001, I^2 = 95.93) and MD/ADC (Q[35] = 746.96, p < .001, I^2 = 95.31). It is likely that at least some of this heterogeneity arose from the fact that the studies assessed different ROIs, which we addressed by examining ROIs separately.

The subgroup analyses revealed that the timing of the DTI, brand of scanner, and scan acquisition parameters did not affect the findings (see Supplementary Table S6 for details); which meant that data acquired at different post-injury intervals (acute, subacute, chronic), from different brands of scanners, and using different acquisition parameters could be combined. However, the subgroup analyses yielded significant findings for magnet strength and injury severity. More specifically, the mean FA effect size for studies that used a 1.5Tesla (T) scanner was significantly larger than that for studies using a 3T scanner. Closer inspection of the data

revealed that moderate to severe TBI was more frequently examined using 1.5T, and mild TBI was examined more using 3T, which meant that magnet strength and injury severity were confounded. In the case of injury severity, the mean effect sizes — both for FA and MD/ADC — for mild TBI samples (FA: $N_{studies}$ = 29, MD: $N_{studies}$ = 19) were significantly smaller than those obtained from moderate to severe samples (FA: $N_{studies}$ = 20, MD: $N_{studies}$ = 10). Thus, these analyses suggest that it was not appropriate to combine the data from studies that examined mild TBI with those examining moderate-severe TBI. As a consequence, a further 14 studies — 1 examining mild and moderate TBI and 13 examining mild, moderate and severe TBI — had to be excluded from further analysis. Therefore, all subsequent analyses were based on data from 44 studies.

Results

The final sample of 44 studies provided DTI data for 1,321 adults who had sustained a TBI and 940 Controls (see Table 1 for summary information). The samples ranged in size from 6 to 83 for the TBI group and 6 to 64 for the Controls. Participants in both groups were mostly young to middle-aged males. Few studies reported handedness ($N_{studies}$ = 8), with those that did largely recruiting right-handed persons. GCS scores were only reported by 21 studies, however the majority reported injury category: with mild TBI being investigated most frequently ($N_{studies}$ = 31), followed by severe ($N_{studies}$ = 14), moderate ($N_{studies}$ = 4), and moderate to severe ($N_{studies}$ = 3). Nine studies performed DTI in the acute period (≤ 1 week post-injury), 11 investigated the subacute period (>1 week to ≤ 3months) and 25 investigated the chronic period (> 3 months). Control groups largely comprised healthy persons ($N_{studies}$ = 39), orthopaedic/trauma patients ($N_{studies}$ = 4) or medical patients (headache; $N_{studies}$ = 1), and TBI participants were largely recruited as inpatients ($N_{studies}$ = 24), from rehabilitation/treatment clinics ($N_{studies}$ = 7), or other sources (e.g.,

Table 1: Summary information for the TBI and control groups

	TBI					Control				
	$N_{studies}$	$N_{participants}$	%	*Mean*	*SD*	$N_{studies}$	$N_{participants}$	%	*Mean*	*SD*
Sample size	44	1,321		30.0	21.3	44	940		21.4	13.4
Age	42	1,294		33.5	11.4	40	899		33.3	11.7
Gender	43	1,297				38	833			
males	43	857	66			38	518	62		
females	43	440	34			38	315	38		
Handedness (right)	8	299	94			8	231	98		
GCS	21	804		12.8	3.8					
TBI severity										
mild	31	970	73							
moderate	4	83	6							
severe	14	229	17							
moderate to severe	3	39	3							
DTI timing										
acute (≤1 week)	9	231	17							
subacute (1 week-3 months)	11	471	36							
chronic (> 3 months)	25	619	47							
Control group										
healthy	39	1,091	83			39	786	84		
orthopedic/trauma	4	220	17			4	144	15		
headache control	1	10	1			1	10	1		
Recruitment source										
inpatients	24	904	68							
rehab/treatment clinics	7	96	7							
other	13	321	24							
Brand of scanner										
General Electric	15	503	38			15	311	33		
Philips	11	305	23			11	260	28		
Siemens	17	490	37			17	346	37		
not specified	1	23	2			1	23	2		
MRI strength										
1.5 Tesla	19	536	40			19	382	41		
3 Tesla	24	762	58			24	535	57		
not specified	1	23	2			1	23	2		

	Method of analysis					
	$N_{studies}$	$N_{participants}$	%		$N_{studies}$	$N_{participants}$
ROI + VBA	1	6	0	ROI	34	1,005
ROI + TBSS	3	126	10	TBSS	13	487
ROI + tractography	8	180	14	VBA	7	197
ROI + histogram	1	46	3	tractography	10	218
VBA + histogram	1	17	1	histogram	2	63
VBA + TBSS	2	74	6			
ROI + VBA + TBSS	2	91	7			
ROI + VBA + tractography	1	9	1			
ROI	18	547	41			
TBSS	6	196	15			
tractography	1	29	2			

Note. $N_{studies}$ = total number of studies; $N_{participants}$ = total number of participants; TBI = traumatic brain injury; *SD* = standard deviation; GCS = Glasgow Coma Scale; DTI = diffusion tensor imaging; MRI = magnetic resonance imaging; ROI = region of interest; VBA = voxel-based analysis; TBSS = tract-based spatial statistics

advertisements or unspecified sources $N_{studies}$ = 13). Three brands of scanners were used: General Electric ($N_{studies}$ = 15), Philips ($N_{studies}$ = 11) and Siemens ($N_{studies}$ = 17); and 19 studies used a 1.5T scanner, while 24 used a 3T scanner.

Left/right, anterior/posterior and inferior/superior measurements

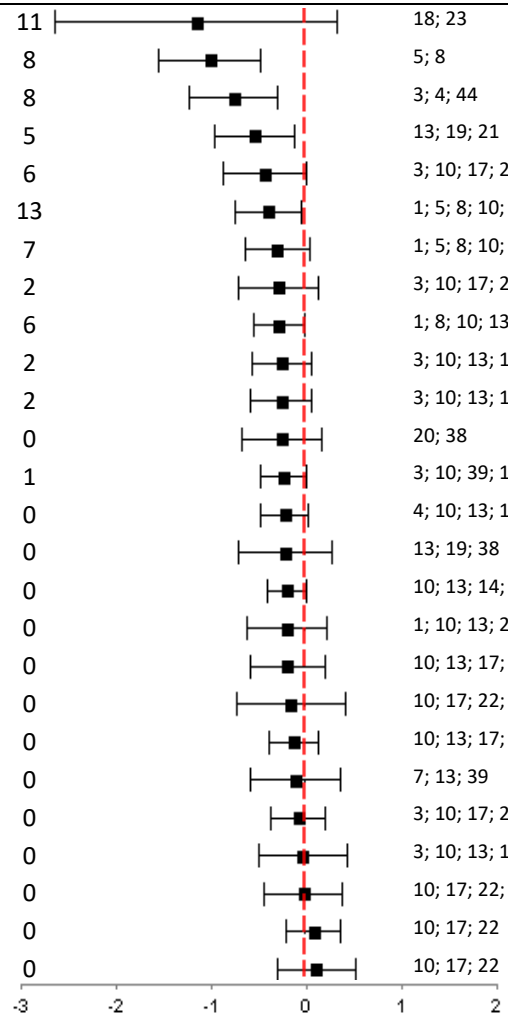
More than 200 different ROIs were examined by these 44 studies, most by only one study. Twenty-seven studies combined left- and right-sided measurements of the same brain structures when reporting their data. Therefore, for consistency, the left- and right-sided measurements (e.g., left and right fornix) from the 17 studies that reported this data separately were averaged. In support of this, Huisman et al. (2004) and Jang et al. (2013) found no differences between their left- and right-sided DTI measurements. Similarly, anterior and posterior, and superior and inferior values for the same brain structures were averaged; again reducing the number of ROIs. In contrast, the genu, body and splenium of the corpus callosum were kept distinct because multiple studies examined these regions and traditional imaging (CT & MRI) has shown this large WM tract is often affected by TBI (Fitsiori, Nguyen, Karentzos, Delavelle, & Vargas, 2011; Uchino et al., 2006). Furthermore, it has been found that the splenium is more commonly affected by TBI than the genu and body of the corpus callosum (Shiramizu et al., 2008).

Fractional anisotropy (FA)

The 29 studies of *mild TBI* measured FA in a total of 35 different ROIs, 9 of which were only examined by single studies. Table 2 displays the findings for the 26 ROIs that were examined by multiple studies ($N_{studies}$ = 2 to 20), with Table S2 in the Supplementary Materials additionally summarizing the findings for ROIs that were examined by single studies. Overall, the effect sizes ranged from large (g = -1.13) to negligible (g = 0.00), with most ROIs (23/26; 88%) showing negative effects, indicating that FA was generally lower in the mild TBI group than in Controls (see Table 2). Furthermore, the effect sizes for the two ROIs that showed the opposite/positive pattern (i.e., higher FA in the TBI group) were very small and non-significant. Notably, three (12%) of the ROIs showed medium to large ($g \geq -.5$) and significant ($p < .05$) decreases in FA, all with

Table 2. Mild TBI: Hedges' *g* effect sizes for FA data for individual ROIs examined by more than one study, rank-ordered by effect sizes

Brain region	$N_{studies}$	N_{TBI}	$N_{Control}$	*g*	*SE*	N_{fs}	*g and 95% CIs*	*Study references*
occipital WM	2	26	37	-1.13	0.76	11		18; 23
centrum semiovale	2	68	43	-0.99***	0.27	8		5; 8
corpus callosum (whole)	3	41	34	-0.74**	0.24	8		3; 4; 44
forceps major	3	49	39	-0.51*	0.21	5		13; 19; 21
fornix	6	209	196	-0.41	0.22	6		3; 10; 17; 22; 25; 37
internal capsule	14	480	335	-0.38*	0.18	13		1; 5; 8; 10; 17; 18; 19; 20; 22; 23; 25; 36; 38; 42
corpus callosum (splenium)	18	580	435	-0.28	0.17	7		1; 5; 8; 10; 13; 14; 15; 17; 19; 20; 22; 23; 25; 29; 36; 38; 42; 43
thalamic radiations	6	219	165	-0.27	0.22	2		3; 10; 17; 22; 25; 36
corpus callosum (genu)	20	671	504	-0.26	0.14	6		1; 8; 10; 13; 14; 15; 17; 18; 19; 20; 21; 22; 23; 25; 29; 36; 38; 39; 42; 43
fronto-occipital fasciculus	10	364	302	-0.24	0.16	2		3; 10; 13; 17; 19; 22; 25; 33; 39; 42
superior longitudinal fasciculus	10	378	295	-0.24	0.16	2		3; 10; 13; 17; 19; 22; 25; 36; 37; 42
pons	2	58	34	-0.23	0.22	0		20; 38
uncinate fasciculus	8	302	243	-0.22	0.12	1		3; 10; 39; 17; 21; 22; 25; 38
corona radiata	12	404	302	-0.20	0.13	0		4; 10; 13; 17; 19; 21; 22; 23; 25; 36; 38; 42
forceps minor	3	80	54	-0.20	0.25	0		13; 19; 38
corpus callosum (body)	12	387	333	-0.18	0.11	0		10; 13; 14; 15; 17; 19; 22; 23; 25; 29; 42; 43
external capsule	7	247	208	-0.18	0.21	0		1; 10; 13; 21; 24; 39; 41
sagittal stratum	7	253	214	-0.17	0.20	0		10; 13; 17; 19; 22; 25; 42
cerebral peduncle	5	193	158	-0.14	0.29	0		10; 17; 22; 25; 38
cingulum	8	319	230	-0.10	0.14	0		10; 13; 17; 21; 22; 25; 36; 42
whole brain	3	114	95	-0.09	0.24	0		7; 13; 39
cerebellar peduncle	7	236	174	-0.06	0.14	0		3; 10; 17; 21; 22; 25; 36
corticospinal tract	6	137	136	-0.02	0.24	0		3; 10; 13; 17; 19; 22
tapetum	4	145	134	0.00	0.21	0		10; 17; 22; 25
medial lemniscus	3	92	94	0.11	0.15	0		10; 17; 22
pontine crossing tract	3	92	94	0.13	0.21	0		10; 17; 22



Note. FA = fractional anisotropy; ROIs = regions of interest; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; $N_{Control}$ = total number of control participants; *g* = Hedges' *g* effect size; *SE* = standard error; *Nfs* = Fail safe N; 95% CIs = 95% confidence intervals; WM = white matter; * $p < .05$, ** $p < .01$, *** $p < .001$

good N_{fs} statistics. Specifically, FA was significantly lower in the TBI group than controls in the centrum semiovale, whole corpus callosum and forceps major.

Moderate to severe TBI was investigated by 20 studies that examined FA in a total of 41 ROIs. Table 3 summarizes the findings for 25 ROIs that were examined by multiple studies ($N_{studies}$ = 2 to 7) (see Supplementary Table S3 for findings for ROIs examined by $N_{studies}$ = 1). As can be seen, most effects were negative (23/25, 92%), with 18 (72%) being medium or larger ($g \geq -.5$) and significant, all with adequate N_{fs} statistics. Specifically, the following regions showed lower FA in the TBI group: the cerebral peduncle, fornix, uncinate fasciculus, corpus callosum (whole, splenium, genu, body), cingulum, forceps minor, thalamic radiations, fronto-occipital fasciculus, superior longitudinal fasciculus, corona radiata, forceps major, sagittal stratum, occipital WM, and external and internal capsule.

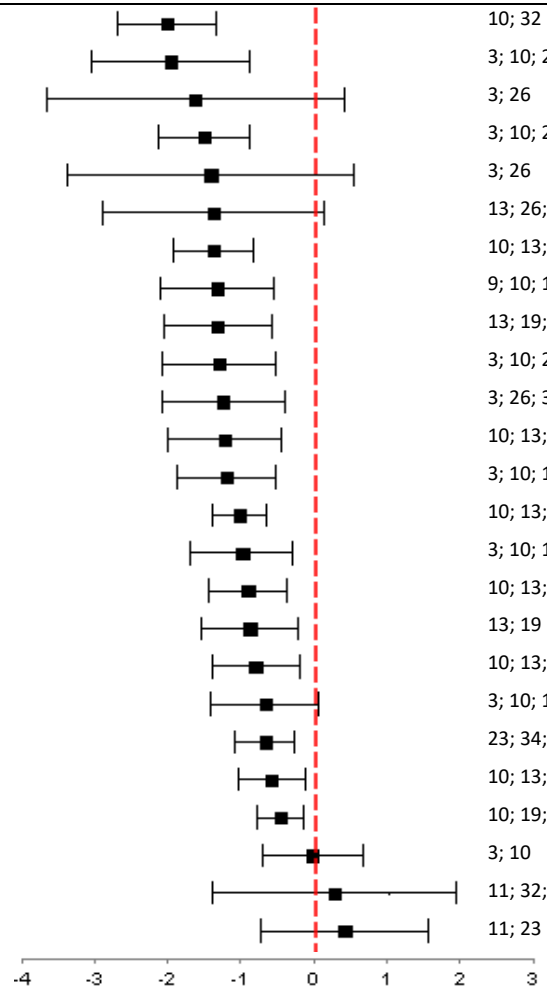
Comparing the findings for the 22 ROIs that were examined in both mild (Table 2) and moderate-severe (Table 3) samples, it can be seen that there were larger effects following moderate-severe TBI for 86% (19/22) of these ROIs, namely: cerebral peduncle, fornix, uncinate fasciculus, whole brain, corpus callosum (whole, splenium, genu, body), cingulum, forceps minor, thalamic radiations, fronto-occipital fasciculus, superior longitudinal fasciculus, corona radiata, forceps major, sagittal stratum, corticospinal tract, and external and internal capsule. For the remaining three ROIs (occipital WM, centrum semiovale, cerebellar peduncle), the effect size for mild TBI was slightly larger than for moderate-severe. Overall, decreases in FA were larger following moderate to severe than mild TBI.

Mean diffusivity/apparent diffusion coefficient (MD/ADC)

MD/ADC data were reported by 19 studies investigating *mild TBI*, with a total of 36 ROIs examined. Table 4 displays the findings for the 19 ROIs that were examined by more than one study ($N_{studies}$ = 2 to 12; see Supplementary Table S4 for ROIs examined by $N_{studies}$ = 1). The effects were consistently negative (18/19, 95% of ROIs), with the whole brain being the only positive,

Table 3. Moderate-severe TBI: Hedges' *g* effect sizes for FA data for individual ROIs examined by more than one study, rank-ordered by effect sizes

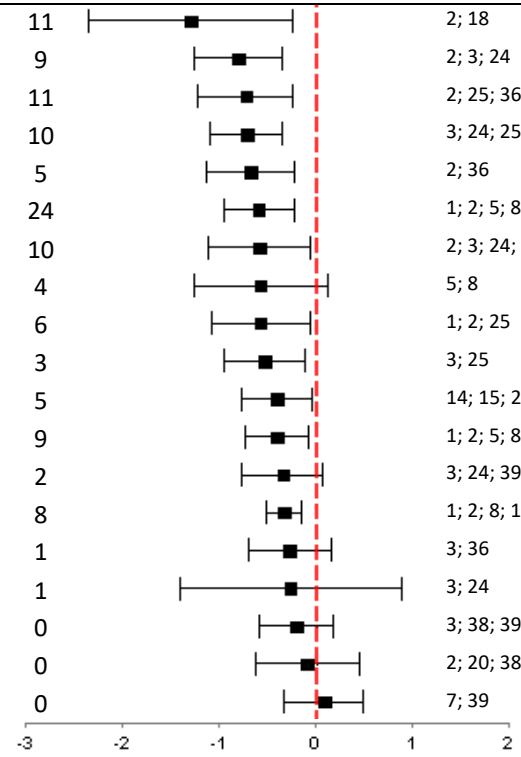
Brain region	$N_{studies}$	N_{TBI}	$N_{Control}$	*g*	*SE*	N_{fs}	*g and 95% CIs*	*Study references*
cerebral peduncle	2	27	26	-2.04***	0.34	18		10; 32
fornix	3	26	40	-1.99***	0.55	27		3; 10; 26
inferior longitudinal fasciculus	2	21	28	-1.65	1.04	15		3; 26
uncinate fasciculus	4	47	61	-1.53***	0.32	27		3; 10; 26; 31
arcuate fasciculus	2	21	28	-1.44	1.00	12		3; 26
whole brain	3	58	56	-1.41	0.77	18		13; 26; 27
corpus callosum (splenium)	7	133	127	-1.40***	0.28	42		10; 13; 14; 19; 23; 32; 40
cingulum	5	68	79	-1.35**	0.40	29		9; 10; 13; 26; 35
forceps minor	3	29	42	-1.35***	0.38	17		13; 19; 35
thalamic radiations	4	32	44	-1.32**	0.40	22		3; 10; 28; 41
corpus callosum (whole)	4	41	53	-1.27**	0.43	21		3; 26; 30; 35
corpus callosum (genu)	7	122	124	-1.25**	0.39	37		10; 13; 14; 19; 23; 40; 41
fronto-occipital fasciculus	5	55	70	-1.22***	0.35	26		3; 10; 13; 19; 26
corpus callosum (body)	6	113	113	-1.04***	0.19	25		10; 13; 14; 19; 23; 41
superior longitudinal fasciculus	5	55	70	-1.01**	0.36	20		3; 10; 13; 19; 26
corona radiata	5	56	80	-0.93**	0.28	18		10; 13; 19; 23; 41
forceps major	2	29	30	-0.91**	0.34	7		13; 19
sagittal stratum	3	34	42	-0.83**	0.30	9		10; 13; 19
corticospinal tract	4	40	54	-0.70	0.37	10		3; 10; 13; 19
occipital WM	3	63	53	-0.69**	0.21	7		23; 34; 40
external capsule	4	76	56	-0.61*	0.24	8		10; 13; 34; 41
internal capsule	6	141	107	-0.48*	0.16	8		10; 19; 23; 32; 34; 40
cerebellar peduncle	2	11	24	-0.05	0.35	0		3; 10
centrum semiovale	3	73	37	0.25	0.85	1		11; 32; 34
frontal WM	2	19	35	0.39	0.58	2		11; 23



Note. FA = fractional anisotropy; ROIs = regions of interest; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; $N_{Control}$ = total number of control participants; *g* = Hedges' *g* effect size; *SE* = standard error; *Nfs* = Fail safe N; 95% CIs = 95% confidence intervals; WM = white matter; * $p < .05$, ** $p < .01$, *** $p < .001$

Table 4. Mild TBI: Hedges' *g* effect sizes for MD/ADC data for individual ROIs examined by more than one study, rank-ordered by effect sizes

Brain region	$N_{studies}$	N_{TBI}	$N_{Control}$	*g*	*g SE*	N_{fs}	*g and 95% CIs*	*Study references*
occipital WM	2	24	24	-1.30*	0.54	11		2; 18
inferior longitudinal fasciculus	3	31	49	-0.81**	0.24	9		2; 3; 24
corona radiata	4	170	97	-0.73**	0.25	11		2; 25; 36; 38
thalamic radiations	4	138	94	-0.72***	0.19	10		3; 24; 25; 36
cingulum	2	68	33	-0.68**	0.23	5		2; 36
corpus callosum (splenium)	12	378	248	-0.60**	0.19	24		1; 2; 5; 8; 14; 15; 20; 25; 29; 36; 38; 43
superior longitudinal fasciculus	5	145	108	-0.59*	0.27	10		2; 3; 24; 25; 36
centrum semiovale	2	68	43	-0.58	0.35	4		5; 8
external capsule	3	66	60	-0.58*	0.26	6		1; 2; 25
fornix	2	66	52	-0.54*	0.21	3		3; 25
corpus callosum (body)	5	178	132	-0.41*	0.19	5		14; 15; 25; 29; 43
internal capsule	9	270	166	-0.41*	0.17	9		1; 2; 5; 8; 18; 20; 25; 36; 38
fronto-occipital fasciculus	3	103	99	-0.35	0.21	2		3; 24; 39
corpus callosum (genu)	12	399	268	-0.34***	0.10	8		1; 2; 8; 14; 15; 18; 20; 29; 36; 38; 39; 43
cerebellar peduncle	2	74	31	-0.28	0.22	1		3; 36
corticospinal tract	2	24	35	-0.27	0.58	1		3; 24
uncinate fasciculus	3	140	100	-0.21	0.20	0		3; 38; 39
pons	3	65	48	-0.10	0.27	0		2; 20; 38
whole brain	2	94	77	0.08	0.21	0		7; 39



Note. MD/ADC = mean diffusivity/apparent diffusion coefficient; ROIs = regions of interest; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; $N_{Control}$ = total number of control participants; *g* = Hedges' *g* effect size; *SE* = standard error; *Nfs* = Fail safe N; 95% CIs = 95% confidence intervals; WM = white matter; * $p < .05$, ** $p < .01$, *** $p < .001$

albeit negligible, effect (g = 0.08). Medium to very large and significant effects, with good N_{fs} statistics, were seen in 9 ROIs (47%); indicating increased MD/ADC in these ROIs — which is suggestive of WM damage — following mild TBI. In particular, large to very large and significant effects were found for the occipital WM and inferior longitudinal fasciculus.

MD/ADC data following *moderate-severe* TBI were available for 24 ROIs ($N_{studies}$ = 10), only seven of which were examined by multiple studies ($N_{studies}$ = 2 to 4, refer to Table 5; $N_{studies}$ = 1 refer to Supplementary Table S5). All seven ROIs displayed negative effects, reflecting higher MD/ADC in the TBI group, compared to controls, and four of these — the splenium of corpus callosum, thalamic radiations, internal capsule, and body of corpus callosum — displayed medium to large and significant increases in MD/ADC in the TBI group, with adequate to very good N_{fs} statistics.

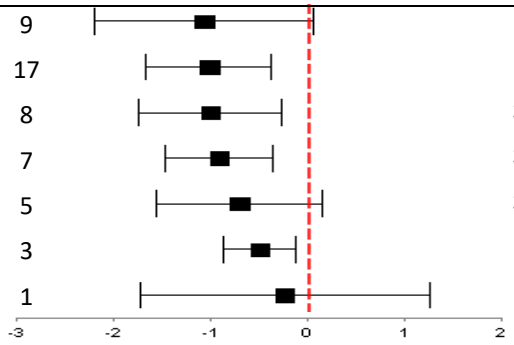
Of the seven ROIs examined in both mild and moderate-severe groups, the effects were notably larger following moderate-severe (Table 5) than mild (Table 4) TBI, relative to controls, in six ROIs: the centrum semiovale, corpus callosum (splenium, body), thalamic radiations, internal capsule, and uncinate fasciculus; indicating larger MD/ADC alterations in more severe injury. The one exception was the genu of corpus callosum, where the effect was larger for mild than moderate-severe TBI.

Single studies: Preliminary findings

Briefly, the findings from ROIs investigated by single studies — often with small samples — can only be considered preliminary, but were not dissimilar to the findings outlined above (see Supplementary Tables S2 to S5). The overwhelming majority of ROIs displayed negative effects, both for FA (mild: 89%, moderate-severe: 95%) and MD/ADC (mild: 89%, moderate-severe: 88%), indicating lower FA and higher MD/ADC in the TBI group compared to Controls. Specifically, FA was significantly lower, by a medium to very large amount, in 20% (7/35) of ROIs following mild TBI and in 66% (27/41) of ROIs following moderate-severe TBI. For MD/ADC data, medium to very

Table 5. Moderate-severe TBI: Hedges' *g* effect sizes for MD/ADC data for individual ROIs examined by more than one study, rank-ordered by effect sizes

Brain region	$N_{studies}$	N_{TBI}	$N_{Control}$	*g*	*SE*	N_{fs}	*g and 95% CIs*	*Study references*
centrum semiovale	2	30	22	-1.08	0.57	9		11; 32
corpus callosum (splenium)	4	103	68	-1.03**	0.33	17		14; 29; 32; 40
thalamic radiations	2	16	21	-1.02**	0.37	8		3; 28
internal capsule	2	31	25	-0.93**	0.28	7		32; 40
uncinate fasciculus	2	27	33	-0.72	0.44	5		3; 31
corpus callosum (body)	2	72	43	-0.51**	0.19	3		14; 29
corpus callosum (genu)	3	81	54	-0.25	0.76	1		14; 29; 40



Note. MD/ADC = mean diffusivity/apparent diffusion coefficient; ROIs = regions of interest; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; $N_{Control}$ = total number of control participants; *g* = Hedges' *g* effect size; *SE* = standard error; *Nfs* = Fail safe N; 95% CIs = 95% confidence intervals; WM = white matter; * $p < .05$, ** $p < .01$, *** $p < .001$

large and significant negative effects were found for 50% (18/36) of ROIs in mild samples and 42% (10/24) of ROIs in moderate-severe samples, indicating higher MD/ADC.

Discussion

The current meta-analysis synthesised the findings from 44 studies that compared the DTI findings from samples that had sustained mild, moderate or severe TBIs with those of Controls and, in doing so, updates and extends a previous meta-analysis that focused solely on mild TBI (Aoki et al., 2012). FA and MD/ADC data were examined in individual ROIs to determine what WM areas were most affected following a TBI, the extent of any such changes, as well the impact of TBI severity and timing of scanning. Initial subgroup analyses revealed that the DTI findings for mild TBI differed significantly from moderate to severe TBI; therefore these data were analysed separately. Moderate TBI could not be examined because few studies investigated this level of injury alone. In contrast, the findings from DTI performed in the acute (≤ 1 week), subacute (>1 week to ≤ 3months) and chronic (> 3 months) intervals did not differ, consequently these data were combined. Similarly, magnet strength, scanner brand, number of diffusion-weighted images and differences in *b*-values did not affect the findings and, therefore, these data could also be combined.

Most regions examined in mild and moderate-severe TBI showed lower FA and higher MD/ADC; which are thought to be indicative of WM damage (Douglas et al., 2015; Shenton et al., 2012). These findings were highly consistent, even for ROIs examined by single studies.

Some ROIs were examined more commonly than others, most notably the corpus callosum (CC), with many studies examining the whole CC or the genu, body and splenium separately. Conventional MRI has shown that the splenium is more affected by TBI than either the genu or body (Shiramizu et al., 2008). Consistent with this, the splenium showed the largest alterations in FA and MD/ADC of all the CC regions, in both mild and moderate to severe injury. It has been suggested that this may be due to the falx cerebri — which restricts the lateral

movement of the two hemispheres of the brain — being anatomically closer to the posterior part of the CC, causing much of the strain from a TBI to be concentrated at the splenium (Fitsiori et al., 2011; Shiramizu et al., 2008). Furthermore, the CC is thinnest at the body-splenium junction, and is therefore more susceptible to injury in this location (Fitsiori et al., 2011; Shiramizu et al., 2008). Interestingly, significant MD/ADC alterations were found in all regions of the CC following mild TBI. This differs from an earlier meta-analysis of mild TBI in which the splenium — but not the genu or body — displayed significantly decreased FA and increased MD (Aoki et al., 2012). These discrepant findings may be due to the inclusion of more studies in the current meta-analysis, leading to a substantially larger sample of mild TBI patients (current N_{TBI} = 970; previous N_{TBI} = 280) or slight differences in the inclusion/exclusion criteria. In the current study, significant WM changes were shown in all regions of the CC: splenium (moderate-severe FA, mild & moderate-severe MD/ADC), genu (moderate-severe FA, mild MD/ADC), body (moderate-severe FA, mild & moderate-severe MD/ADC) and whole CC (mild & moderate-severe FA), indicating that the CC remains a worthwhile region to focus on following a TBI.

Several ROIs that were examined by multiple studies showed larger effects than the CC, including: the centrum semiovale (mild FA); the cerebral peduncle, fornix, and uncinate fasciculus (moderate-severe FA); and occipital WM, inferior longitudinal fasciculus, and corona radiata (mild MD/ADC), suggesting that it may be beneficial to consider these areas when assessing TBI. As these regions were examined by fewer studies than the CC, more research is needed to replicate these findings before determining what ROIs are the best to examine following a TBI.

For those ROIs that were examined in both the mild and moderate-severe groups, moderate-severe TBI resulted in lower FA than mild TBI in 86% (19/22) of ROIs. Additionally, higher MD/ADC values were found following more severe injuries in 86% (6/7) of the ROIs that were examined in both mild and moderate-severe samples, with the exception of the genu of CC. However, many fewer studies used MD/ADC to examine the genu of CC in moderate-severe TBI ($N_{studies}$: 3; N_{TBI}: 81) than mild ($N_{studies}$: 12; N_{TBI}: 399), and one of the three moderate-severe studies

(N_{TBI}: 9) found the opposite effect (potentially due to differing participants or methodologies) — thus more research is needed to replicate this contrary finding. Overall, these findings suggest that more severe injuries lead to greater WM alterations, however our investigation of the impact of injury severity was limited by the fact that moderate and severe TBI could not be examined separately. Additionally, a large range of ROIs were examined across studies, with little overlap in the ROIs investigated in both mild and moderate-severe TBI. Notably, WM changes were found in many ROIs, even after mild TBI. Conventional CT and MRI often fails to detect abnormalities following mild TBI (Shenton et al., 2012), yet 15–30% of individuals who sustain such an injury develop persistent cognitive or functional deficits (McKee & Daneshvar, 2015; Shenton et al., 2012). DTI therefore appears to detect microscopic alterations to WM following more minor injuries, potentially providing a useful biomarker of TBI (Bigler & Bazarian, 2010).

Interestingly, there were more significant findings for MD/ADC than FA (63% versus 15%) in mild TBI. However, the ROIs examined were not identical, which may have contributed to this finding. Even so, it is possible that MD/ADC may be more sensitive to WM damage — at least at the mild level of injury — and therefore future studies may benefit from using MD/ADC in conjunction with FA, especially given that FA is more commonly used than MD/ADC.

With regard to timing, no differences were found between the DTI findings from the acute (≤ 1 week), subacute (>1 week to ≤ 3months; (Amyot et al., 2015) and chronic (> 3 months) intervals. This contrasts with previous research that has found that FA and MD/ADC findings were reversed in the short-term following TBI, possibly due to axonal swelling (Bazarian et al., 2007; Huisman et al., 2004). However, there is little consensus regarding what constitutes 'acute' and/or 'short-term' in the literature: acute has been defined as up to one (Huisman et al., 2004; Zhu et al., 2014) or two weeks (Hulkower et al., 2013), or is often not defined. 'Acute' was defined here as ≤ 1 week, which may be too long to capture immediate WM changes, with Bazarian et al. (2007) finding that FA was higher and MD lower up to 72 hours post-injury. On the other hand, the one week cut-off used here may have been too short; FA and MD/ADC values

have been found to be reversed in the short-term (defined as ≤ 4 weeks) in a recent paediatric meta-analysis (Roberts, Mathias, & Rose, 2014). However, differences in the structure of paediatric and adult brains may also account for these different findings (Pinto, Meoded, Poretti, Tekes, & Huisman, 2012). In addition to difficulties in defining these terms, fewer studies in the current meta-analysis examined the acute period (here defined as ≤ 1 week), making it difficult to fully explore short-term changes to FA and MD/ADC.

Limitations

The current meta-analysis has several limitations. First, few studies examined moderate TBI separately; therefore it was only possible to compare mild with moderate to severe injuries. Furthermore, it was not possible to include data from studies that used mixed samples of mild, moderate and severe because subgroup analyses revealed that the effects for mild and moderate-severe TBI were significantly different (i.e., it was not appropriate to analyse these data together), therefore the number of available studies was reduced. Although it appears that more severe injuries lead to greater changes to FA and MD/ADC, separate data for each category of injury (mild, moderate, severe) are required to determine whether there is a dose-response relationship.

Another limitation arises from the fact that, although WM damage is very common after TBI, the magnitude and location of this damage can vary between individuals (McKee & Daneshvar, 2015). Our examination of group data was more likely to capture changes in the large WM tracts that are most commonly affected by TBI (e.g., CC), but may have underestimated changes that are specific to particular individuals. Moreover, some of our data reduction strategies (e.g., averaging left/right, anterior/posterior measurements for the same brain structures) may have compounded the problem. Longitudinal studies that compare post-injury scans to either pre-injury or normative data would allow for an examination of individual differences in the magnitude and location of WM (Hulkower et al., 2013), however this data is rarely available.

Additionally, most studies presented combined data from the left- and right-side of the same brain structure. It therefore remains to be determined whether there are differences in left- and right-side ROIs following a TBI; more studies are needed examining left and right ROIs separately to explore this.

Next, significant heterogeneity was found between the effect sizes reported by different studies. A number of variables may have contributed to this, including the age of participants, timing of scan, and magnet strength. Participant ages ranged from 18 to 70 years, which may have affected the findings because WM structure differs in both developing and aging brains. Research has found that the brain continues to develop well into the second decade (Johnson, Blum, & Giedd, 2009) and age-related WM degeneration may begin at age 30 (Imperati et al., 2011), leading to decreased FA and increased MD/ADC (Madden et al., 2012). In part, this was overcome by including control participants who were of a similar age.

In addition, DTI was performed at very different times, ranging from less than an hour after injury to over 20 years post-injury. Although no differences were found between the findings from the acute (≤ 1 week), subacute (>1 week to ≤ 3months) and chronic (> 3 months) intervals, it is possible that the one week cut-off may be too long (or too short) to capture short-term WM changes, suggesting the need for a clearer definition of 'acute' timing, based on clinical or theoretical grounds. Furthermore, the examination of data from scans performed at such a broad range of times may have affected the findings. Additionally, different magnet strengths (1.5T and 3T) may have contributed to heterogeneity. Indeed, subgroup analyses revealed that the mean effect for studies that used a 1.5T magnet was larger than that for studies using a 3T magnet (FA findings), which is counterintuitive; however moderate-severe TBI was more commonly investigated using 1.5T and this may have contributed to these findings. It is also possible that differences in the data acquisition techniques, methods of analysis (e.g., voxel-based morphometry, tract-based spatial statistics), identification of ROIs (manual, semi-automated, fully-automated), and pre- and post-processing of DTI data could be sources of heterogeneity

(Amyot et al., 2015), however this information was not always reported and an examination of these variables was beyond the scope of this meta-analysis. Finally, the functional consequences of the changes identified here remains to be determined.

Conclusions

Overall, DTI identified WM changes in a wide range of ROIs, with moderate to severe injury leading to greater alterations to FA and MD/ADC than mild TBI. However, separate data for moderate and severe injuries is needed to fully explore the relationship between injury severity and DTI findings. Importantly, medium to very large and significant effects were seen even after mild TBI — which may not be detected using conventional CT and MRI scans — indicating that DTI could be a useful biomarker. Commonly investigated regions, such as the CC, consistently showed WM alterations, however more research is needed to examine other regions that showed larger effects, in order to determine whether it would be more beneficial to focus on these ROIs when assessing a TBI. These regions include: the centrum semiovale, cerebral peduncle, fornix, occipital WM, corona radiata and inferior longitudinal fasciculus. Furthermore, the usefulness of DTI in predicting functional and cognitive outcomes following a TBI remains to be determined.

3.3 Supplementary material

Appendix A. Logic grids for each database

PubMed Logic Grid

Traumatic brain injury	Diffusion tensor imaging
Brain injuries[mh] OR brain injur*[tw] OR head injuries, closed[mh] OR closed head injur*[tw] OR diffuse axonal injury[mh] OR diffuse axonal injur*[tw] OR brain traum*[tw] OR brain 70iffuse70o*[tw] OR 70iffuse70on*[tw] OR TBI[tw] OR TBIs[tw] OR Glasgow Coma Scale[mh] OR Glasgow Coma Scale[tw]	Diffusion tensor imaging[mh] OR diffusion tensor imag*[tw] OR diffusion magnetic resonance imaging[mh] OR diffusion magnetic resonance imag*[tw] OR diffusion MRI*[tw] OR diffusion weighted imag*[tw] OR diffusion weighted MRI*[tw] OR diffusion tractography[tw] diffusion tensor tractography[tw] OR anisotropy[mh] OR anisotropy[tw] OR apparent diffusion coefficient[tw] OR mean 70iffuse*[tw] OR DTI[tw] OR DWI[tw]

PsycINFO Logic Grid

Traumatic brain injury	Diffusion tensor imaging
Exp traumatic brain injury OR brain injur*.mp OR exp head injuries OR head injur*.mp OR diffuse axonal injur*.mp Or brain traum*.mp OR brain 70iffuse70o*.mp OR 70iffuse70on*.mp OR TBI.mp OR TBIs.mp OR Glasgow Coma Scale.mp	Diffusion tensor imag*.mp OR diffusion magnetic resonance imag*.mp OR diffusion MRI*.mp OR diffusion weighted imag*.mp OR diffusion weighted MRI*.mp OR diffusion tractography.mp OR diffusion tensor tractography.mp OR anisotropy.mp OR apparent diffusion coefficient.mp OR mean 70iffuse*.mp OR DTI.mp OR exp magnetic resonance imaging OR magnetic resonance imaging.mp OR MRI.mp OR DWI.mp

Embase Logic Grid

Traumatic brain injury	Diffusion tensor imaging
'brain injury'/exp OR ' brain injury':de,ti,ab OR 'brain injuries':ti,ab OR 'traumatic brain injury':de,ti,ab OR 'traumatic brain injuries':ti,ab OR 'closed head injury':ti,ab OR 'head injury':de,ti,ab OR 'diffuse axonal injury':de,ti,ab OR 'diffuse axonal injuries':ti,ab OR 'brain trauma':ti,ab OR 'brain contusion':de,ti,ab OR 'brain contusions':ti,ab OR 'concussion'/exp OR 'concussion':de,ti,ab OR 'concussions':ti,ab OR TBI:ti,ab OR TBI:ti,ab OR 'Glasgow Coma Scale':de,ti,ab	'diffusion tensor imaging':de,ti,ab OR 'diffusion tensor images':ti,ab OR 'diffusion magnetic resonance imaging':ti,ab OR 'diffusion MRI':ti,ab OR 'diffusion weighted imaging':de,ti,ab OR 'diffusion weighted images':ti,ab OR 'diffusion tractography':ti,ab OR 'diffusion tensor tractography':ti,ab OR 'anisotropy':de,ti,ab OR 'fractional anisotropy':de,ti,ab OR 'apparent diffusion coefficient':ti,ab OR 'mean diffusivity':ti,ab OR 'DTI':ti,ab OR 'DWI':ti,ab

Web of Science Logic Grid

Traumatic brain injury	Diffusion tensor imaging
TS=('brain injur*' OR 'traumatic brain injur*' OR 'head injur*' OR 'closed head injur*' OR 'diffuse axonal injur*' OR 'brain traum*' OR 'brain contusio*' OR 'concussio*' OR 'TBI' OR 'TBIs' OR 'Glasgow Coma Scale')	TS=('diffusion tensor imag*' OR 'diffusion magnetic resonance imag*' OR 'diffusion MRI' OR 'diffusion MRIs' OR 'diffusion weighted imag*' OR 'diffusion weighted MRI' OR 'diffusion tractography' OR 'diffusion tensor tractography' OR 'anisotrophy' OR 'fractional anisotropy' OR 'apparent diffusion coefficient' OR 'mean diffusi*' OR 'DTI' OR 'DWI')

Note. TS= topic search

Table S1. Summary details for the studies included in this meta-analysis

ref	*reference*	*Telsa*	*brand/model of scanner*	*severity*	*# RH*	*type of control*	*FA or MD/ADC*	*M(SD) time since injury*	*time period*	N_{TBI}	$N_{Control}$
1	Bazarian (2007)	3	Siemens Trio	mild	NS	orthopedic	FA & MD/ADC	within 72 hours	acute	6	6
2	Brandstack (2011)	1.5	General Electric Signa	mild*	NS	healthy	MD/ADC	7 (2) days	acute	7	14
3	D'souza (2015)	3	Siemens Skyra	mild & moderate	NS	healthy	FA & MD/ADC	within 7 days	acute	19	12
4	Dean (2015)	3	Siemens Trio	mild	NS	healthy	FA	6.1 (6.0) years	chronic	16	9
5	Grossman (2012)	3	Siemens Magnetom Trio	mild	NS	healthy	FA & MD/ADC	2.7 (2.7) years	chronic	22	14
6	Hong (2012)	1.5	Philips Gyroscan Intera	severe	NS	healthy	FA & MD/ADC	191.1 (102.2) days	chronic	14	14
7	Ilvesmaki (2014)	3	Siemens Trio	mild	NS	ankle injury/orthopedic	FA & MD/ADC	48.1 (45.4) hours	acute	75	40
8	Inglese (2005)	1.5	Siemens Vision	mild	NS	healthy	FA & MD/ADC	4.1 days (acute)/ 5.7 years (post)	acute & chronic	46	29
9	Jang (2013)	1.5	Philips Gyroscan Intera	severe	NS	healthy	FA & MD/ADC	7.8 (7.9) months	chronic	21	21
10	Kasahara (2012)	1.5	Siemens Symphony	mild & severe	NS	healthy	FA	6.3 years	chronic	15	12
11	Kennedy (2009)	3	Siemens Trio	severe	NS	healthy	FA & MD/ADC	7 (8.6) years	chronic	8	8
12	Kim (2015)	1.5	Philips Gyroscan Intera	mild	NS	healthy	FA & MD/ADC	11.1 months	chronic	32	21
13	Kraus (2007)	3	General Electric Signa	mild & moderate-severe	NS	healthy	FA	107.2 (26.1) months	chronic	37	18
14	Kumar (2009)	1.5	General Electric	mild & moderate	NS	healthy	FA & MD/ADC	8.9 days	subacute	83	33
15	Lange (2012)	3	Philips Achieva	mild	NS	orthopaedic/ trauma	FA & MD/ADC	47.0 (6.3) days	subacute	60	34
16	Lee & Jang (2015)	1.5	Philips Gyroscan Intera	mild	NS	healthy	FA & MD/ADC	3.8 (3.1) months	chronic	29	25
17	Ling (2012)	3	Siemens Trio	mild	NS	healthy	FA	13.9 (4.9) days	subacute	50	50
18	Lipton (2008)	1.5	General Electric Signa Excite	mild	NS	healthy	FA & MD/ADC	8 months–3 years	chronic	17	10
19	Little (2010)	3	General Electric	mild & moderate-severe	NS	healthy	FA	77.3 months	chronic	24	12

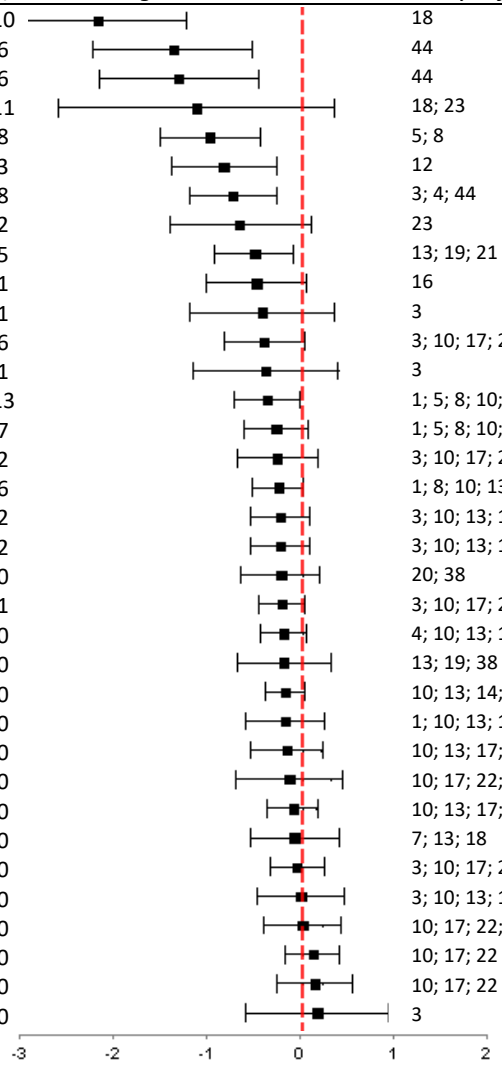
20	Lo (2009)	1.5	General Electric Signa Excite	mild	NS	MRI for headache	FA & MD/ADC	at least 2 years	chronic	10	10
21	Maruta (2010)	3	General Electric Signa Excite	mild	NS	healthy	FA	2.7 years	chronic	17	9
22	Maruta (2016)	3	General Electric Signa Excite	mild	NS	healthy	FA	20 (13.1) months	chronic	32	32
23	Matsushita (2011)	1.5	Philips Gyroscan Intera	mild & moderate	NS	healthy	FA	3.5 days	acute	20	27
24	Messe (2010)			mild	NS	healthy	MD/ADC	17.7 (7.2) days	subacute	23	23
25	Messe (2012)	3	Siemens Trio	mild	NS	healthy	FA & MD/ADC	6 months	chronic	53	40
26	Palacios (2011)	1.5	General Electric Signa	severe	all RH	healthy	FA	278.5 (173.2) hours	subacute	15	16
27	Palacios (2013)	3	Siemens Magnetom	severe	NS	healthy	FA	4.2 (1.1) years	chronic	26	22
28	Palmer (2010)	3	Philips Intera	severe	all RH	healthy	FA & MD/ADC	4.4 (0.5) years	chronic	10	9
29	Rutgers (2008)	1.5	Siemens Sonata	mild & moderate & severe	NS	healthy	FA & MD/ADC	months: 2.8, 0.5, 1.4	subacute	39	10
30	Scott (2015)	3	Philips Intera	moderate-severe	NS	healthy	FA	6.2 (5.3) years	chronic	10	13
31	Seo (2012)	1.5	Philips Gyroscan Intera	severe	NS	healthy	FA & MD/ADC	9.5 (11.6) months	chronic	21	21
32	Sidaros (2008)	1.5	Siemens Magnetom Vision	severe	NS	healthy	FA & MD/ADC	8 weeks	chronic	30	30
33	Smits (2011)	3	General Electric	mild	NS	healthy	FA	30.6 days	subacute	19	12
34	Tollard (2009)	1.5	General Electric Signa	severe	NS	healthy	FA	24 (11) days	subacute	43	15
35	Ubukata (2015)	3	Siemens Magnetom Trio	severe	all RH	healthy	FA	106.9 (79.4) months	chronic	10	12
36	Veeramuthu (2015)	3	General Electric Signa	mild	53 TBI 17 ctrl	healthy	FA & MD/ADC	10.0 (4.3) hours	acute	61	19
37	Wada (2012)	1.5	General Electric Signa	mild	all RH	healthy	FA	35.1 (26.3) months	chronic	51	50
38	Waljas (2014)	3	Siemens Trio	mild	NS	healthy	FA & MD/ADC	27.4 (8.9) days	subacute	48	24
39	Wilde (2016)	3	Philips Intera	mild	all RH	orthopaedic/ trauma	FA & MD/ADC	94 (8.7) days	chronic	79	64
40	Xu (2007)	3	Philips Intera	severe	NS	healthy	FA & MD/ADC	4 years	chronic	9	11

41	Yao (2015)	1.5	General Electric Excite	severe	NS	healthy	FA	2–11 days	acute	11	11
42	Yuh (2014)	3	General Electric Signa Excite	mild	66 TBI 48 ctrl	healthy	FA	11.2 (3.3) days	subacute	76	50
43	Zhang (2010)	3	Siemens Trio	mild	all RH	healthy	FA & MD/ADC	30 (2) days	subacute	15	15
44	Zhu (2014)	1.5	Siemens Magnetom Avanto	mild	NS	healthy	FA	5.5 (2.3) days	acute	12	13

Note. *mild to severe group also studied, not included in analyses; *ref* = study reference number; *# RH* = number of right handed participants; NS = not specified; *FA* = fractional anisotropy; *MD/ADC* = mean diffusivity/apparent diffusion coefficient; *M(SD)* = mean and standard deviation; N_{TBI} = total number of TBI participants; $N_{Control}$ = total number of control participants

Table S2. Mild TBI: Hedges' *g* effect sizes for FA data for individual ROIs, rank-ordered by effect sizes

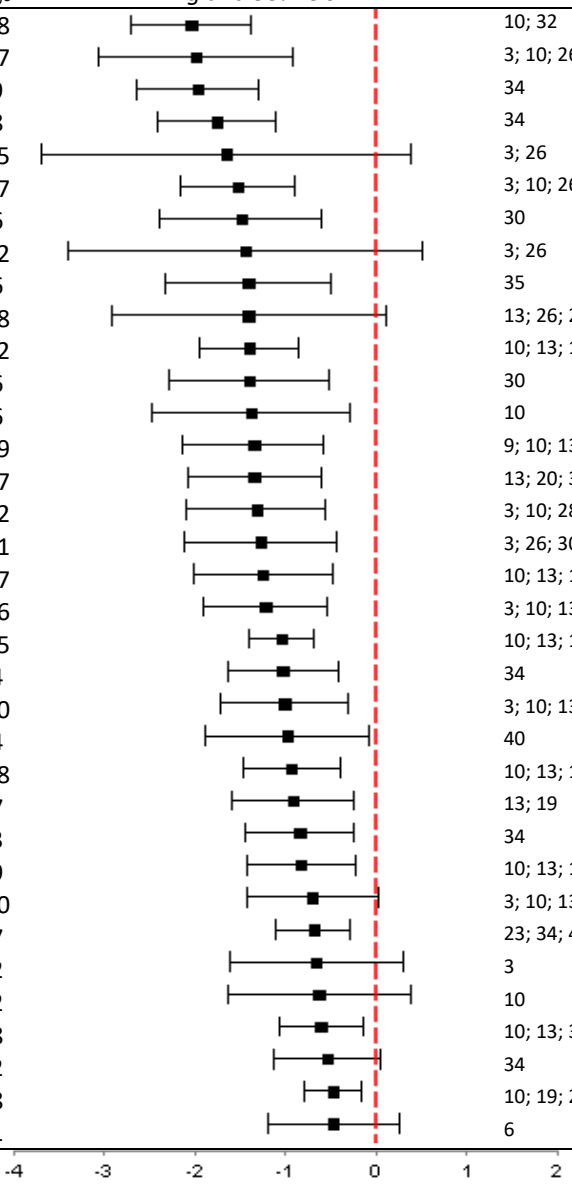
Brain region	$N_{studies}$	N_{TBI}	$N_{Control}$	*g*	*g SE*	N_{fs}	*g and 95% CIs*	*Study references*
orbitofrontal	1	17	10	-2.19***	0.49	10		18
extranuclear	1	12	13	-1.38**	0.43	6		44
subgyral	1	12	13	-1.32**	0.43	6		44
occipital WM	2	26	37	-1.13	0.76	11		18; 23
centrum semiovale	2	68	43	-0.99***	0.27	8		5; 8
spinothalamocortical tract	1	32	21	-0.84**	0.29	3		12
corpus callosum (whole)	3	41	34	-0.74**	0.24	8		3; 4; 44
frontal WM	1	9	27	-0.67	0.38	2		23
forceps major	3	49	39	-0.51*	0.21	5		13; 19; 21
corticoreticular pathway	1	29	25	-0.49	0.27	1		16
arcuate fasciculus	1	13	12	-0.43	0.39	1		3
fornix	6	209	196	-0.41	0.22	6		3; 10; 17; 22; 25; 37
cingulate fasciculus	1	13	12	-0.40	0.39	1		3
internal capsule	14	480	335	-0.38*	0.18	13		1; 5; 8; 10; 17; 18; 19; 20; 22; 23; 25; 36; 38; 42
corpus callosum (splenium)	18	580	435	-0.28	0.17	7		1; 5; 8; 10; 13; 14; 15; 17; 19; 20; 22; 23; 25; 29; 36; 38; 42; 43
thalamic radiations	6	219	165	-0.27	0.22	2		3; 10; 17; 22; 25; 36
corpus callosum (genu)	20	671	504	-0.26	0.14	6		1; 8; 10; 13; 14; 15; 17; 18; 19; 20; 21; 22; 23; 25; 29; 36; 38; 39; 42; 43
fronto-occipital fasciculus	10	364	302	-0.24	0.16	2		3; 10; 13; 17; 19; 22; 25; 33; 39; 42
superior longitudinal fasciculus	10	378	295	-0.24	0.16	2		3; 10; 13; 17; 19; 22; 25; 36; 37; 42
pons	2	58	34	-0.23	0.22	0		20; 38
uncinate fasciculus	8	302	243	-0.22	0.12	1		3; 10; 17; 21; 22; 25; 38; 39
corona radiate	12	404	302	-0.20	0.13	0		4; 10; 13; 17; 19; 21; 22; 23; 25; 36; 38; 42
forceps minor	3	80	54	-0.20	0.25	0		13; 19; 38
corpus callosum (body)	12	387	333	-0.18	0.11	0		10; 13; 14; 15; 17; 19; 22; 23; 25; 29; 42; 43
external capsule	7	247	208	-0.18	0.21	0		1; 10; 13; 17; 22; 25; 42
sagittal stratum	7	253	214	-0.17	0.20	0		10; 13; 17; 19; 22; 25; 42
cerebral peduncle	5	193	158	-0.14	0.29	0		10; 17; 22; 25; 38
cingulum	8	319	230	-0.10	0.14	0		10; 13; 17; 21; 22; 25; 36; 42
whole brain	3	114	95	-0.09	0.24	0		7; 13; 18
cerebellar peduncle	7	236	174	-0.06	0.14	0		3; 10; 17; 21; 22; 25; 36
corticospinal tract	6	137	136	-0.02	0.24	0		3; 10; 13; 17; 19; 22
tapetum	4	145	134	0.00	0.21	0		10; 17; 22; 25
medial lemniscus	3	92	94	0.11	0.15	0		10; 17; 22
pontine crossing tract	3	92	94	0.13	0.21	0		10; 17; 22
inferior longitudinal fasciculus	1	13	12	0.16	0.39	0		3



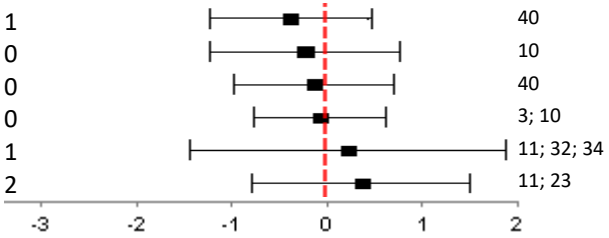
Note. FA = fractional anisotropy; ROIs = regions of interest; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; $N_{Control}$ = total number of control participants; *g* = Hedges' *g* effect size; *SE* = standard error; *Nfs* = Fail safe N; 95% CIs = 95% confidence intervals; WM = white matter; *p< .05, **p< .01, ***p< .001

Table S3. Moderate-severe TBI: Hedges' *g* effect sizes for FA data for individual ROIs, rank-ordered by effect sizes

Brain region	$N_{studies}$	N_{TBI}	$N_{Control}$	*g*	*SE*	N_{fs}	*g and 95% CIs*	*Study references*
cerebral peduncle	2	27	26	-2.04***	0.34	18		10; 32
fornix	3	26	40	-1.99***	0.55	27		3; 10; 26
supratentorial	1	43	15	-1.97***	0.35	9		34
temporal WM	1	43	15	-1.76***	0.34	8		34
inferior longitudinal fasciculus	2	21	28	-1.65	1.04	15		3; 26
uncinate fasciculus	4	47	61	-1.53***	0.32	27		3; 10; 26; 31
thalamocortical projection	1	10	13	-1.49**	0.46	6		30
arcuate fasciculus	2	21	28	-1.44	1.00	12		3; 26
brainstem	1	10	12	-1.41**	0.46	6		35
whole brain	3	58	56	-1.41	0.77	18		13; 26; 27
corpus callosum (splenium)	7	133	127	-1.40***	0.28	42		10; 13; 14; 19; 23; 32; 40
WM skeleton	1	10	13	-1.40**	0.46	6		30
tapetum	1	5	12	-1.38*	0.56	6		10
cingulum	5	68	79	-1.35**	0.40	29		9; 10; 13; 26; 35
forceps minor	3	29	42	-1.35***	0.38	17		13; 20; 35
thalamic radiations	4	32	44	-1.32**	0.40	22		3; 10; 28; 41
corpus callosum (whole)	4	41	53	-1.27**	0.43	21		3; 26; 30; 35
corpus callosum (genu)	7	122	124	-1.25**	0.39	37		10; 13; 14; 19; 23; 40; 41
fronto-occipital fasciculus	5	55	70	-1.22***	0.35	26		3; 10; 13; 19; 26
corpus callosum (body)	6	113	113	-1.04***	0.19	25		10; 13; 14; 19; 23; 41
infratentorial	1	43	15	-1.03**	0.31	4		34
superior longitudinal fasciculus	5	55	70	-1.01**	0.36	20		3; 10; 13; 19; 26
periventricular WM	1	9	11	-0.98*	0.46	4		40
corona radiata	5	56	80	-0.93**	0.28	18		10; 13; 19; 23; 41
forceps major	2	29	30	-0.91**	0.34	7		13; 19
midbrain	1	43	15	-0.84**	0.31	3		34
sagittal stratum	3	34	42	-0.83**	0.30	9		10; 13; 19
corticospinal tract	4	40	54	-0.70	0.37	10		3; 10; 13; 20
occipital WM	3	63	53	-0.69**	0.21	7		23; 34; 40
cingulate fasciculus	1	6	12	-0.66	0.49	2		3
pontine crossing tract	1	5	12	-0.63	0.52	2		10
external capsule	4	76	56	-0.61*	0.24	8		10; 13; 34; 41
pons	1	43	15	-0.54	0.30	2		34
internal capsule	6	141	107	-0.48*	0.16	8		10; 19; 23; 32; 34; 40
medial cholinergic pathway	1	14	14	-0.47	0.37	1		6



deep frontal	1	9	11	-0.37	0.44	1	40
medial lemniscus	1	5	12	-0.21	0.51	0	10
medial orbitofrontal WM	1	9	11	-0.12	0.43	0	40
cerebellar peduncle	2	11	24	-0.05	0.35	0	3; 10
centrum semiovale	3	73	37	0.25	0.85	1	11; 32; 34
frontal WM	2	19	35	0.39	0.58	2	11; 23

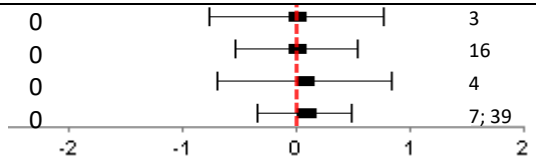


Note. FA = fractional anisotropy; ROIs = regions of interest; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; $N_{Control}$ = total number of control participants; *g* = Hedges' *g* effect size; *SE* = standard error; *Nfs* = Fail safe N; 95% CIs = 95% confidence intervals; WM = white matter; **p*< .05, ***p*< .01, ****p*< .001

Table S4. Mild TBI: Hedges' *g* effect sizes for MD/ADC data for individual ROIs, rank-ordered by effect sizes

Brain region	$N_{studies}$	N_{TBI}	$N_{Control}$	*g*	*g SE*	N_{fs}	*g and 95% CIs*	*Study references*
subcallosal fasciculus	1	7	14	-1.35**	0.49	6		2
midbrain	1	7	14	-1.30**	0.49	1		2
occipital WM	2	24	24	-1.30*	0.54	11		2; 18
cerebral peduncle	1	53	40	-1.17***	0.23	5		25
temporopolar WM	1	7	14	-1.11*	0.48	5		2
posterolateral temporal WM	1	7	14	-1.10*	0.48	5		2
parietal WM	1	7	14	-0.99*	0.47	4		2
forceps minor	1	11	23	-0.95*	0.38	4		24
forceps major	1	11	23	-0.88*	0.37	3		24
tapetum	1	53	40	-0.83***	0.22	3		25
inferior longitudinal fasciculus	3	31	49	-0.81**	0.24	9		2; 3; 24
orbitofrontal	1	17	10	-0.80*	0.40	3		18
sagittal stratum	1	53	40	-0.80***	0.22	3		25
corona radiata	4	170	97	-0.73**	0.25	11		2; 25; 36; 38
thalamic radiations	4	138	94	-0.72***	0.19	10		3; 24; 25; 36
cingulum	2	68	33	-0.68**	0.23	5		2; 36
corpus callosum (splenium)	12	378	248	-0.60**	0.19	24		1; 2; 5; 8; 14; 15; 20; 25; 29; 36; 38; 43
superior longitudinal fasciculus	5	145	108	-0.59*	0.27	10		2; 3; 24; 25; 36
centrum semiovale	2	68	43	-0.58	0.35	4		5; 8
external capsule	3	66	60	-0.58*	0.26	6		1; 2; 25
fornix	2	66	52	-0.54*	0.21	3		3; 25
cerebellum	1	7	14	-0.52	0.45	2		2
corpus callosum (whole)	1	13	12	-0.43	0.39	1		3
corpus callosum (body)	5	178	132	-0.41*	0.19	5		14; 12; 25; 29; 43
internal capsule	9	270	166	-0.41*	0.17	9		1; 2; 5; 8; 18; 20; 25; 36; 38
fronto-occipital fasciculus	3	103	99	-0.35	0.21	2		3; 24; 39
corpus callosum (genu)	12	399	268	-0.34***	0.10	8		1; 2; 8; 14; 15; 18; 20; 29; 36; 38; 39; 43
cerebellar peduncle	2	74	31	-0.28	0.22	1		3; 36
corticospinal tract	2	24	35	-0.27	0.58	1		3; 24
uncinate fasciculus	3	140	100	-0.21	0.2	0		3; 38; 39
spinothalamocortical tract	1	32	21	-0.15	0.28	0		12
pons	3	65	48	-0.10	0.27	0		2; 20; 38

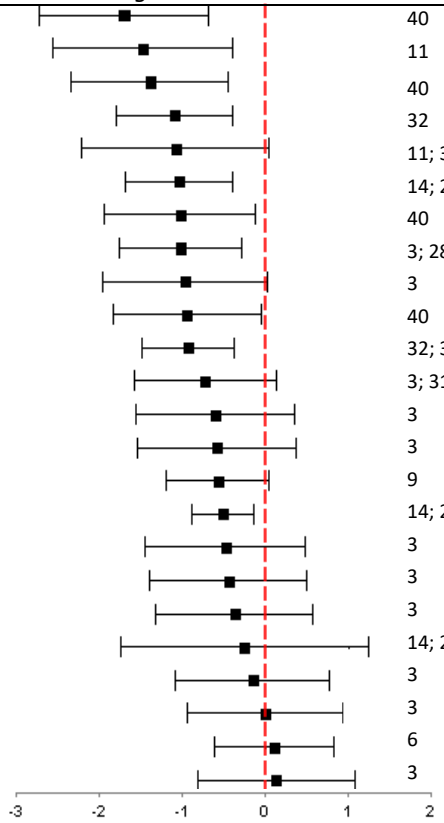
cingulate fasciculus	1	13	12	0.00	0.39	0		3
corticoreticular pathway	1	29	25	0.00	0.27	0		16
arcuate fasciculus	1	13	12	0.07	0.39	0		4
whole brain	2	94	77	0.08	0.21	0		7; 39



Note. MD/ADC = mean diffusivity/apparent diffusion coefficient; ROIs = regions of interest; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; $N_{Control}$ = total number of control participants; *g* = Hedges' *g* effect size; *SE* = standard error; *Nfs* = Fail safe N; 95% CIs = 95% confidence intervals; WM = white matter; **p*< .05, ***p*< .01, ****p*< .001

Table S5. Moderate-severe TBI: Hedges' *g* effect sizes for MD/ADC data for individual ROIs, rank-ordered by effect sizes

Brain region	$N_{studies}$	N_{TBI}	$N_{Control}$	*g*	*SE*	N_{fs}	*g and 95% CIs*	*Study references*
deep frontal	1	9	11	-1.70**	0.52	8		40
frontal WM	1	8	8	-1.47**	0.55	6		11
periventricular WM	1	9	11	-1.39**	0.49	6		40
cerebral peduncle	1	22	14	-1.09**	0.36	4		32
centrum semiovale	2	30	22	-1.08	0.57	9		11; 32
corpus callosum (splenium)	4	103	68	-1.03**	0.33	17		14; 29; 32; 40
medial orbitofrontal WM	1	9	11	-1.02*	0.46	4		40
thalamic radiations	2	16	21	-1.02**	0.37	8		3; 28
inferior longitudinal fasciculus	1	6	12	-0.97	0.51	4		3
occipital WM	1	9	11	-0.94*	0.46	4		40
internal capsule	2	31	25	-0.93**	0.28	7		32; 39
uncinate fasciculus	2	27	33	-0.72	0.44	5		3; 31
corticospinal tract	1	6	12	-0.60	0.49	2		3
fronto-occipital fasciculus	1	6	12	-0.59	0.49	2		3
cingulum	1	21	21	-0.57	0.31	2		9
corpus callosum (body)	2	72	43	-0.51**	0.19	3		14; 29
superior longitudinal fasciculus	1	6	12	-0.48	0.49	1		3
cingulate fasciculus	1	6	12	-0.44	0.48	1		3
arcuate fasciculus	1	6	12	-0.37	0.48	1		3
corpus callosum (genu)	3	81	54	-0.25	0.76	1		14; 29; 40
fornix	1	6	12	-0.15	0.48	0		3
corpus callosum (whole)	1	6	12	0.00	0.48	0		3
medial cholinergic pathway	1	14	14	0.11	0.37	0		6
cerebellar peduncle	1	6	12	0.13	0.48	0		3



Note. MD/ADC = mean diffusivity/apparent diffusion coefficient; ROIs = regions of interest; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; $N_{Control}$ = total number of control participants; *g* = Hedges' *g* effect size; *SE* = standard error; *Nfs* = Fail safe N; 95% CIs = 95% confidence intervals; WM = white matter; *p< .05, **p< .01, ***p< .001

Table S6. Subgroup analyses

group	$N_{studies}$	*g (95% CI)*	*p-value*	*heterogeneity*			*total between p-value*
				Q	*p-value*	I^2	
timing of DTI: FA							**0.428**
acute (≤ 1 week)	8	-0.52 (-0.84+0.20)	0.001	65.56	0.000	89.32	
subacute (1 week-3 months)	10	-0.63 (-1.01+0.25)	0.001	332.52	0.000	97.29	
chronic (> 3 months)	25	-0.78 (-1.01+0.54)	0.000	433.19	0.000	94.46	
overall	43	-0.67 (-0.84+0.51)	0.000	1128.10	0.000	95.27	
timing of DTI: MD/ADC							**0.192**
acute (≤ 1 week)	6	-0.29 (-0.54+0.04)	0.021	28.50	0.000	82.46	
subacute (1 week-3 months)	6	-0.41 (-0.65+0.17)	0.001	22.81	0.000	78.08	
chronic (> 3 months)	15	-0.61 (-0.86+0.36)	0.000	99.93	0.000	85.99	
overall	27	-0.43 (-0.58+0.29)	0.000	170.57	0.000	84.76	
TBI severity: FA							**0.000**
mild	29	-0.45 (-0.62+0.28)	0.000	509.20	0.000	94.50	
moderate-severe	20	-1.06 (-1.29+0.83)	0.000	155.20	0.000	87.76	
overall	49	-0.67 (-0.81+0.53)	0.000	1019.81	0.000	95.29	
TBI severity: MD/ADC							**0.027**
mild	19	-0.40 (-0.59+0.21)	0.000	165.91	0.000	89.15	
moderate-severe	10	-0.72 (-0.94+0.50)	0.000	20.25	0.016	55.55	
overall	29	-0.54 (-0.68+0.39)	0.000	195.02	0.000	85.64	
magnet strength: FA							**0.020**
1.5 Tesla	18	-0.89 (-1.13+0.65)	0.000	171.59	0.000	90.09	
3 Tesla	24	-0.51 (-0.72+0.31)	0.000	503.78	0.000	95.44	
overall	42	-0.67 (-0.83+0.52)	0.000	877.78	0.000	95.33	
magnet strength: MD/ADC							**0.951**
1.5 Tesla	12	-0.46 (-0.63+0.29)	0.000	27.96	0.003	60.66	
3 Tesla	13	-0.47 (-0.72+0.23)	0.000	128.53	0.000	90.66	
overall	25	-0.47 (-0.61+0.33)	0.000	158.17	0.000	84.83	
brand scanner: FA							**0.578**
General Electric	14	-0.80 (-1.12+0.48)	0.000	413.28	0.000	96.85	
Philips	10	-0.67 (-0.98+0.36)	0.000	58.82	0.000	84.70	
Siemens	17	-0.57 (-0.86+0.28)	0.000	396.93	0.000	95.97	
overall	41	-0.67 (-0.85+0.50)	0.000	874.80	0.000	95.43	
brand scanner: MD/ADC							**0.670**
General Electric	5	-0.51 (-0.73+0.29)	0.000	15.36	0.004	73.96	
Philips	8	-0.36 (-0.62+0.10)	0.006	21.02	0.004	66.70	
Siemens	12	-0.48 (-0.74+0.21)	0.000	105.03	0.000	89.53	
overall	25	-0.45 (-0.60+0.31)	0.000	158.17	0.000	84.83	
# DW images: FA							**0.900**
< 30	21	-0.69 (-0.93+0.44)	0.000	302.35	0.000	93.39	
≥ 30	21	-0.67 (-0.90+0.44)	0.000	457.14	0.000	95.63	
overall	42	-0.68 (-0.84+0.51)	0.000	877.78	0.000	95.33	

# DW images: MD/ADC							**0.955**
< 30	12	-0.45 (-0.67+0.24)	0.000	62.90	0.000	82.51	
≥ 30	13	-0.46 (-0.71+0.22)	0.000	92.13	0.000	86.98	
overall	25	-0.46 (-0.62+0.29)	0.000	160.10	0.000	85.01	
b-values: FA							**0.552**
b < 1000	8	-0.59 (-1.01+0.18)	0.005	204.36	0.000	96.58	
b ≥ 1000	33	-0.73 (-0.94+0.53)	0.000	640.02	0.000	95.00	
overall	41	-0.71 (-0.89+0.53)	0.000	882.23	0.000	95.47	
b-values: MD/ADC							**0.300**
b < 1000	5	-0.67 (-1.05+0.29)	0.001	19.23	0.001	79.20	
b ≥ 1000	20	-0.44 (-0.62+0.26)	0.000	146.65	0.000	87.04	
overall	25	-0.48 (-0.65+0.32)	0.000	167.78	0.000	85.70	

Note 1. $N_{studies}$ = number of studies; *g (95% CI)* = Hedges' *g* effect size (95% confidence interval); FA = fractional anisotropy; MD/ADC = mean diffusivity/apparent diffusion coefficient; # DW images = number of diffusion-weighted images

Note 2. DW < 30 was compared to DW ≥ 30 loosely based on Dodd et al.'s (2014) work that found the number of DW images was associated with differences in FA: higher FA (DW ≥ 30) or lower FA (DW ≤ 25) in TBI versus controls. Our analyses were constrained by several studies which had DW images that fell between 25 and 30, thus we compared DW < 30 vs ≥ 30.

Note 3. The majority of studies used b-value = 1,000 (FA $N_{studies}$ = 31; MD/ADC $N_{studies}$ = 19)

3.4 List of studies included in this meta-analysis

[1-44] numbers correspond to the study references given in Tables 2 to 5 & Supplementary Tables S2 to S5

[1] Bazarian, J. J., Zhong, J., Blyth, B., Zhu, T., Kavcic, V., & Peterson, D. (2007). Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. *Journal of Neurotrauma, 24*(9), 1447-1459. doi: 10.1089/neu.2007.0241

[2] Brandstack, N., Kurki, T., Hiekkanen, H., & Tenovuo, O. (2011). Diffusivity of normal-appearing tissue in acute traumatic brain injury. *Clinical Neuroradiology, 21*(2), 75-82. doi: 10.1007/s00062-011-0058-5

[3] D'Souza, M. M., Trivedi, R., Singh, K., Grover, H., Choudhury, A., Kaur, P., . . . Tripathi, R. P. (2015). Traumatic brain injury and the post-concussion syndrome: A diffusion tensor tractography study. *Indian Journal of Radiology and Imaging, 25*(4), 404-414. doi: 10.4103/0971-3026.169445

[4] Dean, P. J. A., Sato, J. R., Vieira, G., McNamara, A., & Sterr, A. (2015). Multimodal imaging of mild traumatic brain injury and persistent postconcussion syndrome. *Brain and Behavior, 5*(1), 45-61. doi: 10.1002/brb3.292

[5] Grossman, E. J., Ge, Y. L., Jensen, J. H., Babb, J. S., Miles, L., Reaume, J., . . . Inglese, M. (2012). Thalamus and cognitive impairment in mild traumatic brain injury: A diffusional kurtosis imaging study. *Journal of Neurotrauma, 29*(13), 2318-2327. doi: 10.1089/neu.2011.1763

[6] Hong, J. H., Jang, S. H., Kim, O. L., Kim, S. H., Ahn, S. H., Byun, W. M., . . . Lee, D. H. (2012). Neuronal loss in the medial cholinergic pathway from the nucleus basalis of Meynert in patients with traumatic axonal injury: A preliminary diffusion tensor imaging study. *Journal of Head Trauma Rehabilitation, 27*(3), 172-176. doi: 10.1097/HTR.0b013e318217192d

[7] Ilvesmaki, T., Luoto, T. M., Hakulinen, U., Brander, A., Ryymin, P., Eskola, H., . . . Ohman, J. (2014). Acute mild traumatic brain injury is not associated with white matter change on diffusion tensor imaging. *Brain: A Journal of Neurology, 137*(7), 1876-1882. doi: 10.1093/brain/awu095

[8] Inglese, M., Makani, S., Johnson, G., Cohen, B. A., Silver, J. A., Gonen, O., & Grossman, R. I. (2005). Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *Journal of Neurosurgery, 103*(2), 298-303. doi: 10.3171/jns.2005.103.2.0298

[9] Jang, S. H., Kim, S. H., Kim, O. R., Byun, W. M., Kim, M. S., Seo, J. P., & Chang, M. C. (2013). Cingulum injury in patients with diffuse axonal injury: a diffusion tensor imaging study. *Neuroscience Letters, 543*, 47-51. doi: 10.1016/j.neulet.2013.02.058

[10] Kasahara, K., Hashimoto, K., Abo, M., & Senoo, A. (2012). Voxel- and atlas-based analysis of diffusion tensor imaging may reveal focal axonal injuries in mild traumatic brain injury - comparison with diffuse axonal injury. *Magnetic Resonance Imaging, 30*(4), 496-505. doi: 10.1016/j.mri.2011.12.018

[11] Kennedy, M. R., Wozniak, J. R., Muetzel, R. L., Mueller, B. A., Chiou, H. H., Pantekoek, K., & Lim, K. O. (2009). White matter and neurocognitive changes in adults with chronic traumatic brain injury. *Journal of the International Neuropsychological Society, 15*(1), 130-136. doi: 10.1017/s1355617708090024

[12] Kim, J. H., Ahn, S. H., Cho, Y. W., Kim, S. H., & Jang, S. H. (2015). The relation between injury of the spinothalamocortical tract and central pain in chronic patients with mild traumatic brain injury. *Journal of Head Trauma Rehabilitation,* 30(6), 40-46. doi: 10.1097/htr.0000000000000121

[13] Kraus, M. F., Susmaras, T., Caughlin, B. P., Walker, C. J., Sweeney, J. A., & Little, D. M. (2007). White matter integrity and cognition in chronic traumatic brain injury: A diffusion tensor imaging study. *Brain: A Journal of Neurology, 130*(10), 2508-2519. doi: http://dx.doi.org.proxy.library.adelaide.edu.au/10.1093/brain/awm216

[14] Kumar, R., Gupta, R. K., Husain, M., Chaudhry, C., Srivastava, A., Saksena, S., & Rathore, R. K. S. (2009). Comparative evaluation of corpus callosum DTI metrics in acute mild and moderate traumatic brain injury: Its correlation with neuropsychometric test. *Brain Injury, 23*(7-8), 675-685. doi: 10.1080/02699050903014915

[15] Lange, R. T., Iverson, G. L., Brubacher, J. R., Madler, B., & Heran, M. K. (2012). Diffusion tensor imaging findings are not strongly associated with postconcussional disorder 2 months following mild traumatic brain injury. *The Journal of Head Trauma Rehabilitation, 27*(3), 188-198. doi: 10.1097/HTR.0b013e318217f0ad

[16] Lee, H. D., & Jang, S. H. (2015). Injury of the corticoreticular pathway in patients with mild traumatic brain injury: A diffusion tensor tractography study. *Brain Injury, 29*(10), 1219-1222. doi: 10.3109/02699052.2015.1045028

[17] Ling, J. M., Pena, A., Yeo, R. A., Merideth, F. L., Klimaj, S., Gasparovic, C., & Mayer, A. R. (2012). Biomarkers of increased diffusion anisotropy in semi-acute mild traumatic brain injury: A longitudinal perspective. *Brain: A Journal of Neurology, 135*(4), 1281-1292. doi: 10.1093/brain/aws073

[18] Lipton, M. L., Gellella, E., Lo, C., Gold, T., Ardekani, B. A., Shifteh, K., . . . Branch, C. A. (2008). Multifocal white matter ultrastructural abnormalities in mild traumatic brain injury with cognitive disability: A voxel-wise analysis of diffusion tensor imaging. *Journal of Neurotrauma, 25*(11), 1335-1342. doi: 10.1089/neu.2008.0547

[19] Little, D. M., Kraus, M. F., Joseph, J., Geary, E. K., Susmaras, T., Zhou, X. J., . . . Gorelick, P. B. (2010). Thalamic integrity underlies executive dysfunction in traumatic brain injury. *Neurology, 74*(7), 558-564. doi: 10.1212/WNL.0b013e3181cff5d5

[20] Lo, C., Shifteh, K., Gold, T., Bello, J. A., & Lipton, M. L. (2009). Diffusion tensor imaging abnormalities in patients with mild traumatic brain injury and neurocognitive impairment. *Journal of Computer Assisted Tomography, 33*(2), 293-297. doi: 10.1097/RCT.0b013e31817579d1

[21] Maruta, J., Suh, M., Niogi, S. N., Mukherjee, P., & Ghajar, J. (2010). Visual tracking synchronization as a metric for concussion screening. *The Journal of Head Trauma Rehabilitation, 25*(4), 293-305.

[22] Maruta, J., Palacios, E. M., Zimmerman, R. D., Ghajar, J., & Mukherjee, P. (2016). Chronic post-concussion neurocognitive deficits. I. Relationship with white matter integrity. *Frontiers in Human Neuroscience, 10*, 35. doi: 10.3389/fnhum.2016.00035

[23] Matsushita, M., Hosoda, K., Naitoh, Y., Yamashita, H., & Kohmura, E. (2011). Utility of diffusion tensor imaging in the acute stage of mild to moderate traumatic brain injury for detecting white matter lesions and predicting long-term cognitive function in adults. *Journal of Neurosurgery, 115*(1), 130-139. doi: 10.3171/2011.2.jns101547

[24] Messe, A., Caplain, S., Paradot, G., Garrigue, D., Mineo, J. F., Soto Ares, G., . . . Lehericy, S. (2010). Diffusion tensor imaging and white matter lesions at the subacute stage in mild traumatic brain injury with persistent neurobehavioral impairment. *Human Brain Mapping, 32*(6), 999-1011. doi: 10.1002/hbm.21092

[25] Messe, A., Caplain, S., Pelegrini-Issac, M., Blancho, S., Montreuil, M., Levy, R., . . . Benali, H. (2012). Structural integrity and postconcussion syndrome in mild traumatic brain injury patients. *Brain Imaging and Behavior, 6*(2), 283-292. doi: 10.1007/s11682-012-9159-2

[26] Palacios, E. M., Fernandez-Espejo, D., Junque, C., Sanchez-Carrion, R., Roig, T., Tormos, J. M., . . . Vendrell, P. (2011). Diffusion tensor imaging differences relate to memory deficits in diffuse traumatic brain injury. *BMC Neurology, 11*(24). doi: 10.1186/1471-2377-11-24

[27] Palacios, E. M., Sala-Llonch, R., Junque, C., Fernandez-Espejo, D., Roig, T., Tormos, J. M., . . . Vendrell, P. (2013). Long-term declarative memory deficits in diffuse TBI: Correlations with cortical thickness, white matter integrity and hippocampal volume. *Cortex, 49*(3), 646-657. doi: 10.1016/j.cortex.2012.02.011

[28] Palmer, H. S., Garzon, B., Xu, J., Berntsen, E. M., Skandsen, T., & Haberg, A. K. (2010). Reduced fractional anisotropy does not change the shape of the hemodynamic response in survivors of severe traumatic brain injury. *Journal of Neurotrauma, 27*(5), 853-862. doi: 10.1089/neu.2009.1225

[29] Rutgers, D. R., Fillard, P., Paradot, G., Tadie, M., Lasjaunias, P., & Ducreux, D. (2008). Diffusion tensor imaging characteristics of the corpus callosum in mild, moderate, and severe traumatic brain injury. *American Journal of Neuroradiology, 29*(9), 1730-1735. doi: 10.3174/ajnr.A1213

[30] Scott, G., Hellyer, P. J., Ramlackhansingh, A. F., Brooks, D. J., Matthews, P. M., & Sharp, D. J. (2015). Thalamic inflammation after brain trauma is associated with thalamo-cortical white matter damage. *Journal of Neuroinflammation, 12*, 224. doi: 10.1186/s12974-015-0445-y

[31] Seo, J. P., Kim, O. L., Kim, S. H., Chang, M. C., Kim, M. S., Son, S. M., & Jang, S. H. (2012). Neural injury of uncinate fasciculus in patients with diffuse axonal injury. *NeuroRehabilitation, 30*(4), 323-328. doi: 10.3233/nre-2012-0762

[32] Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., . . . Rostrup, E. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: A longitudinal study. *Brain: A Journal of Neurology, 131*(2), 559-572. doi: 10.1093/brain/awm294

[33] Smits, M., Houston, G. C., Dippel, D. W., Wielopolski, P. A., Vernooij, M. W., Koudstaal, P. J., . . . van der Lugt, A. (2011). Microstructural brain injury in post-concussion syndrome after minor head injury. *Neuroradiology, 53*(8), 553-563. doi: 10.1007/s00234-010-0774-6

[34] Tollard, E., Galanaud, D., Perlbarg, V., Sanchez-Pena, P., Le Fur, Y., Abdennour, L., . . . Puybasset, L. (2009). Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: Preliminary results. *Critical Care Medicine, 37*(4), 1448-1455. doi: 10.1097/CCM.0b013e31819cf050

[35] Ubukata, S., Ueda, K., Sugihara, G., Yassin, W., Aso, T., Fukuyama, H., & Murai, T. (2015). Corpus callosum pathology as a potential surrogate marker of cognitive impairment in diffuse axonal injury. *The Journal of Neuropsychiatry & Clinical Neuroscience*. doi: 10.1176/appi.neuropsych.15070159

[36] Veeramuthu, V., Narayanan, V., Kuo, T. L., Delano-Wood, L., Chinna, K., Bondi, M. W., . . . Ramli, N. (2015). Diffusion tensor imaging parameters in mild traumatic brain injury and Its correlation with early neuropsychological impairment: A longitudinal study. *Journal of Neurotrauma,* 32(19), 1497-1509. doi: 10.1089/neu.2014.3750

[37] Wada, T., Asano, Y., & Shinoda, J. (2012). Decreased fractional anisotropy evaluated using tract-based spatial statistics and correlated with cognitive dysfunction in patients with mild traumatic brain injury in the chronic stage. *American Journal Neuroradiology, 33*(11), 2117-2122. doi: 10.3174/ajnr.A3141

[38] Waljas, M., Lange, R. T., Hakulinen, U., Huhtala, H., Dastidar, P., Hartikainen, K., . . . Iverson, G. L. (2014). Biopsychosocial outcome after uncomplicated mild traumatic brain injury. *Journal of Neurotrauma, 31*(1), 108-124. doi: 10.1089/neu.2013.2941

[39] Wilde, E. A., Li, X., Hunter, J. V. M., Narayana, P. A., Hasan, K. M., Biekman, B., . . . Levin, H. S. (2016). Loss of consciousness is related to white matter injury in mild traumatic brain injury. *Journal of Neurotrauma, 33*(22) 2000-2010. doi: 10.1089/neu.2015.4212

[40] Xu, J., Rasmussen, I. A., Lagopoulos, J., & Haberg, A. (2007). Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. *Journal of Neurotrauma, 24*(5), 753-765. doi: 10.1089/neu.2006.0208

[41] Yao, S., Song, J., Gao, L., Yan, Y., Huang, C., Ding, H., . . . Xu, G. (2015). Thalamocortical sensorimotor circuit damage associated with disorders of consciousness for diffuse axonal injury patients. *Journal of the Neurological Sciences, 356*(1-2), 168-174. doi: 10.1016/j.jns.2015.06.044

[42] Yuh, E. L., Cooper, S. R., Mukherjee, P., Yue, J. K., Lingsma, H. F., Gordon, W. A., . . . Track-Tbi, I. (2014). Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: A TRACK-TBI study. *Journal of Neurotrauma, 31*(17), 1457-1477. doi: 10.1089/neu.2013.3171

[43] Zhang, K., Johnson, B., Pennell, D., Ray, W., Sebastianelli, W., & Slobounov, S. (2010). Are functional deficits in concussed individuals consistent with white matter structural alterations: Combined FMRI & DTI study. *Experimental Brain Research, 204*(1), 57-70. doi: 10.1007/s00221-010-2294-3

[44] Zhu, Y., Li, Z., Bai, L., Tao, Y., Sun, C., Li, M., . . . Zhang, M. (2014). Loss of microstructural integrity in the limbic-subcortical networks for acute symptomatic traumatic brain injury. *Biomed Research International*. doi: 10.1155/2014/548392

CHAPTER 4: META-ANALYSIS – RELATIONSHIP BETWEEN DIFFUSION TENSOR IMAGING AND COGNITION FOLLOWING TRAUMATIC BRAIN INJURY

4.1 Preamble

This chapter consists of a paper entitled "The relationship between diffusion tensor imaging findings and cognitive outcomes following adult traumatic brain injury: A meta-analysis", which has been published in *Neuroscience and Biobehavioral Reviews* (2018).

The previous chapter examined the location and extent of WM changes, which were detected using DTI, following adult TBI by meta-analysing the findings from 44 studies. This study found that the corpus callosum, internal capsule, occipital white matter, centrum semiovale, fornix and thalamic radiations displayed the largest and most consistent differences in FA and MD/ADC. It also concluded that mild TBI generally led to smaller effects than moderate to severe TBI.

The relationship between DTI findings and cognitive outcomes following TBI have also been examined, but the findings are disparate. Thus, the next study meta-analysed the findings from studies that examined the relationship between DTI and cognitive outcomes following adult TBI to determine whether, and to what extent, DTI findings and cognitive outcomes are related.

Tables and Figures have been provided within the text to make it easier for the reader. Supplementary material for this paper is provided at the end of the chapter (pages 120-131), comprising:

- Logic grids for each database (Appendix A)

- Study and sample characteristics of studies included in the meta-analysis (Table S1)
- Scanner specifications and acquisition details of studies included in the meta-analysis (Table S2)
- Categorisation of cognitive tests used by individual studies (Table S3)
- Study reporting quality: number and percentage of studies reporting each item of the STROBE checklist (Table S4)
- FA findings: correlations between ROIs and cognitive domains, ordered by ROIs (alphabetical) (Table S5)
- MD/ADC findings: correlations between ROIs and cognitive domains, ordered by ROIs (alphabetical) (Table S6)

A list of the studies included in this meta-analysis is provided at the end of the chapter, with the superscript number ([1-20]) corresponding to the reference number used in the tables. A complete list of all references for the thesis, including those for this paper, is provided at the end of the thesis (pages 216-236).

CHAPTER 4: PAPER 2

The relationship between diffusion tensor imaging findings and cognitive outcomes following adult traumatic brain injury: A meta-analysis

Authors: E.J. Wallace, J.L. Mathias, L. Ward

Statement of authorship is on the following page

Reference: Wallace, E. J., Mathias, J. L., & Ward, L. (2018b). The relationship between diffusion tensor imaging findings and cognitive outcomes following adult traumatic brain injury: A meta-analysis. Neuroscience & Biobehavioral Reviews, 92, 93-103. doi:10.1016/j.neubiorev.2018.05.023

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Name of Principal Author (Candidate)	Erica Wallace		
Contribution to the Paper	Conducted literature searches, coded articles, analysed and interpreted data, and wrote manuscript		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

iv. the candidate's stated contribution to the publication is accurate (as detailed above);

v. permission is granted for the candidate in include the publication in the thesis; and

vi. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Jane Mathias		
Contribution to the Paper	Supervised and contributed to the study design, analysis and data interpretation, and manuscript preparation, and acted as corresponding author		
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Name of Co-Author	Lynn Ward		
Contribution to the Paper	Assisted in analysing and interpreting data, and evaluating and editing the manuscript		
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4.2 Paper two

Abstract

Cognitive impairments are common following a traumatic brain injury (TBI) and frequently result from white matter (WM) damage. This damage can be quantified using diffusion tensor imaging (DTI), which measures the directionality (fractional anisotropy: FA) and amount (mean diffusivity/apparent diffusion coefficient: MD/ADC) of water diffusion in WM, with high FA and low MD/ADC thought to indicate greater WM integrity. However, the relationship between DTI and cognitive outcomes is currently unclear. The data from 20 studies that examined the relationship between WM integrity (measured using DTI) and cognition (categorised into seven domains) following mild-severe adult TBI were meta-analysed. Overall, high FA and low MD/ADC in most brain regions was associated with better cognitive performance, with memory and attention most strongly related to DTI findings. Specifically, memory and/or attention were very strongly related to DTI findings in the corpus callosum, fornix, internal capsule, arcuate and uncinate fasciculi. However, most findings were based on single studies and therefore await replication. Larger-scale, longitudinal studies are now needed to determine the predictive utility of DTI.

The relationship between diffusion tensor imaging and cognitive outcomes following adult traumatic brain injury: A meta-analysis

Introduction

Non-penetrating traumatic brain injuries (TBIs) often lead to a range of cognitive impairments that affect memory, attention, executive functioning, and language (Dikmen et al., 2009). Although common, these impairments are heterogeneous, ranging from transient symptoms to long-term problems that can affect many aspects of everyday life, such as school, work and interpersonal relationships (Cristofori & Levin, 2015; Ponsford, 2013; Stocchetti & Zanier, 2016). Diffuse axonal injury (DAI) involves a microscopic shearing injury that affects white matter (WM) and is thought to be one of the main causes of cognitive impairments following a TBI (Arfanakis et al., 2002; Huisman et al., 2004; Hulkower et al., 2013). However, DAI is often not visible on computed tomography or conventional magnetic resonance imaging (Shenton et al., 2012; Voelbel et al., 2012). Diffusion tensor imaging (DTI), on the other hand, better identifies microscopic alterations to WM, allowing DAI to be measured following TBIs of all severities (Shenton et al., 2012; Wallace, Mathias, & Ward, 2018a).

DTI assesses WM damage by quantifying the direction and amount of diffusion of water molecules within axons (Niogi & Mukherjee, 2010). In healthy WM, diffusion is highly directional and primarily occurs parallel to myelinated axons (Douglas et al., 2015; Niogi & Mukherjee, 2010); referred to as anisotropic diffusion (Huisman, 2010; Mueller et al., 2015). When WM is damaged, diffusion is less restricted by the internal organisation of WM tracts and, at the extreme, occurs equally in all directions; known as isotropic diffusion (Huisman, 2010; Mueller et al., 2015). Changes to the directionality (or shape) of diffusion are measured using fractional anisotropy (FA), with values ranging from 0 (isotropic diffusion; indicative of WM damage) to 1 (highly directional, anisotropic diffusion; reflecting WM integrity) (Niogi & Mukherjee, 2010).

The average amount of diffusion (distance), on the other hand, is measured using the apparent diffusion coefficient (ADC), also referred to as mean diffusivity (MD) (Niogi & Mukherjee, 2010). In healthy brains, the amount of diffusion is restricted by the internal organisation of the WM tracts, with low MD/ADC values reflecting WM integrity and, following a TBI, higher values indicative of less restricted diffusion due to WM damage (Shenton et al., 2012). Thus, high FA and low MD/ADC are thought to indicate WM integrity, while low FA and high MD/ADC reflect WM damage.

The WM damage caused by TBI has been shown to affect DTI findings, with most researchers reporting lower FA and higher MD/ADC (for reviews see Douglas et al., 2015; Shenton et al., 2012). Although a small number of studies (e.g., Bazarian et al., 2007; Dodd et al., 2014; Huisman et al., 2004) have found the reverse when DTI was performed in the acute post-injury interval (higher FA, lower MD/ADC) — which was attributed to early axonal swelling — a recent meta-analysis of 44 studies reported that timing did not affect the findings (Wallace et al., 2018a). More specifically, Wallace et al., (2018a) found that FA was lower and MD/ADC higher in most of the regions that had been examined following TBI, with no significant differences in the findings from studies that performed DTI in the acute (≤1 week), subacute (>1 week-3 months) or chronic (>3 months) intervals. In particular, the corpus callosum, internal capsule, occipital white matter, centrum semiovale, fornix and thalamic radiations displayed the largest and most consistent differences in FA and MD/ADC, with mild TBI samples generally showing smaller effects than moderate-severe TBI (Wallace et al., 2018a).

Numerous studies have extended this research by examining the relationship between DTI (FA, MD/ADC) and cognitive outcomes following TBI, with one review reporting that WM integrity (higher FA, lower MD/ADC) and cognitive outcomes were positively related in some studies, but negatively or not related in others (Hulkower et al., 2013). However, this review combined data from both paediatric and adult samples (aged 2 to 70 years), all injury severities

(mild, moderate, severe), and studies that performed DTI at very different post-injury intervals (acute to chronic; ranging from days to years); all of which may have contributed to these inconsistent findings. In contrast, a recent meta-analysis of paediatric TBI (age ≤ 15 years) found that, in the medium to long-term (> 4 weeks), higher FA was associated with better cognitive performance in a variety of domains (Roberts, Mathias, & Rose, 2016). For example, higher FA in the corpus callosum was associated with better general cognition, attention, construction, and academic achievement, and higher FA in the cingulate and uncinate fasciculus was associated with better memory. However, the findings from studies that performed DTI in the shorter-term (≤ 4 weeks) were inconsistent and based on small samples (*n* = 12 to 17), highlighting the need for larger-scale studies (Hawryluk & Bullock, 2016; Schwab, Gudmudsson, & Lew, 2015).

At least some of the aforementioned discrepant findings may have arisen from differences in the ROIs and cognitive domains that have been investigated, and the many tests that have been used to assess cognition. However, there have been conflicting findings even for studies that have examined the same ROIs and cognitive domains. For example, both positive (Gu et al., 2013; Little et al., 2010) and negative (Kraus et al., 2007) associations have been reported between WM integrity in the corona radiata and attention. In addition, the impact of injury severity and post-injury interval both need to be considered because the extent and timing of the pathophysiological changes that occur as a consequence of a TBI are known to vary according to the severity of an injury and in the time after an injury (secondary changes can continue for years) (Johnson et al., 2013). Thus, the results from different studies need to be synthesised, and the potential impact of these variables examined, in order to determine whether the cumulative evidence suggests a link between DTI findings and cognitive outcomes following TBI.

Importantly, not all areas of the brain are equally affected by TBIs, with the corpus callosum, internal capsule, fornix, cerebral white matter, cerebellum, midbrain, pons, medulla, occipital white matter, centrum semiovale, and thalamic radiations being particularly vulnerable

to DAI following TBI (Greenfield, Love, Louis, & Ellison, 2008; McKee & Daneshvar, 2015; Wallace et al., 2018a). In addition, certain cognitive deficits are reportedly more common following TBI; often affecting memory, executive functioning and attention (Cristofori & Levin, 2015; Dikmen et al., 2009; Rabinowitz & Levin, 2014). Whether these cognitive deficits are related to WM integrity/damage, as assessed by DTI of the ROIs most commonly affected by TBI, remains to be determined.

The current study, therefore, meta-analysed the findings from studies that have investigated the association between cognitive performance and DTI following adult mild, moderate and severe TBI. The different cognitive domains were examined separately, as were the DTI metrics (FA/MD/ADC) from individual ROIs. In addition, data permitting, the impact of the post-injury interval (acute vs subacute vs chronic), the timing of the DTI in relation to the cognitive testing (simultaneous vs delayed), injury severity (mild, moderate, severe) and specific scanner variables (magnet strength, scanner brand, *b*-values) were examined prior to examining the findings in order to determine whether the data from studies that varied in terms of these variables could justifiably be combined. It was expected that WM integrity (higher FA, lower MD/ADC) would be associated with better cognitive outcomes.

Method

Literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; (Moher et al., 2009) were followed throughout this meta-analysis. Studies published prior to April 2017, which used cognitive tests and DTI to examine adult TBI, were identified via a comprehensive search of five electronic databases (Embase, PsychINFO, PubMed, Web of Science, Scopus; see Supplementary Material Appendix A for logic grids for each database).

The following criteria were applied to determine study eligibility: (1) the research examined adults (≥ 18 years) who had sustained a non-penetrating TBI (where minimum age was not provided, mean age minus 1 SD ≥ 18 years); (2) DTI was performed, and FA and/or MD/ADC data were reported for one or more ROIs; (3) participants additionally underwent cognitive testing; (4) correlations between cognitive performance and FA and/or MD/ADC values were reported (Pearson's *r*, Spearman's rho, or exact *p*-values provided); and, (5) studies were published in English in a peer-reviewed journal (peer-review status checked via publisher's websites or Scopus). Penetrating injuries, blast injuries and military populations were all excluded due to pathophysiological differences between these and non-penetrating TBIs, and due to the higher frequency of comorbid post-traumatic stress disorder (Bandak et al., 2015; Santiago et al., 2012; Wilde et al., 2015). Case studies, reviews and studies with very small samples (N ≤ 5) were also excluded. Studies of single concussions were included, however multiple concussions were not.

The initial search yielded 13,844 potentially relevant studies (refer to Figure 1). After duplicates were removed, 9,171 titles and abstracts were screened for eligibility using the aforementioned inclusion criteria, resulting in 355 articles for which full-text articles were retrieved. Re-screening of these led to a further 329 being excluded. Two articles did not provide all of the data needed for inclusion, but were otherwise eligible. The corresponding authors for these two studies were contacted, but were not able to provide the requisite information, leading to their exclusion.

All articles were then checked for independence, with the following studies combined and treated as one: three studies by Kumar (Kumar, Gupta, et al., 2009; Kumar, Husain, et al., 2009; Kumar et al., 2010) and three by Palacios (Palacios, Sala-Llonch, Junque, Fernandez-Espejo, et al., 2013; Palacios et al., 2012; Palacios, Sala-Llonch, Junque, Roig, et al., 2013).

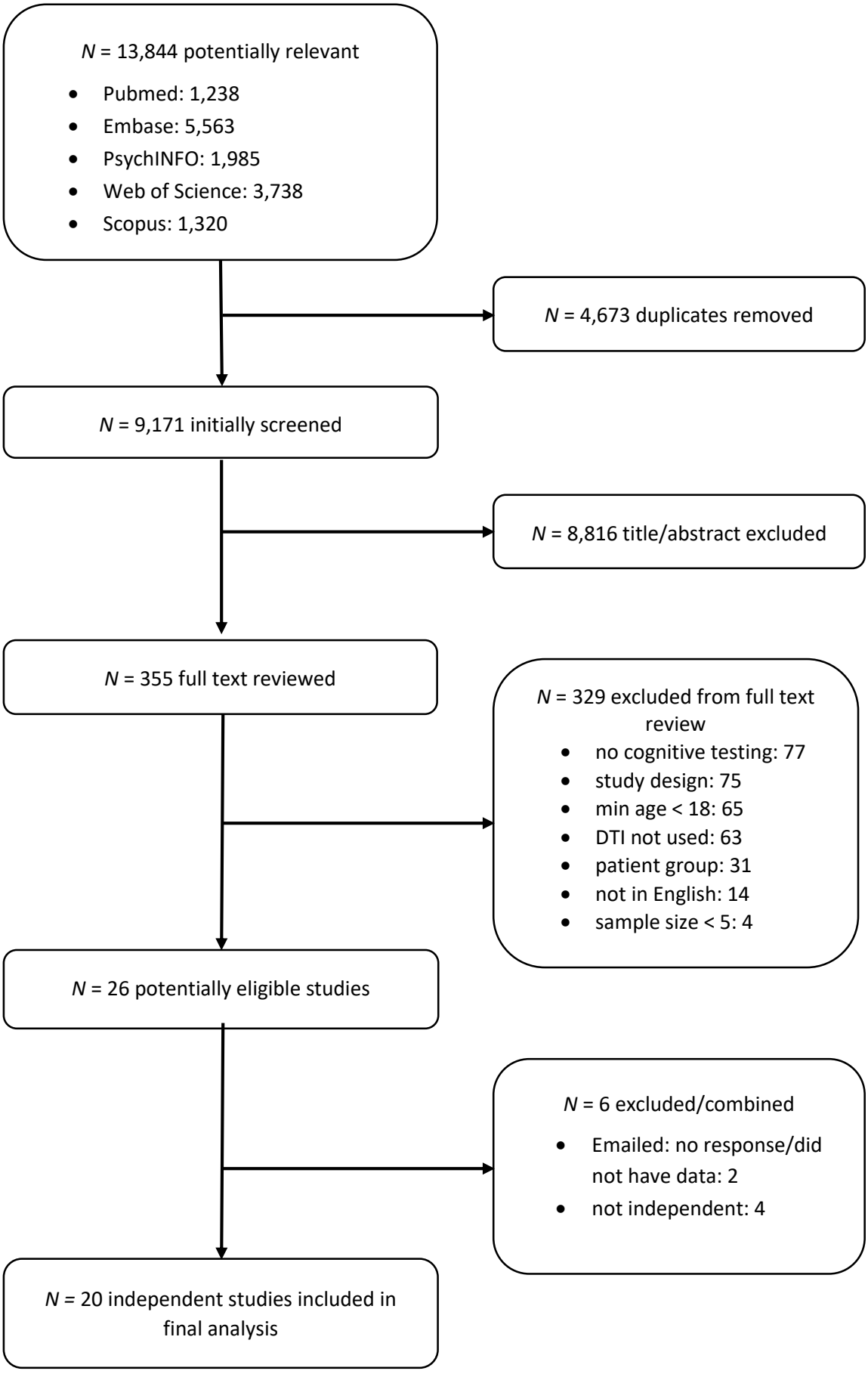


Figure 1: Literature search flow chart

Non-independence was determined on the basis of in-text information indicating that the same sample was examined in separate papers, or the presence of overlapping authors and matching sample characteristics. In total, data were extracted from 20 independent studies.

Data Extraction & Preparation

Where provided, the following information was extracted from each study: demographic details (age, gender, education, handedness), study and injury characteristics (sample size, recruitment source, injury severity [category or Glasgow Coma Scale [GCS] score], time post-injury, timing of DTI and cognitive testing), scanner details (brand, magnet strength [1.5T, 3T]), acquisition parameters (number of diffusion-weighted images, *b*-values, methods of analysis), cognitive tests (test name, score type [errors, time, number correct]), and correlations between the cognitive tests and FA and/or MD/ADC data for each ROI (Pearson's *r*, Spearman's rho, or exact *p*-value).

A large number of different tests were used to assess cognition, it was therefore necessary to categorise them in order to usefully summarize the data. The empirically-based Cattell-Horn-Carroll model, in which cognitive abilities are grouped into ten broad intelligence factors, was considered for this purpose (see Jewsbury, Bowden, & Duff, 2017; Pase & Stough, 2014), but the majority of tests used by the current studies have not yet been classified using this model. Instead, the tests were classified into seven domains based on Lezak's (2012) clinical categories: (1) general cognition, (2) memory, (3) attention, processing speed and working memory, (4) executive functioning, (5) verbal/language skills, (6) concept formation and reasoning, (7) construction and motor performance (see Supplementary Table S3 for a list of tests, their categorisation and the studies that used each test). This method enabled findings to be grouped, making interpretation easier. It is worth noting, however, that very few studies examined the same ROI/cognitive domain combination, and thus few scores could ultimately be combined.

Left and right, anterior and posterior, and superior and inferior measurements of the same brain structure were averaged in order to reduce the number of ROIs examined. Supporting this, (Huisman et al., 2004), and Jang et al. (2013) did not find differences between right- and left-sided DTI measurements of the same brain structures. Further, the majority of studies (80%, 16/20) only presented combined data for left- and right-sided ROIs; thus, for consistency, the left and right measurements from the remaining studies were combined. Additionally, where studies assessed cognition on more than one occasion, only the last assessment was analysed because it was thought to more accurately reflect final levels of cognitive functioning.

Data Analysis

Comprehensive Meta-Analysis Version 3.3 (CMA; 2014, Biostat, Inc., Engelwood, NJ, USA) was used for all calculations. Pearson's *r* or Spearman's Rho was used to assess the relationship between the DTI measure (FA, MD/ADC) for each ROI and individual cognitive domain. Effect sizes (*r*) of 0.1, 0.3, 0.5 and 0.7 corresponded to small/weak, medium/moderate, large/strong and very large/very strong effects, respectively (Cohen, 1992; Rosenthal, 1996), and positive values indicated that greater WM integrity (higher FA, lower MD/ADC) was associated with better cognitive functioning (e.g., fewer errors, faster or more accurate responses). If a study used more than one test for the same cognitive domain, and reported correlations for the same ROI (e.g., attention: Trail Making Test and Digit Span correlated with FA in the corpus callosum), the correlations were averaged using CMA so that each study only contributed one correlation (i.e., the mean correlation) for each ROI and cognitive domain combination.

Several other statistics were computed, namely: probability (*p*) values to determine statistical significance, and fail-safe N statistics (N_{fs}) to assess the potential impact of publication bias (Orwin, 1983; Rothstein et al., 2006). The N_{fs} statistic provides a hypothetical number of unpublished studies with non-significant findings that would need to exist to reduce the correlation between a cognitive domain and the DTI findings for a specific ROI to a weak effect (*r*

= 0.1; weak/small correlation between cognitive domain and DTI findings) (Lipsey & Wilson, 2001).

The inferences made throughout this meta-analysis were based on the following criteria: that greater WM integrity (higher FA, lower MD/ADC) in a specific ROI was associated with better cognitive outcome if the effect size was medium or larger in size ($r \geq 0.3$), statistically significant ($p < .05$), and the N_{fs} statistic was greater than the number of studies that examined a ROI/cognitive domain.

Subgroup analyses

Between-study heterogeneity in the data (correlations) was dealt with in two ways. First, a random-effects model was used because the effect sizes from different studies were expected to vary due to methodological differences and sampling error (Borenstein et al., 2010).

Second, subgroup analyses were planned in order to determine whether specific methodological variables – which could independently affect the DTI and/or cognitive assessments – were associated with significantly different effect sizes and, consequently, whether the data could validly be combined (or, alternatively, whether it should be analysed separately). The variables under consideration were: (1) the post-injury interval of the DTI (acute [≤1 week], subacute [>1 week-3 months] or chronic [>3 months]); (2) the timing of the DTI in relation to the cognitive testing (simultaneous vs delayed cognitive testing); (3) injury severity (mild, moderate, severe); (4) magnet strength (1.5T, 3T); (5) scanner brand (General Electric, Philips, Siemens); (6) differences in *b*-values (<1000, ≥1000); and (7) number of diffusion-weighted images (<30, ≥30, based on Dodd et al., 2014). *Q* and I^2 statistics were calculated as part of these subgroup analyses: *Q* measures between-study heterogeneity, and I^2 measures the proportion of observed variance that cannot be attributed to sampling/random error (Borenstein, Hedges, Higgins, & Rothstein, 2009; Higgins et al., 2003; Huedo-Medina et al., 2006). However, both *Q* and I^2 are underpowered when the number of studies is small ($N_{studies} < 20$) and/or the sample is small

($N_{participants}$ < 80) (Huedo-Medina et al., 2006), which meant that five of the 14 planned subgroup analyses could not be performed (FA: injury severity; MD/ADC: post-injury interval, injury severity, brand of scanner, *b*-values).

Study Reporting Quality

The 'Strengthening the Reporting of Observational Studies in Epidemiology' guidelines (STROBE; (Vandenbroucke et al., 2007) were used to evaluate the reporting quality of each study. The STROBE comprises a list of 22 items that observational studies should report (see Supplementary Table S4). Studies received a score of 1 if they reported the item, .5 if the information was partial or incomplete, 0 if they failed to report the item, or not applicable (N/A) if the item was not applicable to that study (assessed by the first author [EJW] in consultation with the third [LW]). Two scores were calculated: a Total quality score for each study, ([total score ÷ number of applicable items] x 100%), as well as an Item score indicating the percentage of studies that scored 1, .5 or 0 for each item.

Results

Participant & Study Characteristics

Twenty studies were included in the analysis, providing data for a total of 562 participants who had sustained a TBI (see Table 1 for summary information). The sample sizes for individual studies ranged from nine to 83, with the majority of participants being young to middle-aged males, who had completed a mean of 14 years of education ($N_{studies}$ = 14). Only 8 studies reported GCS scores, but many provided the injury category; with mild TBI investigated most frequently ($N_{studies}$ = 7), followed by severe ($N_{studies}$ = 5) and mild/moderate/severe ($N_{studies}$ = 4). DTI was performed over a wide range of post-injury intervals, spanning three days to 8.9 years, and cognitive testing was performed from seven days to 8.9 years after the TBI. In most cases ($N_{studies}$ = 14), DTI and cognitive testing was performed simultaneously, however four studies performed

Table 1. Summary information for the study participants and diffusion tensor imaging

	$N_{studies}$	N_{TBI}	%	*Mean*	*SD*	*Min*	*Max*
sample size	20	562		28.1	18.1	9	83
age	20	562		33.5	10.0	18	64
gender		481					
males	16	320	67				
females	16	161	33				
handedness (right)	5	135	100				
education (years)	14	300		14.3	2.58		
GCS	8	233		11.5	3.9		
TBI severity							
mild	7	229	41				
severe	5	81	14				
mild to moderate	2	94	17				
mild to severe	4	88	16				
not specified	2	70	12				
DTI timing (days post-injury)	20	562		721.2	1208.2	2.8	3216
cognitive testing (days post-injury)	20	562		776.5	1181.8	7	3216
timing of DTI and cognitive testing							
simultaneous DTI & cognitive testing	16	441	78				
early DTI, late cognitive testing	4	121	22				
post-injury interval							
acute	4	85	15				
subacute	6	212	38				
chronic	10	265	47				
DTI metrics							
FA	18	507	90				
MD/ADC	10	289	51				
recruitment source							
inpatients	9	256	46				
outpatients	2	61	11				
rehab/treatment clinics	3	65	12				
other (e.g., advertisements)	3	101	18				
not specified	3	79	14				
brand of scanner							
General Electric	8	300	53				
Philips	5	123	22				
Siemens	7	139	25				
MRI magnet strength							
1.5 Tesla	10	286	51				
3 Tesla	10	276	49				
method(s) of analysis							
ROI	10	288	51				
VBA (including TBSS)	5	147	26				
ROI + VBA/TBSS	2	35	6				
ROI + tractography	2	45	8				
ROI + TBSS + GAMMA	1	47	8				

Note. TBI = traumatic brain injury; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; *SD* = standard deviation; GCS = Glasgow Coma Scale; DTI = diffusion tensor imaging; acute = DTI completed ≤ 1 week after TBI; subacute = DTI completed >1 week to ≤ 3months after TBI; chronic = DTI completed > 3 months after TBI; FA = fractional anisotropy; MD/ADC = mean diffusivity/apparent diffusion coefficient; MRI = magnetic resonance imaging; ROI = region of interest; TBSS = tract-based spatial statistics; VBA = voxel-based analysis; GAMMA = graphical model based multivariate analysis

DTI early and cognitive testing later, and two studies performed DTI and/or cognitive testing at more than one time point. Participants were predominantly recruited from inpatient clinics, with many fewer drawn from rehabilitation/treatment clinics, outpatient clinics, or other sources. Most scanners were manufactured by General Electric, Philips or Siemens, and equal numbers of studies used 1.5T and 3T scanners. A range of different methods were used to process the DTI data, with some studies adopting more than one method: ROI was used most frequently ($N_{studies}$ = 10), followed by voxel-based analysis (including tract based spatial statistics; TBSS) ($N_{studies}$ = 5), ROI plus voxel-based analysis ($N_{studies}$ = 2), ROI plus tractography ($N_{studies}$ = 2), and ROI combined with TBSS and graphical model-based multivariate analysis (GAMMA; $N_{studies}$ = 1).

Subgroup analyses

Summary findings for the nine subgroup analyses that could be completed are provided in Table 2 where it can be seen that, with the exception of the post-injury interval, all subgroup analyses were non-significant. For post-injury interval, studies that conducted the DTI in the subacute period reported significantly higher correlations ($N_{studies}$ = 4; r = .55) than those from the acute ($N_{studies}$ = 4; r = .33) and chronic ($N_{studies}$ = 10; r = .34) periods, although significant heterogeneity remained even after this timing was taken into consideration. Notably, all three post-injury intervals showed moderate to large and positive correlations between FA and cognition. The fact that the effect sizes were all positive does not support the proposal that FA is reversed in the acute post-injury interval (e.g., Bazarian et al., 2007; Dodd et al., 2014). Additionally, the magnet strength subgroup analysis (MD/ADC data) approached significance (p = .05) however, studies using 1.5T ($N_{studies}$ = 7, r = .44) and 3T ($N_{studies}$ = 3, r = .61) both showed moderate to large and positive correlations and very few participants were examined using 3T ($N_{participants}$ = 80). This, combined with the significant heterogeneity that remained, the relatively small number of studies and the large number of ROIs that were investigated, meant that there

Table 2. Subgroup analyses examining impact of specific methodological variables on the effect sizes from different studies (FA and MD/ADC data)

					heterogeneity			total between	
group	$N_{studies}$	N_{TBI}	*r (95% CI)*	*p-value*	*Q*	*p-value*	I^2	*p-value*	*study references*
FA: post-injury interval								0.037*	
acute (≤ 1 week)	4	85	0.33 (-0.25-0.74)	0.258	27.42	0.000	89.06		7, 13, 14, 19
subacute (>1 week-3 months)	4	157	0.55 (0.42-0.67)	0.000	5.48	0.000	45.22		8, 11, 15, 20
chronic (>3 months)	10	265	0.34 (0.25-0.43)	0.000	17.13	0.047	47.46		1, 2, 4, 5, 9, 10, 12, 16, 17, 18
overall	18		0.39 (0.32-0.46)	0.000	68.84	0.000	75.31		
FA: timing of DTI, relative to cognitive assessment (simultaneous vs delayed cognitive assessment)								0.065	
simultaneous	14	386	0.36 (0.24-0.47)	0.000	52.60	0.000	75.29		1, 2, 4, 5, 8, 9, 10, 12, 15, 16, 17, 18, 19, 20
cognitive test later	4	121	0.51 (0.40-0.61)	0.000	2.96	0.398	0.00		7, 11, 13, 14
overall	18	507	0.44 (0.35-0.51)	0.000	63.73	0.000	73.32		
MD/ADC: timing of DTI, relative to cognitive assessment (simultaneous vs delayed cognitive assessment)								0.900	
simultaneous	7	179	0.50 (0.34-0.63)	0.000	12.05	0.061	50.22		2, 3, 4, 6, 8, 9, 20
cognitive test later	3	110	0.49 (0.30-0.63)	0.000	2.99	0.225	33.02		7, 11, 14
overall	10	289	0.49 (0.38-0.60)	0.000	15.53	0.077	42.04		
FA: magnet strength								0.258	
1.5 Tesla	10	286	0.46 (0.33-0.57)	0.000	24.08	0.004	62.62		2, 4, 7, 8, 9, 11, 13, 14, 15, 18
3 Tesla	8	221	0.34 (0.17-0.49)	0.000	32.40	0.000	78.40		1, 5, 10, 12, 16, 17, 19, 20
overall	18	507	0.41 (0.31-0.50)	0.000	68.84	0.000	75.31		
MD/ADC: magnet strength								0.050	
1.5 Tesla	7	209	0.44 (0.29-0.56)	0.000	9.34	0.155	35.74		2, 4, 7, 8, 9, 11, 14
3 Tesla	3	80	0.61 (0.49-0.71)	0.000	1.40	0.496	0.00		3, 6, 20
overall	10	289	0.53 (0.43-0.61)	0.000	15.38	0.081	41.49		
FA: brand scanner								0.445	
General Electric	7	265	0.43 (0.32-0.53)	0.000	29.90	0.000	79.93		5, 7, 10, 11, 12, 15, 18
Philips	5	123	0.22 (-0.20-0.57)	0.295	16.86	0.002	76.27		2, 4, 9, 13, 19

Siemens	6	119	0.50 (0.28-0.68)	0.000	9.46	0.084	47.16		1, 8, 14, 16, 17, 20
overall	18	507	0.43 (0.34-0.52)	0.000	68.84	0.000	75.31		
FA: b-values								0.633	
b ≥ 1000	14	409	0.40 (0.27-0.53)	0.000	57.17	0.000	77.26		2, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
b < 1000	4	98	0.36 (0.21-0.49)	0.000	7.00	0.072	57.12		1, 4, 5, 10
overall	18	507	0.38 (0.28-0.47)	0.000	68.84	0.000	75.31		
FA: no. of DW images								0.616	
< 30	10	251	0.43 (0.32-0.52)	0.000	29.79	0.000	69.79		1, 5, 7, 8, 10, 12, 13, 14, 15, 18
≥ 30	8	256	0.36 (0.06-0.59)	0.000	38.93	0.000	82.02		2, 4, 9, 11, 16, 17, 19, 20
overall	18	507	0.42 (0.32-0.51)	0.000	68.84	0.000	75.31		
MD/ADC: no. of DW images								0.667	
< 30	5	131	0.52 (0.39-0.64)	0.000	4.11	0.392	2.63		2, 3, 7, 8, 14
≥ 30	5	158	0.48 (0.27-0.64)	0.000	11.17	0.025	64.17		4, 6, 9, 11, 20
overall	10	289	0.51 (0.40-0.60)	0.000	15.53	0.077	42.04		

Note. * indicates significant between-group heterogeneity; $N_{studies}$ = number of studies; N_{TBI} = number of TBI participants; *95% CI* = 95% confidence intervals; *r* = Pearson's *r*; *FA* = fractional anisotropy; *MD/ADC* = mean diffusivity/apparent diffusion coefficient; DW images = diffusion-weighted images

was insufficient evidence to justify reporting the findings separately for the acute, subacute and chronic intervals, or for studies that used 1.5 and 3T scanners.

STROBE Ratings

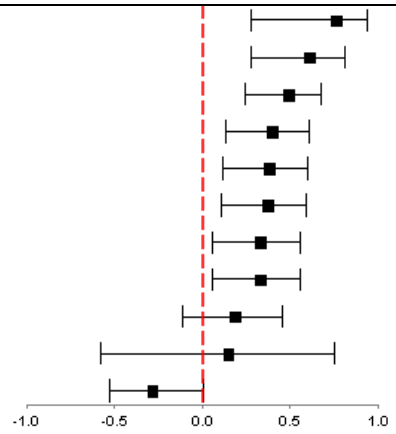
Study reporting quality varied considerably between studies (total quality score range: 60-90%, mean: 80%, SD: 7.3%), although most fell within the high-quality range (>75%). Overall, as can be seen in Supplementary Table S4, introductions contained sufficient information regarding the background/rationale (item 2: 100%) and objectives/hypotheses (item3: 100%). Most studies clearly discussed their eligibility criteria (item 6: 80%), statistical methods (item 12a: 95%), and participant characteristics (item 14a: 95%). Outcome data (item 15: 100%) and key results (item 18: 100%) were consistently summarised, results were cautiously interpreted (item 20: 100%), and the generalisability (item 21: 100%) and limitations (item 19: 70%) of the findings were also frequently discussed. In contrast, explanation of sample size (item 10: 0%) and the management of missing data (item 12c: 0%) were not addressed by any study.

Relationship between FA, MD/ADC and cognition

The correlations between the DTI metrics (FA, MD/ADC) and cognitive functioning are provided in Tables 3 and 4. Studies generally took one of two approaches: either examining a small number of ROIs across a range of cognitive domains (e.g., Chang et al., 2010) or examining a large number of ROIs across fewer cognitive domains (e.g., Wada, Asano, & Shinoda, 2012). Overall, the majority of correlations were medium or larger in size (≥ .3) and statistically significant, with adequate N_{fs} statistics, indicating that either higher FA or lower MD/ADC was associated with better cognitive functioning. However, most correlations (94%) were based on the findings of only one or two studies, with the associated number of participants ranging from nine ($N_{studies}$ = 1) to 133 ($N_{studies}$ = 4).

Table 3. FA findings: Pearson's *r* correlations between ROIs and cognitive domains, ordered by effect size (descending order)

ROI	$N_{studies}$	N_{TBI}	*post-injury interval*	*r*	*95% CIs*	*Nfs*	*study refs*
general cognition							
corpus callosum - splenium	1	11	a	0.75*		7	13
uncinate fasciculus	1	25	s	0.60*		5	20
inferior longitudinal fasciculus	1	51	c	0.48**		4	18
insula	1	51	c	0.39*		3	18
sagittal stratum	1	51	c	0.37*		3	18
cerebellum	1	51	c	0.36*		3	18
lenticular fasciculus	1	51	c	0.32*		2	18
superior longitudinal fasciculus	1	51	c	0.32*		2	18
cingulum	3	107	c, c, c	0.18		2	2, 9, 18
fornix	1	9	c	0.14		0	4
cerebellar peduncles	1	47	a	-0.29*		2	19
memory							
corpus callosum - whole	2	27	c, s	0.66**		11	1, 15
fornix	2	24	c, s	0.65*		11	4, 15
white matter	2	38	a, c	0.51*		8	14, 16
corpus callosum - splenium	2	49	c, c	0.45*		7	1, 10
corpus callosum - genu	1	40	c	0.39*		3	5
forceps major	2	77	c, c	0.38*		6	5, 10
forceps minor	2	77	c, c	0.35*		5	5, 10
uncinate fasciculus	1	40	c	0.34*		2	5
corona radiata	2	77	c, c	0.33*		5	5, 10
mesencephalon	1	34	s	0.33*		2	8
sagittal stratum	1	37	c	0.32		2	10
fronto-occipital fasciculus	1	37	c	0.31		2	10
cingulum	4	133	c, c, c, c	0.27*		7	2, 5, 9, 10
corpus callosum – body	1	37	c	0.03		0	10
attention, processing speed and working memory							
fornix	1	15	s	0.85**		8	15
corpus callosum - whole	3	37	c, s, c	0.78**		20	1, 15, 17
arcuate fasciculus	1	15	s	0.69*		6	15
cingulum	1	15	a	0.62*		5	7
corpus callosum - splenium	1	83	s	0.58**		5	11a,b
superior longitudinal fasciculus	3	54	a, c, s	0.56**		14	7, 12, 15
inferior longitudinal fasciculus	1	15	a	0.55*		5	7
uncinate fasciculus	1	15	a	0.53*		4	7
corpus callosum - genu	2	50	s, c	0.52**		8	11a, 12
corpus callosum - body	1	57	s	0.50**		4	11b
fronto-occipital fasciculus	1	24	c	0.48*		4	12
sagittal stratum	1	24	c	0.42*		3	12
white matter	3	53	a, s, c	0.33*		7	14, 15, 16
forceps major	1	37	c	0.31		2	10
corona radiata	3	76	a, c, c	0.23		4	7, 10, 12
internal capsule	2	39	a, c	0.04		0	7, 12

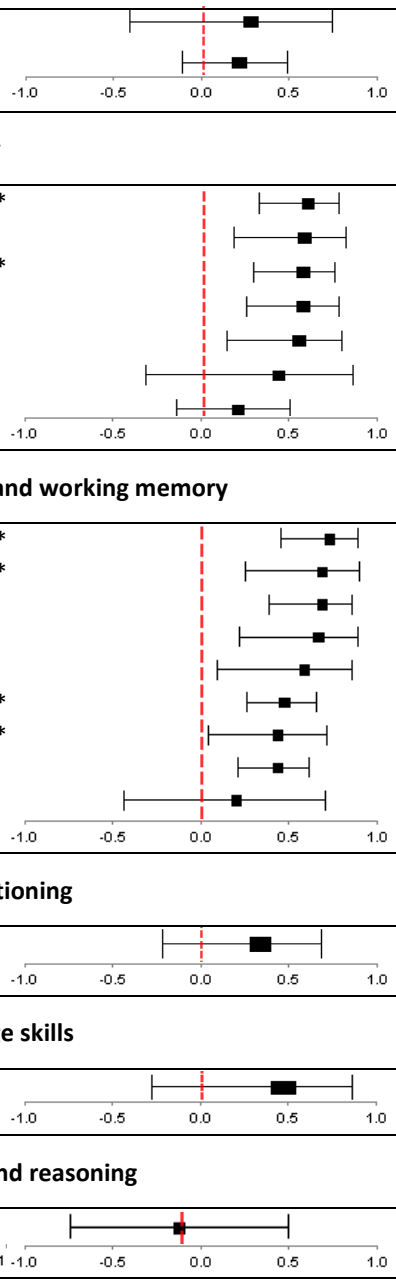


					-1.0 -0.5 0.0 0.5 1.0		
executive functioning							
corpus callosum - genu	1	24	c	0.59*		5	12
sagittal stratum	1	37	c	0.50*		4	10
corona radiata	2	61	c, c	0.41*		6	10, 12
corticospinal tract	1	37	c	0.39*		3	10
corpus callosum - body	1	37	c	0.37*		3	10
corpus callosum - splenium	1	37	c	0.35*		3	10
fronto-occipital fasciculus	1	37	c	0.35*		3	10
superior longitudinal fasciculus	1	37	c	0.31		2	10
cingulum	1	37	c	0.28		2	10
external capsule	1	37	c	0.27		2	10
white matter	1	12	a	-0.27		2	14
forceps minor	1	37	c	-0.28		2	10
forceps major	1	37	c	-0.56**	-1.0 -0.5 0.0 0.5 1.0	5	10
verbal/language skills							
corpus callosum - splenium	1	11	a	0.68*		6	13
fornix	1	9	c	0.08	-1.0 -0.5 0.0 0.5 1.0	0	4
concept formation and reasoning							
corpus callosum - genu	1	57	s	0.50**		4	11b
corpus callosum - body	1	57	s	0.34*		2	11b
white matter	1	12	a	-0.02	-1.0 -0.5 0.0 0.5 1.0	0	14
construction and motor performance							
corpus callosum - genu	1	57	s	0.53**	-1.0 -0.5 0.0 0.5 1.0	4	11b

Note. FA = fractional anisotropy; *ROI* = region of interest; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; *r* = Pearson's *r*; *95%CI* = 95 percent confidence interval; *Nfs* = Fail safe N; a = acute (DTI completed ≤ 1 week after TBI); s = subacute (DTI completed >1 week to ≤ 3months after TBI); c = chronic (DTI completed > 3 months after TBI); * $p < .05$, ** $p < .001$

Table 4. MD/ADC findings: Pearson's *r* correlations between ROIs and cognitive domains, ordered by effect size (descending order)

ROI	$N_{studies}$	N_{TBI}	*post-injury interval*	*r*	*95% CIs*	*Nfs*	*study refs*
general cognition							
fornix	1	9	c	0.29		2	4
cingulum	2	56	c, c	0.22		2	2, 9
memory							
corpus callosum - body	1	34	s	0.59**		5	8
external capsule	1	20	s	0.57*		5	6
fronto-parietal white matter	1	35	s	0.56**		5	3
white matter	2	32	s, a	0.56*		9	6, 14
corpus callosum - whole	1	20	s	0.54*		4	6
fornix	1	9	c	0.42		3	4
cingulum	2	56	c, c	0.19		2	2, 9
attention, processing speed and working memory							
uncinate fasciculus	1	25	s	0.71**		6	20
internal capsule	1	25	s	0.67**		6	20
superior longitudinal fasciculus	1	15	a	0.67*		6	7
inferior longitudinal fasciculus	1	15	a	0.65*		6	7
corona radiata	1	15	a	0.58*		5	7
corpus callosum - genu	1	83	s	0.46**		4	11a,b
corpus callosum - body	1	83	s	0.42**		3	11a,b
corpus callosum - splenium	1	26	s	0.42*		3	11a
white matter	1	12	a	0.19		1	14
executive functioning							
white matter	1	12	a	0.38		3	14
verbal/language skills							
fornix	1	9	c	0.46		4	4
concept formation and reasoning							
white matter	1	12	a	-0.02		0	14



Note. MD/ADC = mean diffusivity/apparent diffusion coefficient; *ROI* = region of interest; $N_{studies}$ = total number of studies; N_{TBI} = total number of TBI participants; *r* = Pearson's *r*; *95%CI* = 95 percent confidence interval; *Nfs* = Fail safe N; a = acute (DTI completed ≤ 1 week after TBI); s = subacute (DTI completed >1 week to ≤ 3months after TBI); c = chronic (DTI completed > 3 months after TBI); * $p < .05$, ** $p < .001$

Fractional Anisotropy (FA)

The FA results for the different cognitive domains are provided in Table 3. In total, 18 studies examined the relationship between FA in 24 different ROIs and seven cognitive domains. Memory was examined by the largest number of studies ($N_{studies}$ = 11), followed by attention and general cognition ($N_{studies}$ = 9 and 7, respectively). Executive functioning was examined by three studies, verbal/language skills and concept formation/reasoning were each examined by two studies, and construction/motor performance was examined by one.

Overall, as seen by the effect sizes marked with an asterisk (Table 3), the majority of correlations (72%) were positive, significant and medium or larger in size (≥ .3), indicating that higher FA was associated with better cognitive performance. Specifically, medium to very large, positive and significant correlations (with adequate N_{fs}) were found between FA and: *general cognition* in eight ROIs (73%); *memory* in 11 ROIs (79%); *attention, processing speed, and working memory* in 13 ROIs (81%); *executive functioning* in seven ROIs (54%); *verbal/language skills* in one ROI (50%); *concept formation/reasoning* in two ROIs (67%); and *construction/motor performance* in one ROI (100%). However, these correlations were largely based on the findings of only one or two studies (55/60 ROIs, 92%), with samples ranging between 9 and 133 participants.

Two medium to large and significant, but contrary, effects were also observed. Specifically, *lower* FA in the cerebellar peduncles was associated with better *general cognition*; and *lower* FA in the forceps major was associated with better *executive functioning*.

Mean diffusivity/apparent diffusion coefficient (MD/ADC)

Fewer studies ($N_{studies}$ = 10) have examined MD/ADC in a smaller number of ROIs (N = 13) and cognitive domains (N = 6) (see Table 4). Once again, memory, attention and general cognition were examined most frequently ($N_{studies}$ = 7, 4 and 3, respectively), with the other cognitive domains each examined by only one study.

As with FA, most findings (62%) were positive, statistically significant and medium or larger in size (≥ .3), indicating that lower MD/ADC was associated with better cognitive performance (see effect sizes marked with an asterisk, Table 4). Specifically, medium to very large, positive and significant correlations (with adequate N_{fs}) were found between MD/ADC and: *memory* in five ROIs (71%); and *attention, processing speed and working memory* in eight ROIs (89%). Medium to large and positive correlations were additionally found between *general cognition* and MD/ADC in the fornix, *executive functioning* and white matter (total), and *verbal/language skills* and fornix; however, none of these latter findings were significant. Once again, all findings were based on one or two studies, with samples ranging from 9 to 83 participants.

Key findings

The preceding analyses examined the relationship between DTI and cognition, with the findings organised by cognitive domains. Most correlations were medium or larger and significant (69% of ROIs), making it difficult to determine which brain regions were most strongly related to cognition. Given the limited number of studies and small sample sizes underpinning these findings, we subsequently narrowed our focus to those effect sizes that were at least large in size (≥ .5), but based on the findings of more than one study, or very large in size (≥ .7), even if based on only 1 study (see Table 5). This was done in order to identify those regions that are most strongly related to cognitive functioning following a TBI (see Supplementary Tables S5 & S6 for all correlations).

As can be seen from Table 5, most key findings were for memory or attention and involved measuring FA. Specifically, multiple studies revealed that *memory* was strongly associated with FA in the corpus callosum (whole), fornix and white matter (total). *Attention* was strongly related to FA in the arcuate fasciculus, corpus callosum (genu, whole), fornix and superior

Table 5. Summary findings for regions and cognitive domains with large ($r \geq .5$) correlations based on the findings of more than one study, or very large ($r \geq .7$) correlations (not necessarily involving more than one study)

	cognitive domain			
ROI	*general cognition*	*memory*	*attention*	*verbal*
FA				
arcuate fasciculus			0.69*	
corpus callosum - genu			**0.52****	
corpus callosum - splenium	0.75*			0.68*
corpus callosum - whole		**0.66****	**0.78****	
fornix		**0.65***	0.85**	
superior longitudinal fasciculus			**0.56****	
white matter		**0.51***		
MD/ADC				
internal capsule			0.67**	
uncinate fasciculus			0.71**	
white matter		**0.56***		

Note. r = Pearson's r; FA = fractional anisotropy; MD/ADC = mean diffusivity/apparent diffusion coefficient; *ROI* = region of interest; * $p < .05$, ** $p < .001$; **bold** = finding based on more than 1 study

longitudinal fasciculus. Furthermore, *general cognition* and *verbal/language skills* were both very strongly related to FA in the corpus callosum (splenium).

In addition, *memory* was strongly associated with MD/ADC in white matter (total); while *attention* was very strongly related to MD/ADC in the internal capsule and uncinate fasciculus. Therefore, the cognitive domains of memory and attention were not only investigated more frequently, but also appear to be most strongly associated with high FA and low MD/ADC in a range of ROIs.

Discussion

This study meta-analysed the findings from 20 studies that examined the relationship between DTI and cognitive function in adults who had sustained mild, moderate and severe TBIs. Subgroup analyses suggested that the findings were not related to the timing of the DTI relative

to the cognitive testing, magnet strength, brand of scanner, *b*-values or number of diffusion-weighted images. However, the relationship between FA and cognition was stronger when DTI was performed in the subacute (1 week-3 months) post-injury interval than in the acute (≤1 week) and chronic (>3 months) stages. All correlations were moderate to large and positive, indicating that higher FA (reflecting WM integrity) was related to better cognitive functioning at each post-injury interval. Given that significant heterogeneity remained and there was insufficient data to examine the impact of post-injury interval on MD/ADC, the acute, subacute and chronic intervals were combined. The reporting quality of the 20 studies was also generally high (mean STROBE rating: 80%), indicating that it was appropriate to analyse all of the available data.

Overall, consistent with predictions, high FA and low MD/ADC — which are thought to reflect greater WM integrity — were associated with better cognitive performance for the majority of ROIs (moderate or larger and significant effects: 69%). The most commonly examined cognitive domains were memory and attention, and these domains were also most strongly related to the DTI findings. Additionally, FA was used more frequently than MD/ADC and appeared to be more strongly associated with cognitive performance. Furthermore, several brain regions were related to cognitive performance in more than one domain, including the corpus callosum, fornix, inferior longitudinal and uncinate fasciculi.

Despite largely consistent findings, there were two exceptions, both from single studies. More specifically, significant negative correlations were found for two cognitive domain/ROI combinations, such that *decreased* WM integrity was associated with better cognitive functioning (FA: cerebellar peduncles and general cognition, forceps major and executive functioning). In one case (lower FA in the cerebellar peduncles related to better general cognition), DTI was performed within seven days of injury (Wang et al., 2016); thus early axonal swelling may account for this finding (Bazarian et al., 2007). Most of the other acute findings, however, did not support this. In the other case (lower FA in the forceps major correlated with better executive

functioning), DTI was performed several years post-injury (107 months; (Kraus et al., 2007) and the reason why lower WM integrity was related to better functioning is unclear. Overall, the changes that occur over time as a result of DAI — including axonal stretching, swelling, shearing, disconnection and degeneration (Johnson et al., 2013) — and the associated DTI changes are not fully understood; longitudinal studies are needed to examine this phenomenon.

A recent meta-analysis found the largest and most consistent WM alterations following mild to severe TBIs occurred in the corpus callosum, internal capsule, occipital white matter, centrum semiovale, fornix and thalamic radiations (Wallace et al., 2018a). Several of these same regions were found to predict cognition in the current study, including the corpus callosum, fornix and internal capsule. These regions appear to not only show the most damage following a TBI, but are also related to performance on various cognitive tasks, highlighting their importance for continued research.

It is not surprising that, as the largest and most widely connected interhemispheric tract (Fitsiori et al., 2011), WM alterations in the corpus callosum were associated with poorer functioning in all seven cognitive domains. More specifically, WM alterations in the genu, which connects the left and right frontal lobes, were strongly related to executive functioning. WM alterations in the splenium, which connects the parieto-occipital regions of each hemisphere, were related to attention. Associations such as these are well-established in the literature (see Goldstein & Mesfin, 2017; Rosen & Viskontas, 2008; Ubukata et al., 2015b). The fornix, which connects the hippocampus and the frontal lobes, has long been associated with memory (see Douet & Chang, 2014 for a review); a finding supported by the current study. Finally, the arcuate fasciculus was strongly related to attention (FA), possibly due to its proximity to the superior longitudinal fasciculus; indeed, these two tracts were previously considered to be part of the same structure (Schmahmann & Pandya, 2006). The superior longitudinal fasciculus is involved in attention (Ptak, 2012; Voets, Bartsch, & Plaha, 2017), however the relationship between the

arcuate fasciculus and attention is rarely examined and may warrant further research. Moreover, no study examined the relationship between this tract and verbal/language skills, which is notable given that the arcuate fasciculus connects Wernicke's and Broca's areas (Noggle, 2011).

Cognitive impairments in memory, executive functioning and attention are commonly reported following a TBI (Cristofori & Levin, 2015; Dikmen et al., 2009). Not surprisingly, these same domains were frequently investigated by the studies examined in this meta-analysis. Of these, memory and attention strongly correlated with WM integrity (high FA, low MD/ADC) in several brain regions. In contrast, executive functioning was strongly related to WM integrity in very few brain regions, possibly because executive functioning is poorly defined and understood, is used as an "umbrella term" to reflect a range of cognitive abilities (e.g., planning, working memory, problem solving), and is difficult to assess in isolation (Chan et al., 2008; Jewsbury et al., 2016). General cognition was also very strongly related to FA in the splenium of the corpus callosum, however, this finding is not particularly informative because tests of general cognition — primarily designed to test "intelligence" or work aptitude — assess a broad range and/or combination of abilities (Lezak, Howieson, Bigler, & Tranel, 2012).

Based on the current findings, memory and attention are not only examined most frequently, but are most strongly related to DTI findings in a number of brain regions. Specifically, the brain regions that were strongly (based on the findings of multiple studies) or very strongly related to memory or attention are: the corpus callosum, fornix, internal capsule, white matter (total), and arcuate, uncinate, and superior longitudinal fasciculi. These regions appear to be the most promising for examination and may be useful in the prediction of memory and attention impairments, which frequently occur following a TBI.

Limitations

This study has several limitations. First, a large number of brain regions and cognitive domains were examined, limiting the data that could be combined; consequently, the samples

tended to be small (mean sample size *N* = 38). In fact, most results were based on the findings from one to two studies, suggesting that the conclusions should be treated cautiously. A large number of different tests (and subtests) were used to assess cognition, necessitating their categorisation into broad cognitive domains (Lezak et al., 2012). However, not all tests were easily categorised and the method we used has been criticised for being arbitrary (Pase & Stough, 2014). Although consideration was given to the Cattell-Horn-Carroll method of test categorisation (Jewsbury et al., 2017), many of the current tests were not included in this model; thus it could not feasibly be used. Notably, our categorisation of tests had a limited impact on the findings because very few tests were ultimately combined and the method largely served as a means by which to organise the findings.

Second, some previous research has found that DTI performed in the early stages after a TBI leads to higher FA and lower MD/ADC (Bazarian et al., 2007; Huisman et al., 2004), suggesting that the data obtained from different post-injury intervals should be reported separately. We performed a subgroup analysis to examine this and found that the relationship between FA and cognition was stronger in the subacute (>1 week-3 months) than the acute (≤1 week) and chronic (>3 months) post-injury intervals. However, the effect sizes for all three intervals were positive and medium or larger in size; consequently we combined the data. At present, there is no consensus regarding the definition of 'acute', with researchers variously defining it as less than one (Huisman et al., 2004; Zhu et al., 2014) or two weeks (Eierud et al., 2014; Hulkower et al., 2013; Kumar, Gupta, et al., 2009), and some not specifying the interval that they used (Niogi & Mukherjee, 2010; Strauss et al., 2015). It may be that one week is too long to detect any early post-injury reversal in the direction of the DTI findings. Additional research is now needed to provide a finer-grained analysis of the impact of post-injury interval on DTI, particularly in the very early period after injury.

Third, the location and magnitude of WM damage following TBI can vary significantly and, as such, the analysis of group data has been criticised because it may overlook inter-subject variability. That is, it may highlight the more severe pathology of a few participants or downplay the less extreme and more heterogeneous alterations evident in other participants (Ware et al., 2017). One alternative would be to compare the findings from individual cases to normative data or pre-injury scans, allowing inter-subject variability to be examined (Hulkower et al., 2013; Ware et al., 2017); however this data was not available.

Fourth, it was not possible to conduct some of the planned subgroup analyses (FA: injury severity; MD/ADC: post-injury interval, injury severity, brand of scanner, *b*-values) due to limited available data (*Q* and I^2 are underpowered when $N_{studies} < 20$ and/or $N_{participants} < 80$; (Huedo-Medina et al., 2006). Therefore, it is not known whether these variables were associated with differences in effect sizes. It is also possible that the current subgroup analyses were underpowered — potentially resulting in non-significant findings — due to the small numbers of studies and/or small samples.

Fifth, we did not correct for multiple comparisons because the consequence of making a Type II error (concluding that WM damage is not associated with cognition following TBI) was considered equally problematic as a Type I error (concluding that WM damage is associated with cognition following TBI). This study was designed to be exploratory and, had more stringent levels of significance been adopted, findings that warrant further investigation may have been excluded. Finally, differences in the pre- and post-processing of DTI data, identification of ROIs (automatic, manual), voxel size, and methods of analysis (e.g., ROI, TBSS) may have affected the DTI results (Amyot et al., 2015); however, this information was not always reported and these analyses were beyond the scope of this study.

Implications for practice and research

Although only preliminary, the results of this meta-analysis add to the substantial body of research examining the relationship between specific areas of the brain and cognition. Importantly, this research has identified the brain structures that are strongly related to memory and attention; both of which are commonly impaired following TBI (Cristofori & Levin, 2015; Dikmen et al., 2009). Additionally, several ROIs were strongly associated with cognitive performance in more than one domain (i.e., corpus callosum, fornix, inferior longitudinal and uncinate fasciculi). Therefore, particular focus should be given to these ROIs when researching TBI. The reporting quality of studies was evaluated using selected items from the STROBE checklist, but more recently developed reporting guidelines for MRI research (see Nichols et al., 2017) may prove more suited to future DTI studies.

From a clinical perspective, it would be useful if DTI metrics obtained soon after injury had predictive utility for long-term cognitive outcomes and recovery because the identification of individuals who are most likely to exhibit cognitive impairments following a TBI may be helped by early intervention. This is of considerable clinical significance because the risk of long-term deficits may be reduced through early medical, therapeutic or rehabilitative interventions (Matsushita et al., 2011; Mittenberg, Tremont, Zielinski, Fichera, & Rayls, 1996). However, few studies have conducted DTI in the acute phase in order to predict long-term cognitive outcomes; longitudinal studies are now needed.

Despite its importance, there is a paucity of large-scale studies examining the relationship between WM integrity and cognition following TBI (Hawryluk & Bullock, 2016; Schwab et al., 2015). Larger samples should be used in future studies to increase the reliability of findings and, importantly, the findings of small-scale or underpowered studies should not be overstated.

Conclusions

Overall, greater WM integrity (high FA, low MD/ADC) was related to better cognitive functioning in the majority of ROIs following mild, moderate and severe adult TBI. The corpus callosum was commonly examined and strongly associated with performance in all seven cognitive domains, highlighting the importance of this region. Interestingly, memory and attention, which are commonly impaired following a TBI, were very strongly related to DTI findings for the corpus callosum, fornix, internal capsule, arcuate and uncinate fasciculi — suggesting that these structures may be useful for predicting long-term cognitive outcomes. However, researchers tended to focus on very disparate brain regions and cognitive domains; thus, most results were based only on single studies and/or relatively small sample sizes, and therefore these findings await replication in large-scale studies.

4.3 Supplementary material

Appendix A. Logic grids for each database

PubMed Logic Grid

Traumatic brain injury	Diffusion tensor imaging
Brain injuries[mh] OR brain injur*[tw] OR head injuries, closed[mh] OR closed head injur*[tw] OR diffuse axonal injury[mh] OR diffuse axonal injur*[tw] OR brain traum*[tw] OR brain 120iffuse120o*[tw] OR 120iffuse120on*[tw] OR TBI[tw] OR TBIs[tw] OR Glasgow Coma Scale[mh] OR Glasgow Coma Scale[tw]	Diffusion tensor imaging[mh] OR diffusion tensor imag*[tw] OR diffusion magnetic resonance imaging[mh] OR diffusion magnetic resonance imag*[tw] OR diffusion MRI*[tw] OR diffusion weighted imag*[tw] OR diffusion weighted MRI*[tw] OR diffusion tractography[tw] diffusion tensor tractography[tw] OR anisotropy[mh] OR anisotropy[tw] OR apparent diffusion coefficient[tw] OR mean 120iffuse*[tw] OR DTI[tw] OR DWI[tw]

PsycINFO Logic Grid

Traumatic brain injury	Diffusion tensor imaging
Exp traumatic brain injury OR brain injur*.mp OR exp head injuries OR head injur*.mp OR diffuse axonal injur*.mp Or brain traum*.mp OR brain 120iffuse120o*.mp OR 120iffuse120on*.mp OR TBI.mp OR TBIs.mp OR Glasgow Coma Scale.mp	Diffusion tensor imag*.mp OR diffusion magnetic resonance imag*.mp OR diffusion MRI*.mp OR diffusion weighted imag*.mp OR diffusion weighted MRI*.mp OR diffusion tractography.mp OR diffusion tensor tractography.mp OR anisotropy.mp OR apparent diffusion coefficient.mp OR mean 120iffuse*.mp OR DTI.mp OR exp magnetic resonance imaging OR magnetic resonance imaging.mp OR MRI.mp OR DWI.mp

Embase Logic Grid

Traumatic brain injury	Diffusion tensor imaging
'brain injury'/exp OR ' brain injury':de,ti,ab OR 'brain injuries':ti,ab OR 'traumatic brain injury':de,ti,ab OR 'traumatic brain injuries':ti,ab OR 'closed head injury':ti,ab OR 'head injury':de,ti,ab OR 'diffuse axonal injury':de,ti,ab OR 'diffuse axonal injuries':ti,ab OR 'brain trauma':ti,ab OR 'brain contusion':de,ti,ab OR 'brain contusions':ti,ab OR 'concussion'/exp OR 'concussion':de,ti,ab OR 'concussions':ti,ab OR TBI:ti,ab OR TBI:ti,ab OR 'Glasgow Coma Scale':de,ti,ab	'diffusion tensor imaging':de,ti,ab OR 'diffusion tensor images':ti,ab OR 'diffusion magnetic resonance imaging':ti,ab OR 'diffusion MRI':ti,ab OR 'diffusion weighted imaging':de,ti,ab OR 'diffusion weighted images':ti,ab OR 'diffusion tractography':ti,ab OR 'diffusion tensor tractography':ti,ab OR 'anisotropy':de,ti,ab OR 'fractional anisotropy':de,ti,ab OR 'apparent diffusion coefficient':ti,ab OR 'mean diffusivity':ti,ab OR 'DTI':ti,ab OR 'DWI':ti,ab

Web of Science Logic Grid

Traumatic brain injury	Diffusion tensor imaging
TS=('brain injur*' OR 'traumatic brain injur*' OR 'head injur*' OR 'closed head injur*' OR 'diffuse axonal injur*' OR 'brain traum*' OR 'brain contusio*' OR 'concussio*' OR 'TBI' OR 'TBIs' OR 'Glasgow Coma Scale')	TS=('diffusion tensor imag*' OR 'diffusion magnetic resonance imag*' OR 'diffusion MRI' OR 'diffusion MRIs' OR 'diffusion weighted imag*' OR 'diffusion weighted MRI' OR 'diffusion tractography' OR 'diffusion tensor tractography' OR 'anisotrophy' OR 'fractional anisotropy' OR 'apparent diffusion coefficient' OR 'mean diffusi*' OR 'DTI' OR 'DWI')

Note. TS= topic search

Table S1: Study and sample characteristics of studies included in the meta-analysis

ref #	*reference*	*severity*	*# RH*	*FA or MD/ADC*	*M(SD) time since injury*		*M(SD) education*	*GCS*	N_{TBI}
					DTI scan	*cog testing*	*(years)*		
1	Arenth (2014)	mild-severe	all RH	FA	1.7 (0.58) years	1.7 (0.58) years	14.7 (2.3)	10.5 (4.2)	12
2	Baek (2013)	NS	NS	FA & ADC	251.2 (112.6) days	255.3 (113.8) days	NS	NS	35
3	Bendlin (2008)	NS	NS	MD	56 days	56 days	13.3 (1.6)	6-13	35
4	Chang (2010)	severe	NS	FA & ADC	152.44 (13.65) days	152.44 (13.65) days	14 (1.3)	NS	9
5	Geary (2010)	mild	NS	FA	5.29 (1.01) years	5.29 (1.01) years	16.4 (2.1)	13-15	40
6	Grossman (2013)	mild	NS	MD	**22.1 (15.4)** & 369.6 (112.1) days later**	**22.1 (15.4)** & 369.6 (112.1) days later**	15.2 (1.9)	14.9 (0.4)	20
7	Gu (2013)	mild-severe	NS	FA & MD	2.8 (1.86) days	17.3 (4.3) months	11.9 (2.9)	9.6 (3.6)	15
8	Holli (2010)	mild	NS	FA & ADC	within 3 weeks	within 6 weeks	NS	NS	34
9	Jang (2013)	severe	NS	FA & ADC	7.8 (7.9) months	7.8 (7.9) months	13.4 (1.4)	NS	21
10	Kraus (2007)	mild-severe	NS	FA	107.2 (26.1) months	107.2 (26.1) months	16.1 (0.8)	NS	37
11	Kumar (2009)	mild & moderate	NS	FA & MD	8.9 days	6 months	NS	mod=10.6 mild=14.5	83*
12	Little (2010)	mild-severe	NS	FA	77.3 (81.1) months	77.3 (81.1) months	16.3 (0.5)	NS	24
13	Matsushita (2011)	mild-moderate	NS	FA	3.5 days (median)	560 days	14.2 (1.9)	14 (median)	11
14	Miles (2008)	mild	NS	FA & MD	4.05 days	4.05 days & **after 6 months**	NS	NS	12
15	Palacios (2011)	severe	all RH	FA	278.5 (173.2) hours	278.5 (173.2) hours	11.3 (2.7)	5.1 (1.8)	15
16	Palacios (2013)	severe	NS	FA	4.2 (1.14) years	4.2 (1.14) years	13.7 (2.7)	5.2 (1.7)	26
17	Ubukata (2015)	severe	all RH	FA	106.9 (79.4) months	106.9 (79.4) months	11.3 (1.7)	NS	10
18	Wada (2012)	mild	all RH	FA	35.1 (3.7) months	35.1 (3.7) months	NS	14.8 (0.6)	51

19	Wang (2016)	mild	all RH	FA	within 7 days	within 7 days	NS	NS	47
20	Xiong (2014)	mild	NS	FA & MD	32.1 (3.6) days	32.1 (3.6) days	12.8 (3.1)	NS	25

* mild and moderate groups analysed separately, (N_{TBI} *mild* = 26, N_{TBI} *moderate* = 57); ** first time point used in this study; **bold** = indicates the time-points included in analyses; *#RH* = number of right handed participants; *FA* = fractional anisotropy; *MD/ADC* = mean diffusivity/apparent diffusion coefficient; *M(SD)* = mean and standard deviation; *DTI* = diffusion tensor imaging; *cog* = cognitive; *GCS* = Glasgow Coma Scale; N_{TBI} = number of TBI participants; NS = not specified

Table S2: Scanner specifications and acquisition details of studies included in the meta-analysis

ref #	*reference*	*Telsa*	*brand/model of scanner*	*acquisition voxel size (mm) reconstruction voxel size (mm), b-values*
1	Arenth (2014)	3	Siemens Allegra	matrix = 128 x 128 x 34, FOV = 200, slice thickness = 3mm, b values = 0, 850
2	Baek (2013)	1.5	Philips Gyroscan Intera	acquisition matrix = 96×96, reconstructed to matrix = 128×128 matrix, FOV = 221×221 mm2, slice thickness = 2.3mm, b-values = 0, 1000
3	Bendlin (2008)	3	General Electric Signa	matrix = 120 x 120, FOV = 240 x 240, slice thickness = 3mm; acquired voxel size = 2×2×3 mm interpolated to 0.9375mm isotropic dimensions (256×256 in plane image matrix)
4	Chang (2010)	1.5	Philips Gyroscan Intera	matrix = 128 × 128, FOV = 221 mm, slice thickness = 2.3 mm, b-values = 0, 600
5	Geary (2010)	3	General Electric	b-values = 0, 750, voxel size = 1.5 × 1.5 × 5 mm^3
6	Grossman (2013)	3	Siemens Magnetom	matrix = 82 x 82, FOV = 222 x 222 mm^2, slice thickness = 2.7mm, b-values = 0, 1000, 2000, voxel size = 2.7 x 2.7 x 2.7 mm^3
7	Gu (2013)	1.5	General Electric	FOV = 240mm, slice thickness = 2mm, b-values = 0, 1000; one additional image was simultaneously acquired at a value of b equal to 0 s/mm2 using a 128 x 128 matrix resolution that was zero filled during reconstruction to a size of 256 x 256
8	Holli (2010)	1.5	Siemens Magnetom Avanto	matrix = 128 x 128, FOV = 230mm, slice thickness = 5mm, slice gap = 1.5mm, b-values = 0, 1000
9	Jang (2013)	1.5	Philips Gyroscan Intera	matrix = 128 × 128, FOV = 221 × 221 mm2, slice thickness = 2.3mm, b-values = 0, 1000
10	Kraus (2007)	3	General Electric Signa	matrix = 132 x 132 (reconstructed to 256 x 256), FOV = 22cm, slice thickness = 5mm, b-values = 0, 750
11	Kumar (2009)	1.5	General Electric	matrix = 128 x 80 (a homodyne algorithm was used to reconstruct to 128x128; this was zero filled to reconstruct an image matrix of 256 x 256), FOV= 240 x 240, slice thickness = 3 mm, no interslice gap, b-values = 0, 1000
12	Little (2010)	3	General Electric	matrix = 256 x 256, FOV = 20 x 20 cm^2, slice thickness/gap = 3/0mm, b = 0, 1000
13	Matsushita (2011)	1.5	Philips Gyroscan Intera	matrix = 128 × 128, FOV = 230 × 230 mm × 90%, slice thickness = 2.5 mm, b-values = 0, 1000
14	Miles (2008)	1.5	Siemens Vision	matrix = 128 x 128, FOV = 240 x 240mm, slice thickness = 5mm, b-values = 0, 1000, voxel size = 1.9 x 1.9 x 5mm^3
15	Palacios (2011)	1.5	General Electric Signa	matrix = 128 × 128, FOV = 100, slice thickness = 5 mm, gap = 2 mm, b-values = 0, 1000
16	Palacios (2013)	3	Siemens Magnetom Trio	FOV = 240mm^2, slice thickness = 2 mm, no gap, b-values = 0, 1000, voxel size = 2.0 x 2.0 x 2.0 mm^3
17	Ubukata (2015)	3	Siemens Magnetom Trio	matrix = 96 x 96, FOV = 192 x 192mm, slice thickness = 2mm, b-values = 0, 1500
18	Wada (2012)	1.5	General Electric Signa	matrix = 128 x 128, FOV = 250 x 250mm, slice thickness = 3 mm, b-values = 0, 1000
19	Wang (2016)	3	Philips Achieva	FOV = 256 x 256, in-plane image resolution = 2 x 2mm, slice thickness = 2mm, b-values = 0, 1000
20	Xiong (2014)	3	Siemens Trio	matrix = 128 x 128, FOV = 240 x 240 mm, slice thickness = 3 mm, b-values = 0, 1000

Note. FOV = field of view

Table S3. Categorisation of cognitive tests used by individual studies

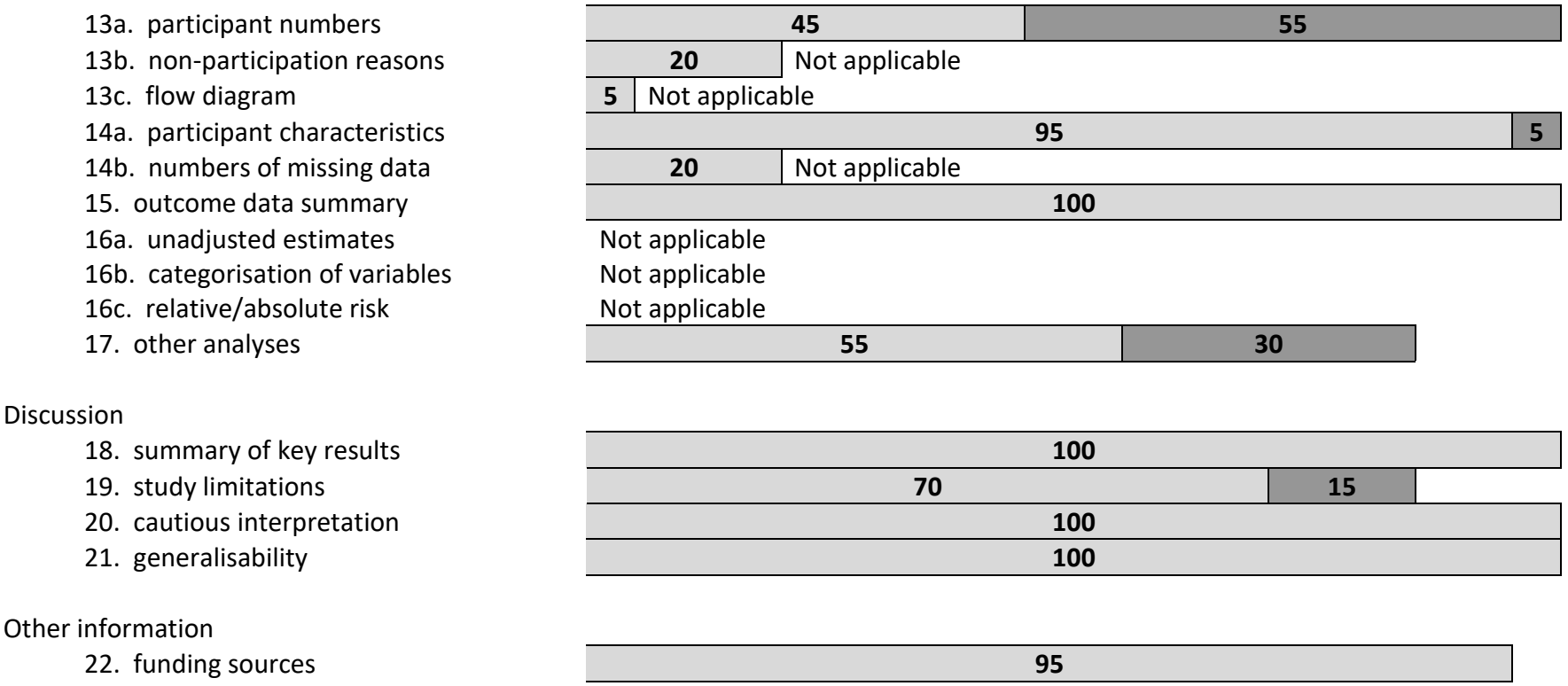
test	*study reference*
general cognition	
Wechsler Adult Intelligence Scale-Full IQ (WAIS-FIQ)	Baek et al., 2013; Chang et al., 2010; Jang et al., 2013; Matsushita et al., 2011; Wada et al., 2012
Mini-Mental State Exam (MMSE)	Chang et al., 2010; Wada et al., 2012; Xiong et al., 2014
Wechsler Adult Intelligence Scale-Performance IQ (WAIS-PIQ)	Chang et al., 2010; Matsushita et al., 2011
The NIH Toolbox Fluid Cognition Score	Wang et al., 2016
memory	
Brief Visuospatial Memory Test, Revised (BVMT)	Bendlin et al., 2008; Kraus et al., 2007
California Verbal Learning Test-II (CVLT-II)	Arenth et al., 2014; Bendlin et al., 2008; Geary et al., 2010; Grossman et al., 2013; Kraus et al., 2007; Little et al., 2010
Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Subtest (CANTAB-PAL)	Holli et al., 2010;
Four Word Short-Term Memory Test	Holli et al., 2010
Headminder: Memory & Learning	Miles et al., 2008
Memory Assessment Scale (MAS)	Baek et al., 2013; Chang et al., 2010; Jang et al., 2013
Rey Auditory Verbal Learning Test (RAVLT)	Holli et al., 2010; Palacios et al., 2013
Rey-Osterrieth Complex Figure Test-immediate recall	Holli et al., 2010
Rivermead Behavioural Memory Test (RBMT) Complex figure test – delayed recall	Palacios et al., 2011
attention, processing speed and working memory	
2-back d-prime index	Palacios et al., 2011

Continuous Performance Test (CPT)	Kraus et al., 2007; Little et al., 2010
Digit Span (from WAIS)	Gu et al., 2013; Kraus et al., 2007; Little et al., 2010; Palacios et al., 2013
Digit Symbol Test (from WAIS)	Gu et al., 2013; Kumar et al., 2009; Palacios et al., 2013
Finger Connection Test (FCT)	Kumar et al, 2009
Headminder: Attention/Concentration, Response Speed, Processing Speed	Miles et al., 2008
Letter-Number Sequencing (from WAIS)	Palacios et al., 2013
Number Connection Test (NCT)	Kumar et al., 2009
Paced Auditory Serial Addition Test (PASAT)	Kraus et al., 2007; Little et al., 2010
Processing Speed Index (from WAIS)	Ubukata et al., 2015; Xiong et al., 2014
Spatial Span (from WAIS)	Kraus et al., 2007; Little et al., 2010
Stroop Test	Gu et al., 2013; Kraus et al., 2007; Little et al., 2010; Miles et al., 2008; Palacios et al., 2013
Trail Making Test (TMT)	Arenth et al., 2014; Kraus et al., 2007; Little et al., 2010; Palacios et al., 2013
Weinberg Visual Cancellation Test	Miles et al., 2008
Working Memory Index (from WAIS)	Xiong et al., 2014
executive functioning	
Controlled Oral Word Association Test (COWAT)	Kraus et al., 2007; Little et al., 2010; Miles et al., 2008
Tower of London	Kraus et al., 2007; Little et al., 2010
Ruff Figural Fluency Test (RFFT)	Kraus et al., 2007; Little et al., 2010
verbal/language skills	
Wechsler Adult Intelligence Scale-Verbal IQ (WAIS-VIQ)	Chang et al., 2010; Matsushita et al., 2011
concept formation and reasoning	

Picture Completion Test (from WAIS)	Kumar et al., 2009
Rusk Institute of Rehabilitation Medicine-Similarities (RIRMS) – adaptation of Similarities from WAIS	Miles et al., 2008
construction and motor performance	
Block Design Test (from WAIS)	Kumar et al., 2009

Table S4: Study reporting quality: number and percentage of studies reporting each item of the STROBE checklist (Vandenbroucke et al., 2007)

STROBE item	*percentage of studies meeting/partially meeting criteria*
Title and abstract	
1a. indicate study design	80 / 10
1b. informative and balanced summary	25 / 75
Introduction	
2. background and rationale	100
3. specific objectives/hypotheses	100
Methods	
4. study design	100
5. setting, locations and dates	20 / 55
6. participant eligibility criteria and selection	80 / 20
7. variables defined	70 / 25
8. variable measurement	40 / 60
9. attempts to address potential bias	45 / 40
10. study size explanation	0
11. variable explanation	50 / 50
12a. statistical methods	95 / 5
12b. subgroup analyses	45 / 5
12c. management of missing data	Not applicable
12d. sampling strategy	90
12e. sensitivity analyses	Not applicable



Note. *STROBE* = Strengthening the Reporting of Observational Studies in Epidemiology

criteria met/item reported criteria partially met/item partially reported

Table S5. FA findings: correlations between ROIs and cognitive domains, ordered by ROIs (alphabetical)

	cognitive domain						
ROI	*general cognition*	*memory*	*attention*	*executive*	*verbal*	*concept formation*	*Constr-uction*
arcuate fasciculus			0.69*				
cerebellar peduncles	-0.29*						
cerebellum	0.36*						
cingulum	0.18	0.27*	0.62*	0.28			
corona radiata		0.33*	0.23	0.41*			
corpus callosum - body		0.03	0.50**	0.37*		0.34*	
corpus callosum - genu		0.39*	0.52**	0.59*		0.50**	0.53**
corpus callosum - splenium	0.75*	0.45*	0.59**	0.35*	0.68*		
corpus callosum - whole		0.66**	0.78**				
corticospinal tract				0.39*			
external capsule				0.27			
forceps major		0.38*	0.31	-0.56**			
forceps minor		0.35*		-0.28			
fornix	0.14	0.65*	0.85**		0.08		
fronto-occipital fasciculus		0.31	0.48*	0.35*			
inferior longitudinal fasciculus	0.48**		0.55*				
insula	0.39*						
internal capsule			0.04				
lenticular fasciculus	0.32*						
mesencephalon		0.33*					
sagittal stratum	0.37*	0.32	0.42*	0.50*			
superior longitudinal fasciculus	0.32*		0.56**	0.31			
uncinate fasciculus	0.60*	0.34*	0.53*				
white matter		0.51*	0.33*	-0.27		-0.02	

Note. FA = fractional anisotropy; *ROI* = region of interest; * $p < .05$, ** $p < .001$

Table S6. MD/ADC findings: correlations between ROIs and cognitive domains, ordered by ROIs (alphabetical)

	cognitive domain						
ROI	*general cognition*	*memory*	*attention*	*executive*	*verbal*	*concept formation*	*Constr-uction*
cingulum	0.22	0.19					
corona radiata			0.58*				
corpus callosum - body		0.59**	0.43**				
corpus callosum - genu			0.46**				
corpus callosum - splenium			0.42*				
corpus callosum - whole		0.54*					
external capsule		0.57*					
fornix	0.29	0.42			0.46		
fronto-parietal white matter		0.56**					
inferior longitudinal fasciculus			0.65*				
internal capsule			0.67**				
superior longitudinal fasciculus			0.67				
uncinate fasciculus			0.71**				
white matter		0.56*	0.19	0.38		-0.02	

Note. MD/ADC = mean diffusivity/apparent diffusion coefficient; *ROI* = region of interest; * $p <$ .05, ** $p <$ .001

4.4 List of studies included in this meta-analysis

[1-20] numbers correspond to the study references given in Tables 2 to 4

[1] Arenth, P. M., Russell, K. C., Scanlon, J. M., Kessler, L. J., & Ricker, J. H. (2014). Corpus callosum integrity and neuropsychological performance after traumatic brain injury: A diffusion tensor imaging study. Journal of Head Trauma Rehabilitation, 29(2), E1-E10. doi:10.1097/HTR.0b013e318289ede5

[2] Baek, S. O., Kim, O. L., Kim, S. H., Kim, M. S., Son, S. M., Cho, Y. W., . . . Jang, S. H. (2013). Relation between cingulum injury and cognition in chronic patients with traumatic brain injury; diffusion tensor tractography study. NeuroRehabilitation, 33(3), 465-471. doi:10.3233/NRE-130979

[3] Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., . . . Johnson, S. C. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. NeuroImage, 42(2), 503-514. doi:10.1016/j.neuroimage.2008.04.254

[4] Chang, M. C., Kim, S. H., Kim, O. L., Bai, D. S., & Jang, S. H. (2010). The relation between fornix injury and memory impairment in patients with diffuse axonal injury: A diffusion tensor imaging study. NeuroRehabilitation, 26(4), 347-353. doi:10.3233/NRE-2010-0572

[5] Geary, E. K., Kraus, M. F., Pliskin, N. H., & Little, D. M. (2010). Verbal learning differences in chronic mild traumatic brain injury. Journal of the International Neuropsychological Society, 16(3), 506-516. doi:10.1017/S135561771000010X

[6] Grossman, E. J., Jensen, J. H., Babb, J. S., Chen, Q., Tabesh, A., Fieremans, E., . . . Grossman, R. I. (2013). Cognitive impairment in mild traumatic brain injury: A longitudinal diffusional kurtosis and perfusion imaging study. American Journal of Neuroradiology, 34(5), 951-957. doi:10.3174/ajnr.A3358

[7] Gu, L., Li, J., Feng, D. F., Cheng, E. T., Li, D. C., Yang, X. Q., & Wang, B. C. (2013). Detection of white matter lesions in the acute stage of diffuse axonal injury predicts long-term cognitive impairments: A clinical diffusion tensor imaging study. Journal of Trauma and Acute Care Surgery, 74(1), 242-247. doi:10.1097/TA.0b013e3182684fe8

[8] Holli, K. K., Wäljas, M., Harrison, L., Liimatainen, S., Luukkaala, T., Ryymin, P., . . . Dastidar, P. (2010). Mild Traumatic Brain Injury. Tissue Texture Analysis Correlated to Neuropsychological and DTI Findings. Academic Radiology, 17(9), 1096-1102. doi:10.1016/j.acra.2010.04.009

[9] Jang, S. H., Kim, S. H., Kim, O. R., Byun, W. M., Kim, M. S., Seo, J. P., & Chang, M. C. (2013). Cingulum injury in patients with diffuse axonal injury: a diffusion tensor imaging study. *Neuroscience Letters, 543*, 47-51. doi: 10.1016/j.neulet.2013.02.058

[10] Kraus, M. F., Susmaras, T., Caughlin, B. P., Walker, C. J., Sweeney, J. A., & Little, D. M. (2007). White matter integrity and cognition in chronic traumatic brain injury: A diffusion tensor imaging study. *Brain: A Journal of Neurology, 130*(10), 2508-2519. doi: http://dx.doi.org.proxy.library.adelaide.edu.au/10.1093/brain/awm216

[11] Kumar, R., Gupta, R. K., Husain, M., Chaudhry, C., Srivastava, A., Saksena, S., & Rathore, R. K. S. (2009). Comparative evaluation of corpus callosum DTI metrics in acute mild and moderate traumatic brain injury: Its correlation with neuropsychometric test. *Brain Injury, 23*(7-8), 675-685. doi: 10.1080/02699050903014915

[12] Little, D. M., Kraus, M. F., Joseph, J., Geary, E. K., Susmaras, T., Zhou, X. J., . . . Gorelick, P. B. (2010). Thalamic integrity underlies executive dysfunction in traumatic brain injury. *Neurology, 74*(7), 558-564. doi: 10.1212/WNL.0b013e3181cff5d5

[13] Matsushita, M., Hosoda, K., Naitoh, Y., Yamashita, H., & Kohmura, E. (2011). Utility of diffusion tensor imaging in the acute stage of mild to moderate traumatic brain injury for detecting white matter lesions and predicting long-term cognitive function in adults. *Journal of Neurosurgery, 115*(1), 130-139. doi: 10.3171/2011.2.jns101547

[14] Miles, L., Grossman, R. I., Johnson, G., Babb, J. S., Diller, L., & Inglese, M. (2008). Short-term DTI predictors of cognitive dysfunction in mild traumatic brain injury. Brain Injury, 22(2), 115-122. doi:10.1080/02699050801888816

[15] Palacios, E. M., Fernandez-Espejo, D., Junque, C., Sanchez-Carrion, R., Roig, T., Tormos, J. M., . . . Vendrell, P. (2011). Diffusion tensor imaging differences relate to memory deficits in diffuse traumatic brain injury. *BMC Neurology, 11*(24). doi: 10.1186/1471-2377-11-24

[16] Palacios, E. M., Sala-Llonch, R., Junque, C., Fernandez-Espejo, D., Roig, T., Tormos, J. M., . . . Vendrell, P. (2013). Long-term declarative memory deficits in diffuse TBI: Correlations with cortical thickness, white matter integrity and hippocampal volume. *Cortex, 49*(3), 646-657. doi: 10.1016/j.cortex.2012.02.011

[17] Ubukata, S., Ueda, K., Sugihara, G., Yassin, W., Aso, T., Fukuyama, H., & Murai, T. (2015). Corpus callosum pathology as a potential surrogate marker of cognitive impairment in diffuse axonal injury. *The Journal of Neuropsychiatry & Clinical Neuroscience*. doi: 10.1176/appi.neuropsych.15070159

[18] Wada, T., Asano, Y., & Shinoda, J. (2012). Decreased fractional anisotropy evaluated using tract-based spatial statistics and correlated with cognitive dysfunction in patients with mild traumatic brain injury in the chronic stage. *American Journal Neuroradiology, 33*(11), 2117-2122. doi: 10.3174/ajnr.A3141

[19] Wang, Z., Wu, W., Liu, Y., Wang, T., Chen, X., Zhang, J., . . . Chen, R. (2016). Altered cerebellar white matter integrity in patients with mild traumatic brain injury in the acute stage. PLoS ONE, 11(3). doi:10.1371/journal.pone.0151489

[20] Xiong, K. L., Zhu, Y. S., Zhang, L., Yin, Z. Y., Zhang, J. N., Qiu, M. G., & Zhang, W. G. (2014). White matter integrity and cognition in mild traumatic brain injury following motor vehicle accident. Brain Research, 1591, 86-92. doi:10.1016/j.brainres.2014.10.030

CHAPTER 5: CHRONIC WHITE MATTER CHANGES DETECTED USING DIFFUSION TENSOR IMAGING FOLLOWING ADULT TRAUMATIC BRAIN INJURY AND THEIR RELATIONSHIP TO COGNITION

5.1 Preamble

This chapter consists of a paper entitled "Chronic white matter changes detected using diffusion tensor imaging following adult traumatic brain injury and their relationship to cognition", which has been submitted for publication and is currently under review.

The preceding meta-analyses examined the location and extent of WM alterations following adult TBI, and the relationship between DTI findings and cognitive outcomes following adult TBI. Several brain regions were found both to be commonly affected by TBI (see Chapter 3) and moderately to strongly related to cognitive findings following TBI (see Chapter 4): the genu, body and splenium of the corpus callosum (CC), fornix, and superior longitudinal fasciculus (SLF). In addition, memory, attention and executive functioning were the cognitive domains which, in addition to being commonly affected by TBI, were also the most frequently examined and most strongly related to DTI findings. Thus, the CC (genu, body, splenium), fornix and SLF appear to be the most promising regions for further research, along with the cognitive domains of memory, attention and executive functioning.

However, these meta-analyses were restricted because very few studies examined the same brain regions and cognitive domains. As a result, the majority of correlations (94%) were based on the findings of one to two studies, with relatively small samples (i.e., 60% of studies from the two meta-analyses had fewer than 30 participants). The current study was therefore designed to overcome some of these shortcomings by examining a larger sample of mild, moderate and severe TBI participants, and healthy and orthopaedic controls. Participants

underwent MRI with DTI and completed cognitive tests. This study used a ROI approach to determine whether WM alterations were detected in the CC, fornix and SLF, in people with mild and moderate to severe TBI relative to controls. In addition, it examined whether DTI findings were related to memory, attention and executive functioning. The brain regions and cognitive domains were chosen based on the findings of the two meta-analyses.

Tables and Figures are provided within the text to make it easier to read. Supplementary material for this paper is provided at the end of the chapter (pages 167-168), comprising:

- Comparison of healthy and orthopaedic control groups in terms of demographic information, cognitive performance and diffusion tensor imaging (Table S1)

A complete list of all references for the thesis is provided at the end of the thesis (pages 216-236).

CHAPTER 5: PAPER 3

Chronic white matter changes detected using diffusion tensor imaging following adult traumatic brain injury and their relationship to cognition

Authors: E.J. Wallace, J.L. Mathias, L. Ward, K. Pannek, J. Fripp, S. Rose

Statement of authorship is on the following page

Reference: Wallace, E. J., Mathias, J. L., Ward, L., Pannek, K., Fripp, J., & Rose, S. (2020). *Chronic white matter changes detected using diffusion tensor imaging following adult traumatic brain injury and their relationship to cognition.* Manuscript under review.

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Erica Wallace		
Contribution to the Paper	Study inception, design, methodology (including literature searches, statistical analysis and data interpretation), wrote manuscript, and acted as corresponding author		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/4/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

vii. the candidate's stated contribution to the publication is accurate (as detailed above);

viii. permission is granted for the candidate in include the publication in the thesis; and

ix. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Supervised and contributed to the study design, data analysis and interpretation, and manuscript preparation		
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Contribution to the Paper	Assisted with data analysis and manuscript review		
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5.2 Paper three

Abstract

Objective: White matter (WM) changes detected using diffusion tensor imaging (DTI) are reportedly related to cognitive outcomes following traumatic brain injury (TBI), but much existing research is underpowered or has only examined general outcomes, rather than cognitive functioning. ***Method:*** A large sample of adults who had sustained mild, moderate or severe TBIs seven months prior (N=165) and a control group (N=106) underwent DTI and cognitive testing. Fractional anisotropy and mean diffusivity were calculated for five regions (corpus callosum: genu, body, splenium; fornix; superior longitudinal fasciculus) that recent meta-analyses identified as being affected by TBI and related to cognition following TBI. Memory, attention and executive functioning, which are often affected by TBI, were assessed. ***Results:*** Overall, mild TBI did not show significant WM or cognitive changes, relative to controls, but moderate to severe TBI was associated with large WM alterations (all regions) and poorer cognitive performance. No significant correlations were found between DTI findings and cognition in the moderate to severe group. ***Conclusions:*** The findings have shown that moderate to severe TBI leads to considerable WM and cognitive changes. Early and ongoing examination of mild TBI is needed to determine whether WM and cognitive changes are initially present and, if so, when they resolve.

Chronic white matter changes detected using diffusion tensor imaging following adult traumatic brain injury and their relationship to cognition

Introduction

Diffusion tensor imaging (DTI) better detects microstructural changes to brain tissue than conventional neuroimaging techniques (computed tomography, structural magnetic resonance imaging; MRI) following traumatic brain injury (TBI) (Oehr & Anderson, 2017; Rugg-Gunn, Symms, Barker, Greenwood, & Duncan, 2001). More particularly, DTI has been used to identify diffuse axonal injury (DAI), which is thought to contribute to the cognitive problems that people experience after a TBI (Voelbel et al., 2012).

DTI quantifies the diffusion of water molecules in the brain and involves the calculation of a 'diffusion tensor' (see Mukherjee, Berman, Chung, Hess, & Henry, 2008 for a detailed explanation). The diffusion tensor can be visualised as a 'diffusion ellipsoid', with its shape being dependent on the type of tissue that is being examined (e.g., white or grey matter) and any physiological changes caused by primary and secondary trauma (Hutchinson, Schwerin, Avram, Juliano, & Pierpaoli, 2018). Where there are no microstructural elements constraining diffusion, as is the case for cerebrospinal fluid, diffusion occurs equally in all directions (Huisman, 2010). This is known as isotropic diffusion and results in a spherical diffusion ellipsoid (Amyot et al., 2015; Huisman, 2010). In contrast, the microstructural organisation of healthy white matter (WM) restricts diffusion; diffusion occurs freely parallel to the axons, while being restricted in other directions. This causes the diffusion ellipsoid to become elongated, with the long, principal axis aligned with the white matter pathway (Huisman, 2010; Shenton et al., 2012; Suri & Lipton, 2018). This directional diffusion is known as anisotropic diffusion (Koerte et al., 2016). The DTI metric used to quantify the directional dependence of diffusion is fractional anisotropy (FA), which is measured on a scale of 0 (indicating spherical/isotropic diffusion) to 1 (reflecting directional/anisotropic diffusion) (Suri & Lipton, 2018). In WM regions in adults, higher values

may reflect WM integrity, while lower values may reflect WM damage (Koerte et al., 2016; Voelbel et al., 2012). In contrast, mean diffusivity (MD) or apparent diffusion coefficient measure the magnitude of diffusion, providing an average of diffusion along the three axes of the ellipsoid (Amyot et al., 2015; Douglas et al., 2018; Voelbel et al., 2012). MD is also restricted by the microstructural organisation of the WM; low MD values may indicate healthy WM and high MD values may reflect WM damage (Niogi & Mukherjee, 2010).

DTI has increasingly been used in studies of TBI, with most reporting lower FA and higher MD following injury (Amyot et al., 2015; Shenton et al., 2012). Specifically, higher FA and lower MD have been found in a range of brain regions following mild TBI, including the corpus callosum, internal capsule, external capsule, superior longitudinal fasciculus, corticospinal tract and sagittal stratum (e.g., Arfanakis et al., 2002; Dean, Sato, Vieira, McNamara, & Sterr, 2015; Inglese et al., 2005; Kraus et al., 2007; Zhu et al., 2014). These WM changes tend to be larger more following severe injuries (i.e., lower FA, higher MD) (e.g., Kraus et al., 2007; Matsushita et al., 2011). However, the changes to FA and MD may be reversed when DTI is performed soon after injury, with FA reported to be higher and MD lower 72 hours after a mild TBI (Bazarian et al., 2007) and MD being lower within one week of sustaining a TBI (Huisman et al., 2004).

A recent meta-analysis examining the location and extent of WM changes found that, following a TBI, there were widespread WM alterations (lower FA, higher MD) in a large number of brain regions (regions of interest: ROIs), regardless of when the DTI was performed (Wallace et al., 2018a). These changes were evident even after mild TBI, which is notable given that this damage is rarely detected using conventional imaging (Shenton et al., 2012; Strauss et al., 2015), despite 15% to 30% of people purportedly experiencing long-term cognitive impairments following mild TBI (McKee & Daneshvar, 2015; Niogi & Mukherjee, 2010).

Disparate findings have also been reported by studies that have examined the relationship between cognitive outcomes and DTI following TBI. In particular, one review found that higher FA and/or lower MD were positively related to better cognitive functioning in a

number of studies but, in other studies, the relationships were reversed or non-significant (Hulkower et al., 2013). Indeed, even studies that have investigated the relationship between the same cognitive domain and ROI have reported inconsistent findings. For example, the relationship between memory performance and FA in the cingulum has been found to be both positive (e.g., Geary, Kraus, Pliskin, & Little, 2010; Kraus et al., 2007) and negligible (e.g., Jang et al., 2013) in different studies.

Another meta-analysis, which examined the relationship between DTI and cognition following TBI, reported that WM integrity (high FA, low MD) was associated with cognitive functioning following mild, moderate and severe TBI (Wallace, Mathias, & Ward, 2018b). Specifically, WM integrity in the corpus callosum was related to better general cognition, memory, attention, executive functioning, construction and motor performance, verbal and language skills, and concept formation and reasoning. WM integrity in the fornix was associated with better memory, attention and verbal/language skills and, in the superior longitudinal fasciculus, it was related to better general cognition, attention and executive functioning. Memory, attention and executive functioning were the most frequently examined of all of the cognitive domains, with memory and attention most strongly related to the DTI findings in the corpus callosum, fornix and superior longitudinal fasciculus (Wallace et al., 2018b). These findings were from studies that examined people with TBIs of all severities (mild to severe) at a range of post-injury intervals (acute to chronic), based on initial subgroup analyses that suggested these findings could be combined. However, it is possible that this method led to important differences being missed, given that FA and MD findings may differ in mild compared to more severe injuries and when DTI is performed in the acute compared to later time periods (see reviews by Asken, DeKosky, Clugston, Jaffee, & Bauer, 2017; Shenton et al., 2012). In addition, there was limited overlap in the brain regions and/or cognitive domains that were examined by the contributing studies, with most of the findings from this meta-analysis based only on one or two studies (94%) and relatively small samples ($N_{participants}$ <26 in 60% of the studies). Thus, the current literature

largely consists of studies with low statistical power, which may contribute to the so-called 'replication crisis' whereby studies with insufficient statistical power fail to replicate expected findings (see Shrout & Rodgers, 2018).

More recently, there has been a large-scale study that examined the relationship between DTI performed in the subacute period (median = 19 days post-injury) and general recovery in a large moderate to severe TBI sample (N = 217) (Castano-Leon et al., 2018). This study found that lower FA in most of the examined regions was associated with unfavourable outcomes (strongest correlations: corpus callosum, cingulum, cerebral peduncles), which was measured using the extended Glasgow Outcome Scale at six and 12 months post-injury. Although large in scale, this study did not examine specific cognitive outcomes or mild TBI, highlighting the need for continued research to strengthen the knowledge-base.

The current study therefore examined the DTI and cognitive data from a large TBI sample, in addition to a control group (comprising healthy persons and people with orthopaedic injuries), in order to assess the reliability and generalisability of the findings from the aforementioned meta-analyses (Wallace et al., 2018a, 2018b). To this end, it examined whether: (1) WM integrity was compromised (lower FA, higher MD) in the corpus callosum (genu, body, splenium), fornix and superior longitudinal fasciculus following mild and moderate to severe TBI, relative to controls and whether damage was more notable following more severe injuries; (2) the mild and moderate to severe TBI groups performed more poorly on tests of memory, attention and executive functioning; and (3) cognitive performance was related to WM integrity/damage following TBI, and whether these relationships were equivalent in the controls. These five ROIs were chosen based on of the findings from two recent meta-analyses (Wallace et al., 2018a, 2018b). Memory, attention and executive functioning were examined because, in addition to being commonly affected by TBIs (Cristofori & Levin, 2015), were frequently examined by the meta-analysed studies (Wallace et al., 2018b). WM integrity was expected to be lower following

mild and moderate to severe TBI (relative to controls), and related to cognitive functioning (memory, attention, executive functioning), which was expected to be poorer following a TBI.

Method

Participants

The study participants were all adults who were involved in a larger research project that examined outcomes after TBI, which was undertaken at the Royal Adelaide Hospital (2008-2012). Three groups were recruited for this study: TBI, orthopaedic controls and healthy controls. The TBI participants had all sustained a non-penetrating TBI and the orthopaedic controls had sustained an orthopaedic injury that did not involve the head or face (to avoid the possibility of a concussion or mild TBI). A separate group of healthy controls was additionally recruited, consisting of family or friends of the TBI sample and visitors to the Royal Adelaide Hospital. Eligible participants: (1) were aged between 18 and 80 years; (2) spoke English as their first language (necessary to complete the cognitive assessments); (3) did not have any known psychiatric or neurological disorders, intellectual disabilities, or history of substance abuse; and (4) were able to undergo MRI (no contraindications) and cognitive testing. TBI severity was classified as mild, moderate or severe, based on Glasgow Coma Scale (GCS) scores (mild: 13-15; moderate: 9-12; severe: ≤8), duration of loss of consciousness score (mild: <20 mins; moderate: 20 mins–6 hours; severe: >6 hours) (Bohnen et al., 1994; Smajic, 2019), and/or duration of post-traumatic amnesia (mild: <60 mins; moderate: 60 mins–24 hours; severe: >24 hours) (Amyot et al., 2015). Where a participant experienced symptoms that crossed into two or more severity categories, the severity was determined by agreement between two severity indicators. For instance, if a patient had a GCS of 14 (mild), 30 minutes loss of consciousness (moderate), and post-traumatic amnesia for 5 hours (moderate), they would be categorised as having sustained a moderate TBI.

A total of 221 people who had sustained a non-penetrating TBI, 84 orthopaedic and 84 healthy control participants were initially recruited. In total, 117 participants were excluded (N_{TBI}=56, $N_{orthopaedic}$=37, $N_{healthy}$=24) because they did not have usable MRI images (e.g., failed to have an MRI, excessive head movement, scanner artefacts; N_{TBI}=41, $N_{orthopaedic}$=15, $N_{healthy}$=8), they had minor asymptomatic brain abnormalities on their MRI (identified by the radiologist as "incidental findings of no consequence"; N_{TBI}=11, $N_{orthopaedic}$=22, $N_{healthy}$=16), or the time between the injury and the MRI was excessive (i.e., identified as extreme outliers; more than 400 days; N_{TBI}=4) (Tukey, 1977). One healthy control participant who was found to have previously sustained a head injury was also excluded (i.e., TBI occurred prior to the study recruitment period). The final sample therefore consisted of 165 people with TBI (N_{mild}=134, $N_{moderate}$=15, N_{severe}=16), 47 orthopaedic controls and 59 healthy controls. The moderate and severe groups were both small, therefore they were combined for all subsequent analyses.

The two control groups were compared in terms of demographic, cognitive and DTI variables, based on a recent study in which WM integrity differed in orthopaedic compared to healthy controls (Wilde et al., 2019). Consistent with the findings from a larger sample taken from this research project (Mathias, Dennington, Bowden, & Bigler, 2013), the orthopaedic and healthy control groups did not differ significantly in terms of their: age (t(104)= -.474, p=.637), education (t(102)=.312, p=.755), proportion of males and females (χ^2 (1)=3.628, p=.057), cognitive performance, or FA and MD values from the five ROIs (see Supplementary Table S1 for additional summary descriptive data and statistical comparisons). Therefore, these two groups were combined to form a single control group ($N_{controls}$ = 106) for use in all subsequent analyses.

Measures

Cognitive tests

Memory, attention and executive functioning were assessed using two subtests from the Wechsler Memory Scale-Third Edition (WMS-III) (Wechsler, 1997), two computerised reaction time tasks, and the Controlled Oral Word Association Test (COWA) (Spreen & Straus, 1998),

respectively. These measures formed part of a larger battery of tests and self-report scales that were completed by all participants.

Memory was assessed using the WMS-III Logical Memory and Visual Reproduction subtests (immediate and delayed recall/trials). The Logical Memory task requires participants to verbally recall two stories, both immediately after hearing each story (immediate recall; LM-I) and after a delay of 25 to 35 minutes (delayed recall; LM-II). The Visual Reproduction task involves participants drawing five geometric designs from memory having seen each design for 10 seconds, both immediately (immediate recall; VR-I) and after a delay of 25 to 35 minutes (delayed recall; VR-II). Scores on both tests were age-scaled, to control for age-related differences in ability, and standardized to a mean of 10 (SD=3) using the normative data provided in the WMS-III manual (Wechsler, 1997).

Attention was assessed using 4-choice compatible and 4-choice incompatible visual reaction time tasks (Mathias, Beall, et al., 2004; Mathias, Bigler, et al., 2004). Reaction time tasks assess information processing speed, which is strongly associated with attention (Chiaravalloti & DeLuca, 2008; Mathias, Bigler, et al., 2004; Ponsford & Kinsella, 1992). Briefly, participants were presented with four white rectangles (stimuli) on a computer screen, two on each side of a central fixation point. Participants were required to respond as quickly and accurately as possible when one of the rectangles turned red by pressing a button (response) with their middle (outer rectangle) or index (inner rectangle) finger. The compatible task required participants to respond to the cue using the corresponding finger of the hand on the same side as the stimulus (i.e., right-handed response to stimuli on the right side of the screen). The incompatible task was designed to be more complex and to require inter-hemispheric processing, with participants responding using the hand on the opposite side to that of the stimulus (i.e., right-handed response to a left-sided stimulus). Median reaction times were calculated from 60 trials for each of the two tasks in order to control for lapses in attention and anticipatory responses (Mathias, Beall, et al., 2004; Mathias, Bigler, et al., 2004).

Executive functioning was assessed using the COWA (Spreen & Straus, 1998). Participants were required to generate as many words as possible starting with the letters F, A and S within 1-minute intervals (per letter), with the requirement that the words not be proper nouns or the same word with a different ending (e.g., sit and sitting). The total number of correct responses (raw scores) was recorded.

Procedure

This study was approved by the Human Research Ethics Committees of the University of Adelaide and the Royal Adelaide Hospital. Participants for the TBI and orthopaedic control groups were identified on a prospective basis via hospital records and sent a letter briefly describing the study and inviting them to participate, while also providing a way to opt-out of the study. Those who did not opt-out within a two-week period were contacted by the researchers. Healthy controls were friends/family of the TBI group or were recruited via flyers, located throughout the hospital, which outlined the study and provided contact details for the researchers. All three groups were screened (by phone) to establish their eligibility (using the aforementioned inclusion criteria) and obtain preliminary verbal consent.

Participants were mailed information sheets containing background information and several self-report questionnaires that were relevant to the larger project (e.g., Rivermead Post-Concussion Symptoms, Community Integration Questionnaire), which they completed prior to 2-3 hours of cognitive testing (participants all tested individually). Written informed consent was obtained at the beginning of the session, prior to being interviewed (regarding background and demographic information, and medical history) and undergoing cognitive testing. Participants additionally underwent MRI with DTI, as detailed below. MRI scans and cognitive testing were completed within one week of each other, an average of seven months post-injury (TBI: 200 days, SD = 41.4, orthopaedic controls: 218 days, SD = 41.8). An honorarium of $40 was paid to all participants to assist with out-of-pocket expenses when travelling to complete the cognitive assessment and MRI. Importantly, all data were collected exclusively for research purposes and

the results of the cognitive testing were not provided to participants, thereby reducing the likelihood they would perform disingenuously or use their performance for litigation purposes.

MRI acquisition

All participants had an MRI at the Royal Adelaide Hospital on a Siemens Tim Trio 3T scanner (Erlangen, Germany), with a high-resolution structural image being acquired for each participant (1 mm^3 isotropic 3D T1 MPRAGE sequence following ADNI recommendations: http://www.loni.ucla.edu/ADNI/Research/Cores/ADNI_Siemens_Human_3TVB15_Trio.pdf). The following parameters were used: FOV = 24×25.6×17.6 cm, TR/TE/TI = 2300/2.26/900ms, flip angle 9°. An optimised diffusion sequence (Jones, Horsfield, & Simmons, 1999) was used to acquire diffusion-weighted images along 64 non-collinear directions (b=3000s/mm^2), along with one non-diffusion-weighted image. The following parameters were used: 60 axial slices, FOV = 25×25cm, TR/TE = 9400/116ms, 2.5mm slice thickness, and acquisition matrix 100×100 with a 2.5mm isotropic image resolution. Two 2D gradient recalled echo images (TE1/TE2 4.76/7.22ms) were used to acquire a field map for diffusion data, which assists when correcting for distortion due to susceptibility inhomogeneities.

Region of interest analysis

DTI images underwent quality control through visual examination and automated detection and removal of volumes that were affected by significant within-volume head motion (Pannek et al., 2017), and were subsequently corrected for head movement, eddy current and susceptibility-induced distortions, using FMRIB's Diffusion Toolbox (FMRIB, Oxford, UK) (Andersson & Sotiropoulos, 2016; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Brain extraction was performed using a multi-atlas approach, with each mask being visually checked by the first author (EJW). Pre-processed diffusion data were upsampled by a factor of 2, and FA and MD maps generated for each participant. A study-specific template was generated using FA maps from 80 randomly selected participants (N_{TBI}=40, $N_{orthopaedic}$=20, $N_{healthy}$=20) using Advanced Normalization Tools (ANTs) (Avants et al., 2011). This template was registered to the

John Hopkins University (JHU) atlas and individual brains were registered to this using ANTs. The regions contained within the JHU atlas were transformed to each participant's diffusion space and visually checked by the first author (EJW). For each selected region, FA and MD values were extracted voxelwise, and the region's median FA and MD values were calculated. The five ROIs that were examined for current purposes were the genu, body and splenium of the corpus callosum (CC), the fornix, and the superior longitudinal fasciculus (SLF).

Statistical analyses

Independent samples *t*-tests and chi-square tests were used to examine whether the TBI and control groups were demographically comparable (age, education, proportion of males and females). All assumptions for the t-tests were met, with the exception of normally distributed data; however as the samples were large (>50) these tests were deemed appropriate (see Lumley, Diehr, Emerson, & Chen, 2002).

Next, the FA and MD values from the mild TBI (N = 134) and moderate-severe (N = 31) TBI subgroups and controls (N = 106) were compared using Welch's F tests (Welch, 1951) and Games-Howell post-hoc comparisons (Toothaker, 1993) — the latter being recommended when samples are unequal in size (Tomarken & Serlin, 1986) — in order to determine whether WM integrity was more compromised following more serious injuries (moderate-severe TBIs). Hierarchical regressions were conducted to determine whether group differences remained after controlling for age, sex and time post-injury, all of which may affect WM. Each ROI was entered as the dependent variable, and age, sex, time post-injury (step one) and group (TBI or control; step two) were entered as independent variables. Hierarchical regressions, rather than ANCOVAs, were performed because the groups differed on the covariates (age and time post-injury), and group assignment was not random (Miller & Chapman, 2001).

The cognitive scores of the mild TBI (N=134) and moderate-severe (N=31) TBI subgroups and the controls (N=106) were then also compared (Welch's F tests and Games-Howell post-hoc comparisons) to determine whether cognitive performance differed according to injury severity.

Hierarchical regressions were conducted to determine whether group differences in cognition remained after controlling for age, sex, time post-injury and years of education because these variables may have impacted on cognitive performance. Cognitive scores were entered as the dependent variable, and age, sex, time post-injury, education (step one) and group (TBI or control; step two) were entered as independent variables.

For all group comparisons, standardised mean differences (Hedges' *g* effect sizes) were calculated to evaluate the extent of any differences, with *g* = -0.2, -0.5, -0.8 and -1.3 corresponding to small, medium, large and very large effects, respectively (Cohen, 1992; Rosenthal, 1996). All effect sizes were calculated so that a negative value indicated that the TBI group had reduced WM integrity (lower FA, higher MD) or poorer cognitive performance, relative to controls.

Finally, partial correlation coefficients were calculated to determine whether WM integrity (FA & MD) in five ROIs was related to memory, attention and executive functioning, above what was accounted for by age, sex, time post-injury and education. These were only examined in the moderate to severe TBI group (the mild group did not show WM or cognitive changes, relative to controls), and only for those cognitive tests in which the moderate to severe group performed worse than the controls, after controlling for the effects of age, sex, time post-injury and education. The same associations were then examined separately in the control group, to determine whether the relationships were equivalent in these subgroups. All coefficients were calculated in such a way that a positive correlation indicated that better cognitive functioning (e.g., more accurate responses, faster reaction times) was related to greater WM integrity (higher FA, lower MD). Correlations (*r*) of 0.1, 0.3 and 0.5 corresponded to weak, moderate/medium and strong relationships, respectively (Cohen, 1992). Bonferroni corrections (Holland & Copenhaver, 1988) were used throughout to compensate for the fact that multiple statistical analyses were performed.

Results

Participants

Summary background, demographic and injury details for the TBI (provided for the full group [all TBI], mild and moderate-severe TBI subgroups) and control groups are provided in Table 1. The TBI and control participants were predominantly young to middle-aged, right-handed males. On average, both groups had completed more than one-year post-secondary education. Most participants reported that they had not sustained a previous TBI and only a limited number were involved in any litigation related to their injury. The TBI group largely sustained mild injuries (N=134, 81.2%), with many fewer having moderate (N=15) or severe (N=16) injuries; the latter two being combined (moderate-severe TBI: N=31, 18.7%) when examining the impact of injury severity (see Table 1 for summary details for these subgroups). TBIs were most commonly caused by motor vehicle accidents, followed by falls, bicycle accidents, assaults and sporting injuries.

When the demographic characteristics of the TBI (all TBI) and control groups were compared, they were found to differ in terms of sex (χ^2(1)=16.36, p=.000), age (t(269)= -2.080, p=.038, g=.26), education (t(262)=2.724, p=.007, g=.37) and interval between injury and examination (i.e., compared to orthopaedic controls; t(203)=2.61, p=.010, g=.44), with the TBI group having significantly more males, being older, having completed fewer years of education and having a shorter interval between injury and examination (the TBI group was on average 4.4 years older, had completed 12 months less education than the controls and were examined 18.3 days earlier than the orthopaedic controls). Given that WM and cognitive performance can be impacted by age, sex, time post-injury and education, these variables were examined further. The

Table 1. Summary background information for the traumatic brain injury and control groups

variable	all TBI (N = 165)				mild TBI (N = 134)				moderate-severe TBI (N = 31)				controls[1] (N = 106)			
	N	*mean*	*SD*	*range*	*N*	*mean*	*SD*	*range*	*N*	*mean*	*SD*	*range*	*N*	*mean*	*SD*	*range*
age	165	43.6	16.8	19-80	134	43.8	17.0	19-80	31	42.5	15.9	20-72	106	39.2	16.7	18-77
education (years)	160	13.1	2.6	7-22	129	13.3	2.5	8-20	31	12.6	3.2	7-22	104	14.1	2.8	7-20
days since accident	160	200.0	41.4	98-338	129	194.3	38.2	98-338	31	223.6	46.5	135-336	45[2]	218.3	41.8	136-344
GCS	143	13.3	3.1	3-15	114	14.5	0.7	13-15	29	8.3	3.9	3-14				
LOC (hours)	126	1.7	15.0	0-168	111	0.3	1.3	0-10	15	12.3	43.2	0-168				
PTA (hours)	133	31.8	107.0	0-576	107	7.4	49.2	0-504	26	132.4	192.64	0-576				
		N	*%*			*N*	*%*			*N*	*%*			*N*	*%*	
gender		165				134				31				106		
females		35	21.2			30	22.4			5	16.1			47	44.3	
males		130	78.8			104	77.6			26	83.9			59	55.7	
handedness		157				126				31				103		
right		138	87.9			111	88.1			27	87.1			96	93.2	
left		19	12.1			15	11.9			4	12.9			7	6.8	
previous TBI (self-report)		159				128				31				103		
yes		45	28.3			40	31.3			5	16.1			0	0	
no		114	71.7			88	68.8			26	83.9			103	100	
involved in litigation		159				128				31				44[2]		
yes		30	18.9			24	18.8			6	19.4			2	4.5	
no		129	81.1			104	81.3			25	80.6			42	95.5	
TBI severity		165				134				31						
mild		134	81.2			134	100			0						
moderate		15	9.1			0				15	48.4					
severe		16	9.7			0				16	51.6					
cause of injury		165				134				31				47[2]		
motor vehicle		40	24.2			32	23.9			8	25.8			1	2.1	
fall		40	24.2			29	21.6			11	35.5			11	23.4	
bicycle		34	20.6			28	20.9			6	19.4			7	14.9	
assault		30	18.2			26	19.4			4	12.9			0	0.0	

sport	11	6.7	11	8.2	0		18	38.3
pedestrian	4	2.4	2	1.5	2	6.5	1	2.1
other	6	3.6	6	4.5	0		9	19.1

Note. TBI = traumatic brain injury; N = number of participants; SD = standard deviation; GCS = Glasgow Coma Scale; LOC = loss of consciousness; PTA = post-traumatic amnesia; DTI = diffusion tensor imaging; orthopaedic controls N = 47; healthy controls N = 59; [1] all controls (orthopaedic + community controls); [2] orthopaedic controls only

TBI and control groups did not differ in terms of the number of volumes remaining after rejecting those for motion ($t(269)=-.94$, $p=.347$). Similarly, there were no group differences in the number of volumes remaining between the mild TBI, moderate-severe TBI and control groups ($F(2, 94.28)=.56$, $p=.573$), thus this variable was not controlled for in the analyses.

Fractional anisotropy

FA values for the TBI subgroups (mild, moderate-severe) and controls were compared to determine whether WM was compromised following TBI and whether more severe injuries led to larger WM alterations in each ROI (see Table 2). The FA values for the mild TBI and control groups did not differ significantly, with the associated effects sizes all being relatively small. In contrast, all five FA values for the moderate-severe TBI and control groups differed significantly (Bonferroni corrected $p<.01$), equating to medium (fornix: $g = -.62$) to very large differences (CC genu: $g = -1.44$). Moreover, these differences remained even after correcting for age, sex and time post-injury (see Table 3). Lastly, moderate and severe TBIs led to significantly lower FA values than mild TBI in the CC (genu, body, splenium), but not the fornix or SLF. Thus, more severe injuries led to less directional/anisotropic diffusion, suggesting greater WM damage.

Mean diffusivity

MD values for the TBI subgroups (mild, moderate-severe) and controls were compared to examine whether more severe injuries had a greater impact on the magnitude of diffusion (see Table 2). The mild TBI and control groups did not differ significantly in any ROI, but the moderate-severe TBI and control groups showed medium to large and significant differences in all five ROIs ($g = -.59$ to -1.16). Again, these differences could not be attributed to age, sex or time post-injury (see Table 3). Finally, the moderate-severe TBI group showed significantly higher MD than the mild TBI group in the CC (genu, splenium) and SLF, but not the body of CC or fornix. Taken together, these findings suggest that more severe injuries led to a greater magnitude of diffusion, indicative of more WM damage.

Table 2. Fractional anisotropy and mean diffusivity values for the mild TBI, moderate-severe TBI and control groups

region of interest (ROI)	**mild TBI** (N = 134)		**moderate-severe TBI** (N = 31)		**controls** (N = 106)			**mild TBI *vs* controls**		**moderate-severe TBI *vs* controls**		**moderate-severe TBI *vs* mild**	
							fractional anisotropy (FA)						
	mean	*SD*	*mean*	*SD*	*mean*	*SD*	*Welch's F*	*Hedges' g*	*p*	*Hedges' g*	*p*	*Hedges' g*	*p*
corpus callosum – genu	.48	.05	.42	.07	.49	.04	$F(2, 77.54) = 13.87$, $p = .000$	-.22	.021	-1.44	**.000**	-1.10	**.002**
corpus callosum – body	.53	.05	.49	.07	.54	.04	$F(2, 76.57) = 8.41$, $p = .000$	-.22	.202	-1.03	**.001**	-.073	**.006**
corpus callosum – splenium	.61	.04	.57	.05	.62	.04	$F(2, 79.19) = 10.71$, $p = .000$	-.25	.159	-1.17	**.000**	-.95	**.002**
fornix	.30	.09	.28	.08	.33	.08	$F(2, 89.56) = 7.10$, $p = .001$	-.35	.028	-.62	**.003**	-.23	.224
superior longitudinal fasciculus	.44	.02	.42	.03	.44	.02	$F(2, 78.67) = 5.01$, $p = .009$	.00	.881	-.88	**.008**	-.90	.016
							mean diffusivity (MD)						
	mean	*SD*	*mean*	*SD*	*mean*	*SD*	*Welch's F*	*Hedges' g*	*p*	*Hedges' g*	*p*	*Hedges' g*	*p*
corpus callosum – genu	.53	.04	.56	.05	.52	.03	$F(2, 77.78) = 13.03$, $p = .000$	-.28	.027	-1.12	**.000**	-.71	**.004**
corpus callosum – body	.52	.04	.55	.05	.51	.03	$F(2, 76.73) = 6.52$, $p = .002$	-.28	.260	-1.12	**.003**	-.71	.022
corpus callosum – splenium	.51	.03	.53	.04	.50	.02	$F(2, 77.43) = 12.34$, $p = .000$	-.38	.031	-1.16	**.000**	-.62	**.005**
fornix	.86	.14	.90	.11	.83	.12	$F(2, 90.96) = 5.12$, $p = .008$	-.23	.217	-.59	**.007**	-.30	.141
superior longitudinal fasciculus	.48	.02	.49	.03	.47	.02	$F(2, 78.85) = 7.63$, $p = .001$	-.50	.548	-.88	**.001**	-.45	**.006**

Note. TBI = traumatic brain injury; effect sizes; N = number of participants; SD = standard deviation; Games-Howell post-hoc comparisons used to generate p-values; Bonferroni corrected $p < .01$ considered significant

Table 3. Regression analyses of fractional anisotropy and mean diffusivity (moderate to severe TBI compared to controls)

fractional anisotropy (FA)					**mean diffusivity** (MD)				
variables	**adjusted R^2**	**ΔR^2**	**standardised β**	***p***	**variables**	**adjusted R^2**	**ΔR^2**	**standardised β**	***p***
corpus callosum – genu					corpus callosum – genu				
step 1	.099	.099			step 1	.080	.080		
age			-.372	.001	age			.331	.004
sex			-.049	.660	sex			-.048	.674
time since injury			-.019	.864	time since injury			.011	.925
step 2	.351	.			step 2	.380	.		
group (TBI, control)			-.522	**<.001**	group (TBI, control)			.567	**<.001**
corpus callosum – body					corpus callosum – body				
step 1	.120	.120			step 1	.102	.102		
age			-.373	.001	age			.325	.005
sex			-.003	.977	sex			-.080	.478
time since injury			.120	.275	time since injury			-.114	.305
step 2	.327	.			step 2	.307	.		
group (TBI, control)			-.475	**<.001**	group (TBI, control)			.474	**<.001**
corpus callosum – splenium					corpus callosum – splenium				
step 1	.016	.016			step 1	.004	.004		
age			-.222	.061	age			.118	.316
sex			-.084	.473	sex			-.053	.653
time since injury			.080	.490	time since injury			-.149	.202
step 2	.229	.			step 2	.273	.		
group (TBI, control)			-.483	**<.001**	group (TBI, control)			.539	**<.001**

<u>fornix</u>					<u>fornix</u>				
step 1	.397	.397			step 1	.342	.342		
age			-.647	<.001	age			.563	<.001
sex			-.016	.860	sex			-.116	.229
time since injury			.064	.479	time since injury			-.099	.298
step 2	.479	.			step 2	.489	.		
group (TBI, control)			-.304	**.001**	group (TBI, control)			.401	**<.001**
<u>superior longitudinal fasciculus</u>					<u>superior longitudinal fasciculus</u>				
step 1	.093	.093			step 1	-.008	-.008		
age			-.331	.004	age			.101	.395
sex			.094	.406	sex			-.128	.282
time since injury			-.017	.876	time since injury			-.023	.846
step 2	.205	.			step 2	.226	.		
group (TBI, control)			-.359	**.001**	group (TBI, control)			.505	**<.001**

Note. TBI = traumatic brain injury

Cognitive outcomes

The cognitive scores for the TBI subgroups (mild, moderate-severe) and control group were examined to determine the type and extent of the impairments following TBI and whether performance varied with injury severity (see Table 4). Although none of the scores for the mild TBI and control groups differed significantly (Bonferroni corrected $p>.007$), the moderate-severe TBI group performed significantly worse than controls ($p<.007$) on the delayed Visual Reproduction trial (VR-II; g =-.70), the compatible reaction time task (g =-.86), and the COWA task (g =-.75).

However, as noted above, the TBI group was older, had less of a smaller interval between injury and examination (compared to orthopaedic controls), and had a significantly lower level of education than the control group, which may have contributed to these differences. Three hierarchical linear regressions were therefore performed for those cognitive tests that differed between the moderate-severe TBI and control groups (VR-II, compatible reaction time, COWA) in order to determine whether they differed significantly after taking the differences in age, sex, time post-injury and education into account (see Table 5). Cognitive scores were entered as the dependent variable, with age, sex, time post-injury, education (step one) and group (TBI or control; step two) entered as predictors. These analyses revealed that group membership (moderate-severe TBI or control) accounted for a significant amount of variance on the three tests, even after controlling for differences in age, sex, time post-injury and education. Overall, the mild TBI group performed comparably to the controls on all of the cognitive tests, but those with moderate-severe TBI performed significantly worse than controls on three of the tests; findings that were not attributable to age, sex, time post-injury or education.

Table 4. Summary cognitive data for mild TBI, moderate-severe TBI and control groups

cognitive test	mild TBI		moderate-severe TBI		controls			mild TBI vs controls		moderate-severe vs controls		moderate-severe vs mild	
	mean	*SD*	*mean*	*SD*	*mean*	*SD*	*Welch's F*	*Hedges' g*	*p*	*Hedges' g*	*p*	*Hedges' g*	*p*
WMSIII - Logical Memory immediate (LM-I)	9.70	3.25	8.77	3.34	10.63	3.05	$F(2, 82.52) = 4.72$, $p = .012$	-.29	.065	-.59	.025	-.28	.373
WMSIII - Logical Memory delayed (LM-II)	10.27	3.01	9.35	3.83	11.27	2.95	$F(2, 79.10) = 5.011$, $p = .009$	-.33	.032	-.60	.036	-.29	.433
WMSIII - Visual Reproduction immediate (VR-I)	10.90	3.02	8.90	3.46	10.83	3.09	$F(2, 81.30) = 4.50$, $p = .014$	-.02	.982	-.60	.021	-.64	.014
WMSIII - Visual Reproduction delayed (VR-II)	12.10	3.29	10.23	3.08	12.55	3.37	$F(2, 86.52) = 6.53$, $p = .002$	-.13	.562	-.70	**.002**	-.57	.012
4-choice compatible visual RT task	453.79	83.43	522.83	123.84	436.59	90.86	$F(2, 74.47) = 6.34$, $p = .003$	-.20	.304	-.86	**.003**	-.74	.017
4-choice incompatible visual RT task	687.07	194.91	779.34	219.43	637.99	174.61	$F(2, 75.58) = 5.73$, $p = .005$	-.26	.114	-.76	.008	-.46	.107
COWA	40.07	11.89	33.68	13.14	43.11	12.43	$F(2, 82.18) = 6.47$, $p = .002$	-.25	.147	-.75	**.003**	-.52	.045

Note. TBI = traumatic brain injury; SD = standard deviation; WMSIII = Wechsler Memory Scale-third edition (N_{mild}=128, $N_{moderate\text{-}severe}$=31, $N_{controls}$=103); RT = reaction time; 4-choice compatible visual RT task (N_{mild}=127, $N_{moderate\text{-}severe}$=30, $N_{controls}$=102); 4-choice incompatible visual RT task (N_{mild}=126, $N_{moderate\text{-}severe}$=29, $N_{controls}$=102); COWA = Controlled Oral Word Association Test (N_{mild}=128, $N_{moderate\text{-}severe}$=31, $N_{controls}$=103); Bonferroni corrected p<.007 considered significant

Table 5. Regression analyses of the cognitive tests (moderate to severe TBI compared to controls)

variables	adjusted R^2	ΔR^2	standardised β	p
WMSIII - Logical Memory immediate				
step 1	.307	.307		
age			.122	.218
sex			-.218	.035
education			.459	<.001
time since injury			.083	.392
step 2	.321	.		
group (TBI, control)			-.160	.120
WMSIII - Logical Memory delayed				
step 1	.245	.245		
age			.153	.139
sex			-.273	.012
education			.343	.001
time since injury			.044	.661
step 2	.260	.		
group (TBI, control)			-.166	.122
WMSIII - Visual Reproduction immediate				
step 1	.130	.130		
age			-.285	.011
sex			-.161	.160
education			.259	.023
time since injury			.100	.360
step 2	.144	.		
group (TBI, control)			-.170	.140

variables	adjusted R^2	ΔR^2	standardised β	p
4-choice compatible visual RT task				
step 1	.349	.349		
age			.548	<.001
sex			-.090	.368
education			-.312	.002
time since injury			.052	.581
step 2	.423	.		
group (TBI, control)			.295	**.002**
4-choice incompatible visual RT task				
step 1	.383	.383		
age			.573	<.001
sex			-.064	.511
education			-.324	.001
time since injury			.031	.738
step 2	.459	.		
group (TBI, control)			.299	**.002**
Controlled Oral Word Association Test				
step 1	.097	.097		
age			.187	.098
sex			.019	.870
education			.230	.047
time since injury			-.224	.046
step 2	.186	.		
group (TBI, control)			-.329	**.004**

	WMSIII - Visual Reproduction delayed			
step 1	.104	.104		
age			-.222	.050
sex			-.176	.131
education			.255	.027
time since injury			.096	.386
step 2	.186	.		
group (TBI, control)			-.317	.**006**

Note. TBI = traumatic brain injury; WMSIII = Wechsler Memory Scale-third edition; RT = reaction time; COWA = Controlled Oral Word Association Test

Relationship between cognition and fractional anisotropy

Next, the relationship between cognitive performance and FA (in each of five ROIs) was examined in the moderate-severe TBI group (see Supplementary Table S2; note that the mild TBI group was not examined because it did not show WM alterations or cognitive impairments, relative to controls). Correlations were examined for those cognitive tests in which the moderate-severe TBI group performed significantly worse than controls (VR-II, compatible reaction time task, COWA), after taking into account the effects of age, sex, time post-injury and education. Medium or large, significant and positive correlations ($r \geq .3$, Bonferroni corrected $p<.003$) indicate that better cognitive performance (more accurate responses, faster reaction times) was related to greater WM integrity (higher FA). Overall, none of the correlations were significant ($p>.003$).

These relationships were then compared to those seen in the control group to see whether they were equivalent in people with and without TBI (see Supplementary Table S2). Again, none of the correlations were significant ($p>.003$). Therefore, after corrections for age, sex, time post-injury and education, no significant relationships were found between cognitive performance and FA in any of the five ROIs in the moderate-severe TBI or control groups.

Relationship between cognition and mean diffusivity

The relationship between cognition (VR-II, compatible reaction time task, COWA) and MD in the five ROIs was also examined in the moderate-severe TBI group. Medium to strong, significant and positive correlations ($r \geq .3$, Bonferroni corrected $p<.003$) were again interpreted as indicating that better cognitive performance was related to greater WM integrity (lower MD). As can be seen in Supplementary Table S2, none of the correlations were significant ($p>.003$).

Similarly, there were no significant correlations between cognition and MD in the five ROIs in the control group. Therefore, cognitive performance was not related to MD in any of the

five ROIs in the moderate-severe TBI and control groups, after controlling for the effects of age, sex, time post-injury and education.

Discussion

The current study examined WM alterations in the CC, fornix and SLF, and the relationship between WM integrity and cognitive functioning seven months after people had sustained a mild, moderate or severe TBI. These regions were investigated because they appear to be most affected following a TBI (Wallace et al., 2018a) and are also strongly related to post-injury cognitive outcomes (Wallace et al., 2018b). Most existing research has used relatively small samples (e.g., Brandstack, Kurki, Hiekkanen, & Tenovuo, 2011; Matsushita et al., 2011; Ubukata et al., 2015a), with the resulting low statistical power potentially limiting the reliability and generalisability of the findings. As noted, appropriate analyses must be conducted to ensure that studies have the necessary statistical power to replicate expected findings (Shrout & Rodgers, 2018). One exception to this is a recent study that examined a large sample, but only investigated moderate to severe TBI and general outcomes, which were classified as favourable or unfavourable, rather than specific cognitive outcomes (Castano-Leon et al., 2018). Thus, a large-scale investigation was undertaken in order to determine whether, and to what extent, WM changes were related to cognition following mild, moderate and severe TBI.

Overall, at seven months post-injury, mild TBIs did not result in significant alterations in WM when compared to controls. Although other DTI studies that used similar post-injury periods have reported WM damage following mild injuries (for reviews see Niogi & Mukherjee, 2010; Shenton et al., 2012), a number of reviews have noted that the findings are inconsistent (Asken et al., 2017; Shenton et al., 2012). Indeed, TBI is increasingly being recognised as leading to heterogeneous patterns of injury (Bigler & Stern, 2015; Cristofori & Levin, 2015), raising the possibility that the location and extent of WM damage varied between individuals, but was overlooked at a group level. Alternatively, WM damage in those with mild TBI may have resolved

prior to the study, which was conducted seven months post-injury. For instance, partial recovery of WM alterations has been reported in several longitudinal studies (e.g., between one and nine months after injury; Arfanakis et al., 2002; Grossman et al., 2013; Mayer et al., 2010). In contrast to those with mild TBI, people with moderate to severe TBI displayed WM damage, indicated by less directional/anisotropic and a greater magnitude of diffusion (lower FA, higher MD) in all five regions, relative to controls.

In terms of cognition and consistent with some previous research (Kraus et al., 2007; Mayer et al., 2010), mild TBI was not associated with poorer cognitive performance, despite reviews finding that 15% to 30% of people with mild TBI have long-term cognitive deficits (McKee & Daneshvar, 2015; Shenton et al., 2012). However, it is possible that any cognitive problems may have recovered, given that the sample was assessed an average of seven months post-injury and that most people return to pre-injury cognitive levels three to six months following a mild TBI (Cristofori & Levin, 2015). Those with moderate to severe TBIs performed more poorly than controls on a test of visual memory (VR-II), attention (compatible reaction time) and executive functioning (COWA), even after controlling for differences in age, sex, interval between injury and examination (i.e., compared to orthopaedic controls), and education. These findings support previous research, which has found that approximately 60% of people with moderate TBI and only 15% to 20% of those with severe injuries return to pre-injury cognitive levels (for a review see Cristofori & Levin, 2015).

The relationship between cognitive performance and DTI findings was examined in the moderate to severe TBI group to determine the most promising relationships for further examination. The specific relationships that were examined were between DTI findings (FA, MD) in the CC, fornix and SLF (i.e., WM changes were detected in all five ROIs) and one test each of memory, processing speed and executive functioning (VR-II, compatible reaction time, COWA). These tests were chosen because the moderate to severe TBI group performed more poorly in these tests than the controls, even after accounting for differences in age, sex, the interval

between injury and examination, and education. No correlations were significant. The same associations were then examined in the control group, to determine whether they were equivalent in people with and without TBI. Again, no correlations were significant, although more were positive in the moderate to severe TBI group compared to the controls. Thus, it is possible that the group differences in age, sex, time post-injury and education accounted for any relationship between cognition and WM integrity.

Limitations and directions for future research

This study has several limitations that should be considered. Group comparisons (i.e., ROI analysis) were used to examine WM changes following TBI, however the location and extent of WM damage is likely to have varied between individuals (Cristofori & Levin, 2015). Although useful for identifying broad patterns, group comparisons largely overlook the inter-individual variability that is a hallmark of TBI (Bigler & Stern, 2015; Cristofori & Levin, 2015). This highlights the importance of examining individual differences in WM changes following TBI, possibly by comparing individuals to normative databases (Hulkower et al., 2013; Niogi & Mukherjee, 2010). Longitudinal studies should also be completed to examine the trajectories of WM and cognitive alterations following TBI. Early and continued examination of mild TBI would help to determine whether initial WM and cognitive changes are present and, if so, when they resolve.

Despite an initial sample size considerably larger than that used in much existing DTI and cognition research (N_{TBI}=165), it is worth noting that the primary findings came from the moderate to severe TBI group ($N_{moderate\text{-}severe}$=31), which had a sample size that was not much greater than those used elsewhere in the literature. In addition, previous research has found that the extent of WM damage differs for moderate and severe injuries (Castano-Leon et al., 2018), but it was not possible to examine the three injury categories separately in the current study because very few participants sustained moderate (9.1%) or severe (9.7%) TBIs. The two groups were necessarily collapsed into one, with all analyses based on a combined moderate to severe

TBI group. Additional large-scale studies are needed in which mild, moderate, and severe injuries are more evenly represented.

Multiple previous concussions may also affect WM and/or cognitive performance and should have been included as a covariate in the analyses, however this information was not collected from participants. A head injury exposure guided interview was not administered to participants, thus it is possible that previous head injuries were not reported accurately by participants. Further, the underlying cause of TBI and orthopaedic injuries was not controlled for in the analyses, but may reflect lifestyle differences between the groups. In addition, the time between injury and MRI varied considerably, although a recent meta-analysis showed that DTI findings did not differ depending on post-injury interval (Wallace et al., 2018a). Finally, the DTI measures (e.g., FA, MD) obtained from the fornix may be inaccurate because the fornix is a very thin structure, surrounded by cerebrospinal fluid. This structure may therefore suffer from partial volume effects, especially where there was atrophy (Jones & Cercignani, 2010). Partial volume effects can occur when voxels contain more than one type of tissue (e.g., WM, grey matter, cerebrospinal fluid), each of which have different diffusion properties (Vos, Jones, Viergever, & Leemans, 2011). Several techniques have been developed to help mitigate this problem, including the suppression of cerebrospinal fluid contamination either in the acquisition or analysis of diffusion data (Jones & Cercignani, 2010).

Although widely used, ROI analysis calculates measures (e.g., FA, MD) that are averaged across all of the fibre tracts that are present within each voxel and, therefore, may be inaccurate when a voxel contains crossing fibres and/or more than one fibre tract (Jeurissen et al., 2013; Raffelt et al., 2015). ROI analysis has proven useful in studies with specific hypotheses about where differences will be found (a-priori hypotheses), but recently developed methods — such as fixel-based analysis (FBA; (Raffelt et al., 2015) — can evaluate individual fibre populations in regions where fibres cross and may better determine the nature and extent of WM changes following TBI.

The current findings suggest that moderate to severe TBI leads to WM and cognitive changes, but no association was found between the two. However, participants were only examined at one time-point (i.e., 7 months post-injury). Large-scale, longitudinal studies are now needed to determine whether early DTI findings for the CC, fornix and SLF predict long-term cognitive outcomes (e.g., years post-injury). It is possible that early DTI may help to identify individuals who are more likely to experience long-term cognitive problems in these domains, potentially allowing for early intervention and rehabilitation (e.g., cognitive and/or skills training, group therapy) in order to optimise outcomes and decrease the levels of TBI-related disability.

Conclusions

This study found that moderate to severe TBI leads to WM damage in the CC, fornix and SLF — as reflected in less directional/anisotropic and a greater magnitude of diffusion (higher FA, lower MD) — and impairments to visual memory, attention and executive functioning, when compared to healthy and orthopaedic controls. In contrast, mild TBI was not associated with WM alterations or cognitive impairments seven months post-injury, suggesting a lack, or potential resolution, of WM damage and/or cognitive impairments within this time-frame. An examination of the relationship between cognition and WM integrity in the moderate to severe TBI group revealed no significant associations, suggesting that any potential relationship may have been accounted for by group differences in age, sex, interval between injury and examination (i.e., relative to orthopaedic but not healthy controls), and/or education. Large-scale, longitudinal studies are now needed to determine whether early examination of the CC, fornix and SLF can help to identify people who are most likely to exhibit long-term cognitive problems.

5.3 Supplementary Material

Table S1. Comparison of healthy and orthopaedic control groups (demographic, cognitive performance and diffusion tensor imaging)

	healthy controls			orthopaedic controls					
	N	*mean*	*SD*	*N*	*mean*	*SD*	*t*	*df*	*p-value*
cognitive performance									
WMSIII - Logical Memory immediate (LM-I)	58	10.64	3.12	45	10.62	2.98	-.026	101	.979
WMSIII - Logical Memory delayed (LM-II)	58	11.33	2.97	45	11.20	2.96	-.217	101	.829
WMSIII - Visual Reproduction immediate (VR-I)	58	10.93	3.37	45	10.69	2.71	-.393	101	.695
WMSIII - Visual Reproduction delayed (VR-II)	58	12.22	3.54	45	12.98	3.12	1.129	101	.262
4-choice compatible visual RT task	57	436.96	96.22	45	436.11	84.65	-.047	100	.963
4-choice incompatible visual RT task	57	645.98	200.28	45	627.87	136.93	-.518	100	.605
COWA	58	43.21	11.77	45	42.98	13.37	-.092	101	.927
DTI findings: FA									
corpus callosum – genu	59	.49	.05	47	.49	.04	.140	104	.889
corpus callosum – body	59	.54	.05	47	.54	.04	.741	104	.460
corpus callosum – splenium	59	.62	.04	47	.62	.04	.081	104	.936
fornix	59	.33	.09	47	.33	.08	-.224	104	.823
superior longitudinal fasciculus	59	.44	.02	47	.44	.02	.124	104	.901
DTI findings: MD									
corpus callosum – genu	59	.52	.03	47	.52	.02	-.477	104	.635
corpus callosum – body	59	.52	.04	47	.51	.02	-.854	104	.395

corpus callosum – splenium	59	.50	.02	47	.50	.02	.318	104	751
fornix	59	.84	.14	47	.82	.10	-.705	104	.482
superior longitudinal fasciculus	59	.47	.02	47	.47	.01	-.281	104	.779

Note. N = number of participants; SD = standard deviation; t = t-test; df = degrees of freedom; WMSIII = Wechsler Memory Scale-third edition; RT = reaction time; COWA = Controlled Oral Word Association Test; DTI = diffusion tensor imaging; FA = fractional anisotropy; MD = mean diffusivity

Table S2. Partial correlations[1] (p-value) between cognitive tests[2] and diffusion tensor imaging findings (fractional anisotropy & mean diffusivity) for the moderate to severe TBI and control groups

	CC genu	CC body	CC splenium	fornix	SLF
		fractional anisotropy (FA)			
moderate-severe TBI					
WMSIII - Visual Reproduction delayed	.02 (.915)	-.10 (.612)	-.15 (.462)	-.02 (.933)	-.08 (.718)
4-choice compatible visual RT task	.27 (.180)	.36 (.068)	.45 (.021)	.31 (.127)	.38 (.055)
COWA	.10 (.612)	.14 (.498)	.24 (.234)	-.01 (.951)	.20 (.330)
controls					
WMSIII - Visual Reproduction delayed	-.35 (.026)	-.21 (.183)	-.05 (.746)	-.15 (.337)	-.38 (.014)
4-choice compatible visual RT task	.11 (.507)	.14 (.400)	.05 (.762)	.22 (.162)	.09 (.566)
COWA	-.43 (.005)	-.15 (.359)	-.32 (.045)	.14 (.384)	-.07 (.651)
		mean diffusivity (MD)			
moderate-severe TBI					
WMSIII - Visual Reproduction delayed	.07 (.739)	-.09 (.662)	-.10 (.621)	.01 (.954)	-.08 (.682)
4-choice compatible visual RT task	.31 (.122)	.39 (.051)	.43 (.027)	.22 (.288)	.46 (.018)
COWA	.06 (.755)	.04 (.832)	.07 (.729)	-.05 (.797)	.09 (.648)
controls					
WMSIII - Visual Reproduction delayed	-.29 (.065)	-.18 (.249)	-.02 (.928)	-.12 (.470)	-.24 (.133)
4-choice compatible visual RT task	.03 (.865)	.11 (.515)	.11 (.508)	.12 (.451)	-.06 (.704)
COWA	-.32 (.039)	-.09 (.564)	-.17 (.285)	.10 (.535)	-.13 (.403)

Note. [1]age, sex, time post-injury and education were controlled; [2]correlations were only calculated for cognitive tests in which the moderate to severe TBI performed significantly worse than controls, after controlling for the effects of age, sex, time post-injury and education; TBI = traumatic brain injury; CC = corpus callosum; SLF = superior longitudinal fasciculus; WMSIII = Wechsler Memory Scale-third edition ($N_{moderate\text{-}severe}$=31, $N_{controls}$=103); RT = reaction time; 4-choice compatible visual RT task ($N_{moderate\text{-}severe}$=30, $N_{controls}$=102); COWA = Controlled Oral Word Association Test ($N_{moderate\text{-}severe}$=31, $N_{controls}$=103)

CHAPTER 6: A FIXEL-BASED ANALYSIS OF MICRO- AND MACRO-STRUCTURAL CHANGES TO WHITE MATTER FOLLOWING ADULT TRAUMATIC BRAIN INJURY

6.1 Preamble

This chapter consists of a final paper entitled "A fixel-based analysis of micro- and macro-structural changes to white matter following adult traumatic brain injury", which has been published in *Human Brain Mapping* (2020).

The first study examined the location and extent of WM changes following adult TBI, and the second examined the relationship between DTI findings and cognitive outcomes following adult TBI. Based on these meta-analyses, the third study used a ROI approach to examine DTI findings in the CC, fornix and SLF in a large sample of TBI and control participants. Memory, attention and executive functioning were also examined. Interestingly, moderate to severe TBI led to large WM changes and poorer cognitive performance, but no significant findings emerged for mild participants.

The ROI approach that was used in Study 3 is popular because it is relatively easy to perform and is particularly useful when there are a-priori hypotheses about which regions of the brain will be affected (Hulkower et al., 2013; Niogi & Mukherjee, 2010). However, ROI analyses are not able to differentiate between crossing fibres that are contained within a single voxel, which may affect up to 90% of all voxels (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2013). The final study therefore utilised fixel-based analysis (FBA), a recently developed technique that has been used to analyse diffusion-weighted data (Raffelt et al., 2017). Importantly, FBA is capable of differentiating between different fibre orientations to provide tract-specific information concerning WM microstructure and macrostructure. The same sample was examined

in this study and the previous ROI paper (Chapter 5), however four additional participants were excluded from the fixel analysis because their MRI images were not usable (i.e., images had limited brain coverage, which was not an issue for the ROI analysis), thus there were minor differences in the sample sizes. Reaction time data was also examined in order to determine whether the fixel findings were related to cognitive outcomes.

Tables and Figures have been provided within the text, to make it easier for the reader. Supplementary figures for this paper are provided at the end of the chapter (pages 196-197). A complete list of all references for the thesis, including those for this paper, is provided at the end of the thesis (pages 216-236).

CHAPTER 6: PAPER 4

A fixel-based analysis of micro- and macro-structural changes to white matter following adult traumatic brain injury

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xi. permission is granted for the candidate in include the publication in the thesis; and

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6.2 Paper four

Abstract

Diffusion tensor imaging is often used to assess white matter (WM) changes following traumatic brain injury (TBI), but is limited in voxels that contain multiple fibre tracts. Fixel-based analysis (FBA) addresses this limitation by using a novel method of analysing high angular resolution diffusion-weighted imaging (HARDI) data. FBA examines three aspects of each fibre tract within a voxel: tissue microstructure (fibre density: FD), tissue macrostructure (fibre-bundle cross-section: FC) and a combined measure of both (fibre density and fibre-bundle cross-section: FDC). This study used FBA to identify the location and extent of micro- and macro-structural changes in WM following TBI. A large TBI sample (N_{mild}=133, $N_{moderate\text{-}severe}$=29) and control group (healthy and orthopaedic; N=107) underwent MRI with HARDI and completed reaction time tasks approximately 7 months after their injury (range: 98-338 days). The TBI group showed microstructural differences (lower FD) in the corpus callosum and forceps minor, compared to controls. Subgroup analyses revealed that the mild TBI group did not differ from controls on any fixel metric, but the moderate to severe TBI group had significantly lower FD, FC and FDC in multiple WM tracts, including the corpus callosum, cerebral peduncle, internal and external capsule. The moderate to severe TBI group also had significantly slower reaction times than controls, but the mild TBI group did not. Reaction time was not related to fixel findings. Thus, the WM damage caused by moderate to severe TBI manifested as fewer axons and a reduction in the cross-sectional area of key WM tracts.

A fixel-based analysis of micro- and macro-structural changes to white matter following adult traumatic brain injury

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability, affecting an estimated 69 million people each year (Dewan et al., 2018). Cognitive, physical, psychological and behavioural problems are all common following TBIs and can vary in both severity and duration (Bigler & Stern, 2015; Cristofori & Levin, 2015; Griffen & Hanks, 2014). Diffuse axonal injury (DAI), which alters white matter (WM) microstructure and affects the ability of axons to relay information, is thought to be a primary contributor to these problems (Hill et al., 2016; Huisman et al., 2004; Hulkower et al., 2013). Widely available imaging modalities, such as computed tomography and conventional magnetic resonance imaging (MRI), lack the sensitivity to visualise the full extent of this DAI (Shenton et al., 2012; Voelbel et al., 2012). However, with the development of diffusion weighted imaging, it is now possible to examine microstructural changes to WM (e.g., DAI), even after mild TBI (Shenton et al., 2012; Strauss et al., 2015).

Diffusion weighted imaging assesses WM changes by measuring the movement of water molecules, which is constrained by the cellular structure of axons (Niogi & Mukherjee, 2010). Diffusion tensor imaging (DTI) is the most commonly used model for quantifying the data obtained from diffusion weighted imaging; providing voxel-level information regarding the coherence (fractional anisotropy: FA) and magnitude or amount (mean diffusivity: MD) of diffusion (Asken et al., 2017; Shenton et al., 2012). FA and MD are often used to examine WM changes following TBI, with high FA (range 0 to 1) and low MD both thought to indicate intact WM, and low FA and high MD suggesting WM damage in voxels containing single fibre populations (Niogi & Mukherjee, 2010). Many studies use a region of interest (ROI) approach to analyse DTI data, whereby mean (or median) measures (FA, MD) are extracted from pre-determined regions within the brain (Froeling, Pullens, & Leemans, 2016). Lower FA and higher

MD are typically reported following TBI, particularly in the subacute and chronic periods (Asken et al., 2017; Shenton et al., 2012; Wallace, Mathias, & Ward, 2018b) and after moderate to severe TBIs (Castano-Leon et al., 2018).

The single tensor model does not take into account the different fibre orientations that are contained within a voxel and are therefore of limited use when voxels contain multiple tracts and/or crossing fibres because any damage that is detected cannot be attributed to a specific tract (Raffelt et al., 2017). Fibres cross when a single fibre tract changes direction/orientation or when multiple fibre tracts are contained within a single voxel (Mori & Tournier, 2014), which is estimated to occur in up to 90% of all voxels (Jeurissen et al., 2013). This limitation can be overcome using high angular resolution diffusion-weighted imaging (HARDI), which is a higher-order MRI protocol producing data that can be used to differentiate between fibre orientations when fibres cross (Mori & Tournier, 2014). A number of methods have been developed to estimate fibre orientation distributions (FODs) from HARDI data, including constrained spherical deconvolution (Mori & Tournier, 2014; Tournier, Calamante, & Connelly, 2007). The FODs obtained from constrained spherical deconvolution can be analysed using a recently developed statistical method, known as fixel-based analysis (FBA) (Raffelt et al., 2015), which examines the different fibre orientations within a single voxel in order to provide specific anatomical information about individual WM tracts. A 'fixel' refers to a specific fibre population within a single voxel (Raffelt et al., 2015; Raffelt et al., 2017), with most voxels containing multiple fixels.

FBA assesses tissue micro- and macro-structure using three metrics: fibre density (FD, which assesses microstructure), fibre-bundle cross-section (FC, which assesses macrostructure), and a measure that combines the two (fibre density and fibre-bundle cross-section; FDC) (Raffelt et al., 2017). WM damage that reduces the number of axons within a fibre bundle, but not the area they occupy (i.e., fewer axons less densely packed within the same number of voxels), will lead to a decrease in FD. If the density of axons is not reduced, but the fibre bundle occupies less area/space (fewer voxels), FC will decrease. Finally, if there is both a reduction in the density of

axons within a fibre bundle and the area that the fibre bundle occupies, FDC will decrease (Raffelt et al., 2017).

FBA has been used to examine a number of different neurological conditions, including multiple sclerosis (Gajamange et al., 2018), temporal lobe epilepsy (Vaughan et al., 2017) and Alzheimer's disease (Mito et al., 2018), but has yet to be used with a TBI sample. Overall, FBA appears to provide a promising technique for detecting micro- and macro-structural changes that addresses one of the main limitations of DTI (multiple tracts and crossing fibres) and yields more readily interpreted data.

The current study therefore used FBA to examine WM changes following TBI. Specifically, it compared the FD, FC and FDC obtained from a TBI group to those of a control group (orthopaedic and healthy controls) in order to identify which WM tracts of the brain were most damaged. The impact of injury severity was also investigated by separately examining the mild and moderate to severe injuries (the latter being combined due to low participant numbers); the expectation being that more severe injuries would lead to larger and more spatially extensive changes (i.e., lower FD, FC, FDC).

Method

Participants

Participants were recruited as a part of a larger research project investigating cognitive, psychological and brain imaging outcomes following TBI, which was conducted at the Royal Adelaide Hospital (Adelaide, Australia). Three samples were recruited on a prospective basis between 2008 and 2012, comprising (i) participants who had sustained a mild, moderate or severe TBI; (ii) orthopaedic controls who had sustained injuries that did not involve the face or head; and (iii) healthy controls who were friends or family of the TBI group or visitors to the Royal Adelaide Hospital. Participants were eligible for the research project if: (a) they were aged between 18 and 80 years; (b) English was their first language; (c) they did not have a known

history of substance abuse, intellectual disabilities, or psychiatric or neurological problems; and (d) they were able to complete the cognitive tests and MRI (no contraindications).

The lowest recorded Glasgow Coma Scale (GCS) scores were used to classify TBIs as mild (GCS: 13-15), moderate (GCS: 9-12) or severe (GCS: ≤8). Where this information was not available, the length of loss of consciousness (mild: <20 mins; moderate: 20 mins–6 hours; severe: >6 hours) and/or post-traumatic amnesia (mild: <60 mins; moderate: 60 mins–24 hours; severe: >24 hours) were used.

A total of 221 people who had sustained a TBI and 168 controls (84 healthy, 84 orthopaedic controls) were initially recruited for the research project. Participants who did not have usable MRI images (e.g., did not complete the MRI, image registration failed, MRI signal dropout, excessive participant movement; N_{TBI} =45, $N_{healthy}$ =8, $N_{orthopaedic}$ =15), had incidental findings on their MRI (N_{TBI} =11, $N_{healthy}$ =16, $N_{orthopaedic}$ =22), or who sustained their TBI more than 400 days before the MRI examination (N_{mild}=1, $N_{moderate}$=1, N_{severe}=1) were excluded from the current study. Therefore, the current sample comprised 162 people who had a TBI (N_{mild}=133, $N_{moderate}$=15, N_{severe}=14) and 107 controls ($N_{healthy}$=60, $N_{orthopaedic}$=47). The healthy and orthopaedic controls did not differ demographically (age: $t(105)= -.488$, $p=.626$; education: $t(103)=.432$, $p=.667$; proportion of males and females: $X^2(1)=3.324$, $p=.068$) or in terms of reaction times (compatible reaction time: $t(101) = -.107$, $p = .915$; incompatible reaction time: $t(101) = -.526$, $p = .600$) or fixel findings (see Supplementary Figures), thus all analyses were completed using a combined control group (Mathias et al., 2013; Wallace, Mathias, & Ward, 2020a). The moderate and severe TBI groups were additionally combined for the subgroup analyses because they were too small to examine separately ($N_{moderate\text{-}severe}$ = 29).

Procedure

The original study was approved by the Human Research Ethics Committees at the Royal Adelaide Hospital and the University of Adelaide. All participants provided written informed consent. Hospital records were used to identify potential participants for the TBI and orthopaedic

control groups, who were sent a letter from the Royal Adelaide Hospital providing information about the study and inviting them to participate. Recipients were given an opt-out procedure if they did not want to be contacted by the researchers regarding the study. Healthy controls consisted of friends or family of the TBI group, and visitors to the Royal Adelaide Hospital who responded to flyers promoting the study. All participants were initially screened by phone for study eligibility.

Eligible participants subsequently completed an interview (which collected demographic and medical information), self-report questionnaires (not examined here), and 2 to 3 hours of cognitive testing in a single session with a researcher at the University (selected data only examined here). All participants additionally underwent MRI with HARDI in a separate session within a few days of the cognitive assessment, which occurred after an average of around seven months after the injury (TBI = 209 days, SD = 91.5; orthopaedic controls = 218 days, SD = 41.8). Participants were paid an honorarium of $40 to assist with expenses incurred when travelling for the MRI. All data were collected solely for research purposes and could not be used for litigation.

Image acquisition

Participants underwent MRI using a 3T Siemens scanner (TimTrio, Erlangen, Germany). Importantly, all scans were performed at the same site on the same machine, therefore alleviating the inconsistencies and artefacts that can arise from the use of multiple scanners (e.g., Fortin et al., 2017). An optimised diffusion sequence (Jones et al., 1999) was used to acquire diffusion data for each participant. The following parameters were used: 64 diffusion-weighted images ($b=3000s/mm^2$) and 1 non-diffusion-weighted image; 60 axial slices; FOV = 25x25cm; TR/TE = 9400/116ms; slice thickness = 2.5mm; acquisition matrix = 100x100; isotropic image resolution = 2.5mm. The total acquisition time for diffusion imaging was 10:41mins. A field map was acquired (TE1/TE2 4.76/7.22ms) that assists the correction for susceptibility distortions in diffusion data.

Fixel-based analysis

The diffusion images underwent pre-processing, including corrections for head motion, eddy-current distortions, susceptibility distortions and intensity inhomogeneities using the FMRIB Diffusion Toolbox (FMRIB, Oxford, UK) (Andersson & Sotiropoulos, 2016; Jenkinson et al., 2012). Global intensity normalisation was performed across participants, using the median white matter *b* = 0 intensity using tools implemented in MRtrix3 (www.mrtrix.org; Tournier, Calamante, & Connelly, 2012; Tournier et al., 2019). Next, a group response function was calculated from all participants' fibre response functions, which reflect the signal that would be expected from a voxel containing a single, typical fibre bundle (Tournier, Calamante, Gadian, & Connelly, 2004). Individual fibre response functions were estimated using the convenient and reliable 'tournier' algorithm in MRtrix3 (mrtrix.org), and these were subsequently averaged to result in a group response function. Diffusion-weighted images underwent upsampling by a factor of 2, to improve image resolution. Constrained spherical deconvolution, a technique that uses the response function to estimate the distribution of fibre orientations contained within each voxel (Raffelt et al., 2012; Tournier et al., 2004), was used to estimate the fibre orientation distributions (FOD) (Tournier, Calamante, & Connelly, 2007).

A subset of 40 participants (N_{TBI}=20, $N_{healthy}$=10, $N_{orthopaedic}$=10) were used to generate a study-specific FOD template using both linear and nonlinear registration of FOD images (Raffelt et al., 2011). FOD images from all participants were then nonlinearly registered to this template, and MRtrix3 was used to calculate three fixel metrics: FD, FC and FDC (Raffelt et al., 2017).

Processing speed

Processing speed, which is frequently impaired following a TBI (e.g., Cristofori & Levin, 2015; Rabinowitz & Levin, 2014), was assessed using 4-choice compatible and incompatible visual reaction time tasks (Mathias, Beall, et al., 2004; Mathias, Bigler, et al., 2004). These tasks formed part of a larger battery of cognitive and self-report measures that were administered to all participants. Four white rectangles were presented on a computer screen, two either side of a

central fixation point. When one of the rectangles turned red (stimulus), participants were required to press a button as quickly and accurately as possible (response). For the 4-choice compatible reaction time task, participants were required to press a button using the hand on the same side as the stimulus (e.g., right side stimulus, right hand response), with either their index (inner rectangle) or middle (outer rectangle) finger. The incompatible task required participants to press a button using the hand on the opposite side of the stimulus (e.g., right side stimulus, left hand response), and thus required inter-hemispheric processing. Participants completed 60 trials to control for anticipatory responses and attentional lapses, with median reaction times calculated (Mathias, Beall, et al., 2004; Mathias, Bigler, et al., 2004; Wallace et al., 2019).

Statistical analysis

IBM SPSS Statistics version 21.0 (IBM Corp., 2012) was used to compare the TBI and control groups in terms of their mean age and education (*t*-tests), and the proportion of males and females (chi-square test), and to determine whether reaction times were slower following a TBI (all TBI vs controls). Additionally, Welch's F tests (Welch, 1951) and Games-Howell post-hoc comparisons (Toothaker, 1993) were used to examine whether reaction times differed depending on the presence and severity of injury (mild TBI, moderate-severe TBI, controls). Standardised mean differences (Hedges' *g*) were calculated to assess the extent of the group differences, with *g* = -0.2, -0.5, and -0.8 corresponding to small, medium and large effects, respectively (Cohen, 1992).

MRtrix3 was used for all fixel-based statistical analyses. A WM analysis mask was generated, with a threshold of 0.33 applied to the average FOD amplitude. Connectivity-based fixel enhancement — which identifies fixels that are connected and likely to share anatomy and pathology, using probabilistic tractography — was used to correct for multiple comparisons, with 5000 permutations (Raffelt et al., 2015). FD, FC and FDC values from each WM fixel in the TBI and control groups were compared (Raffelt et al., 2017), and any fixels that showed group differences in terms of the specific measure (FD, FC, FDC) were colour coded by the corresponding *t*-statistic

(thresholded at $p<.05$). WM integrity is often reduced in older people, and males and females show some differences in WM microstructure (Kanaan et al., 2012; Sullivan & Pfefferbaum, 2006), both of which can affect fixel-based analyses. Thus, age and sex were controlled for in these analyses. Time post-injury was also considered as a covariate, given that there was a wide range in the intervals between injury and MRI, and that the progression of WM changes can be affected by time. However, it was found that time post-injury was not associated with fixel findings; as such, it was not controlled for in subsequent analyses. FC and FDC were additionally corrected for brain volume, which is also known to affect these two measures (see Raffelt et al., 2017). Three group comparisons were performed in order to examine whether FD, FC and FDC differed depending on injury severity: TBI group (all) vs controls, mild TBI vs controls, and moderate-severe TBI vs controls. The association between reaction time and fixel findings (FD, FC, FDC) in the TBI group (all TBI, mild TBI, moderate-severe TBI) was also investigated.

Results

Participants

Table 1 summarises the demographic and injury information for the TBI (all TBI, mild TBI, moderate-severe TBI) and control groups. Participants in the TBI (all) and control groups were mostly young to middle-aged adults who had, on average, completed high school (12 years) and one to two years post-secondary training/education. The TBIs and orthopaedic injuries were sustained, on average, 7 months prior to undergoing brain imaging. Consistent with the known risk factors for TBI (Chua et al., 2007), there were many more males than females in this sample (79%), however this was not the case for controls (56%). Also consistent with the epidemiology of TBI (Faul & Coronado, 2015), fewer participants sustained moderate (N = 16) and severe (N=15) TBIs, thus the TBI group was divided into mild (N = 134) and moderate-severe (N = 31) subgroups when examining the impact of injury severity (see Table 1 for summary subgroup data). GCS scores were not available for 22 TBI participants (N_{mild}=20, $N_{moderate\text{-}severe}$=2). TBIs were largely the

Table 1. Summary demographic information for the TBI (all, mild, moderate-severe) and control (combined orthopaedic and healthy) groups

variable	**all TBI (N = 162)**				**mild TBI (N = 133)**				**moderate-severe TBI (N = 29)**				**combined controls[1] (N = 107)**			
	N	*mean*	*SD*	*range*	*N*	*mean*	*SD*	*range*	*N*	*mean*	*SD*	*range*	*N*	*mean*	*SD*	*range*
age (years)	162	43.4	16.6	19-80	133	43.6	16.9	19-80	29	42.6	15.5	20-72	107	39.3	16.6	18-77
education (years)	157	13.1	2.6	7-22	128	13.3	2.5	8-20	29	12.6	3.2	7-22	105	14.0	2.8	7-20
days since injury	157	199.5	41.4	98-338	128	194.4	38.3	98-338	29	222.1	47.6	135-336	45[2]	218.3	41.8	136-344
		N	*%*			*N*	*%*			*N*	*%*			*N*	*%*	
sex		162				133				29				107		
females		34	21.0			30	22.6			4	13.8			47	43.9	
males		128	79.0			103	77.4			25	86.2			60	56.1	
TBI severity		162				133				29						
mild		133	82.1			133	100.0			0						
moderate		15	9.3			0				15	51.7					
severe		14	8.6			0				14	48.3					
cause of injury		162				133				29				47[2]		
motor vehicle		39	24.1			32	24.1			7	24.1			1	2.1	
fall		38	23.5			28	21.1			10	34.5			11	23.4	
bicycle		34	21.0			28	21.1			6	20.7			7	14.9	
assault		30	18.5			26	19.5			4	13.8			0	0.0	
sport		11	6.8			11	8.3			0	0			18	38.3	
pedestrian		4	2.5			2	1.5			2	6.9			1	2.1	
other		6	3.7			6	4.5			0	0			9	19.1	
handedness		154				125				29				104		
right		135	87.7			110	88.0			25	86.2			97	93.3	
left		19	12.3			15	12.0			4	13.8			7	6.7	

previous TBI (self-report)	156		127		29		104	
yes	44	28.2	39	30.7	5	17.2	1	1
no	112	71.8	88	69.3	24	82.8	103	99
involved in litigation	156		127		29		44[2]	
yes	30	19.2	24	18.9	6	20.7	2	4.5
no	126	80.8	103	88.1	23	79.3	42	95.5

Note. TBI = traumatic brain injury; N = number of participants; SD = standard deviation; GCS = Glasgow Coma Scale; healthy controls N = 60; orthopaedic controls N = 47; [1] all controls (orthopaedic + healthy controls); [2] orthopaedic controls only

result of motor vehicle accidents, falls, bicycle accidents or assaults. Most participants were right-handed and had not previously sustained a TBI, and very few were involved in litigation regarding their injuries (TBI or orthopaedic).

When the demographic characteristics of the TBI (all TBI) and control groups were compared, the TBI group was found to be significantly older ($t(270) = -1.978$, $p = .049$, Hedges' $g = .25$), had completed slightly less education ($t(263) = 2.489$, $p = .013$, Hedges' $g = .31$), and had more males ($\chi^2(1) = 15.901$, $p = .000$) than the control group. Not only did the groups differ in terms of age and sex, but these variables are also known to be associated with differences in WM structure (Kanaan et al., 2012; Sullivan & Pfefferbaum, 2006), consequently they were used as covariates in the statistical analyses. Although significant, the difference in education was small and therefore not entered as a covariate. There was no significant difference between the two groups in the number of volumes rejected for motion ($t(267) = -.851$, $p = .396$).

TBI (all) vs controls: FD, FC and FDC

The FD, FC and FDC values for each fixel were compared for the TBI (all TBI: mild, moderate & severe; N = 162) and control (N = 107) groups in order to determine whether TBI affected tissue microstructure and macrostructure and, if so, what regions were most affected. Figure 1 provides eight axial slices overlaid with the fixels that showed significant group differences in FD (Figure 1a), FC (Figure 1b) and FDC (Figure 1c), with Figure 2 labelling the brain regions that were identified by this analysis. The fixels where FD, FC and FDC were significantly lower ($p<.05$) in the TBI group, relative to controls, are colour-coded according to the corresponding *t*-statistic (blue: $t = -5$; red: $t = 5$), thresholded to display only those fixels that are significant at $p < .05$. Age and sex were covariates in all analyses, and brain volume was additionally included in the FC and FDC analyses.

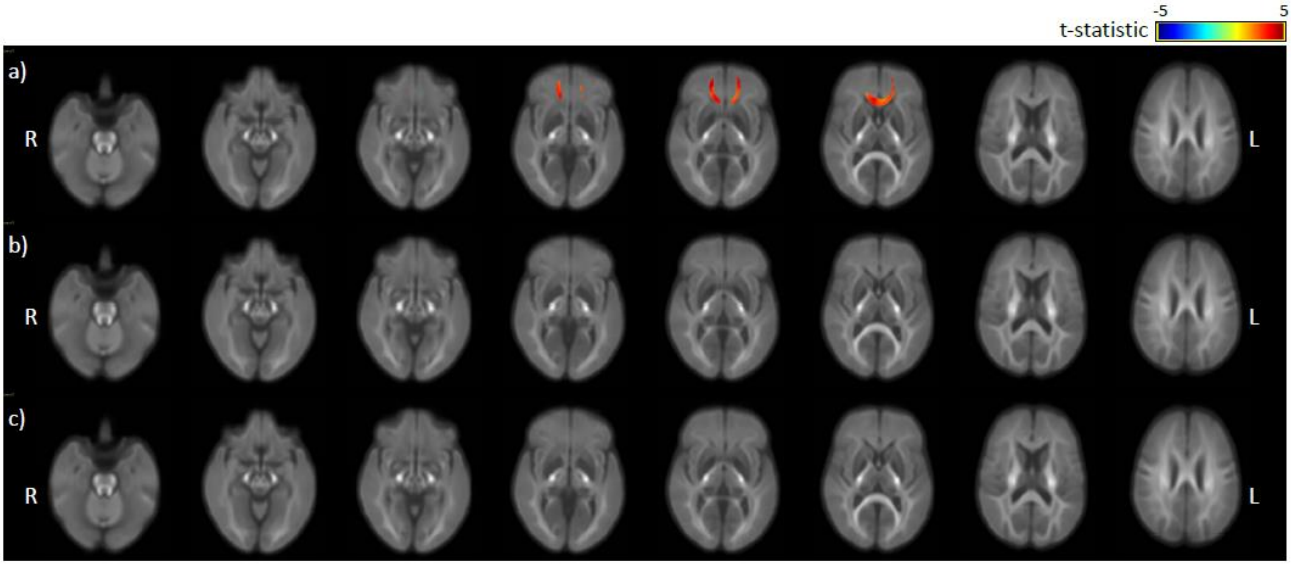


Figure 1. Fixels showing significant differences in the fibre density (FD), fibre-bundle cross-section (FC) and fibre density and bundle cross-section (FDC) of the TBI (all TBI) and control groups, controlling for age and sex (all analyses) and brain volume (FC and FDC), and colour coded by effect size (t-statistic, thresholded at p <.05):
(a) FD;
(b) FC;
(c) FDC

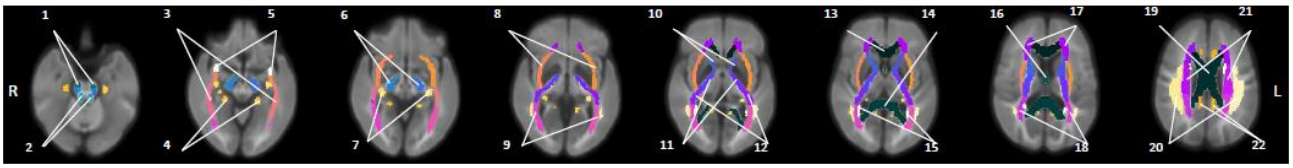


Figure 2. Labels for the brain regions identified by the fixel-based analyses shown in Figures 1 and 3.

1: corticospinal tract, 2: superior cerebellar peduncle, 3: sagittal stratum, 4: cingulum (hippocampus), 5: uncinate fasciculus, 6: cerebral peduncle, 7: fornix (cres)/stria terminalis, 8: external capsule, 9: posterior thalamic radiation, 10: anterior limb of internal capsule, 11: posterior limb of internal capsule, 12: retrolenticular part of internal capsule, 13: genu of corpus callosum, 14: splenium of corpus callosum, 15: tapetum, 16: fornix, 17: anterior corona radiata, 18: posterior corona radiata, 19: body of corpus callosum, 20: superior longitudinal fasciculus, 21: superior corona radiata, 22: cingulum (cingulate gyrus)

As seen in Figure 1a, the TBI group (all TBI) showed significantly lower FD in the corpus callosum (genu, body) and forceps minor (see Figure 2 for labelled regions). Unlike FD, there were no significant group differences in FC (see Figure 1b) or FDC (see Figure 1c). These findings indicate that, approximately seven months after sustaining a TBI, there were changes to WM microstructure that were not attributable age or sex. WM macrostructure (cross-section) was unaffected.

Mild TBI vs controls: FD, FC and FDC

Next, the FD, FC and FDC values of the mild TBI and control groups were compared to determine whether mild injuries caused microstructural and/or macrostructural changes that were detectable using FBA. Supplementary Figure S2 shows eight axial slices overlaid with the fixels that displayed significant group differences (p<.05) in FD, FC and FDC, after correcting for both age and sex (FC & FDC also corrected for brain volume) (blue: t =-5; red: t =5), thresholded to display only those fixels that are significant at p <.05. The mild TBI group did not have significantly lower FD, FC or FDC in any of the fixels, when compared to controls (see Supplementary Figure S2). Therefore, the current sample did not show significantly altered WM micro- or macrostructure approximately seven months after their mild TBI.

Moderate-severe TBI vs controls: FD, FC and FDC

Finally, the moderate-severe TBI and control groups were compared, with Figure 3 showing the brain regions that differed significantly (thresholded at p<.05) in terms of FD (Figure 3a), FC (Figure 3b) and FDC (Figure 3c), after correcting for age and sex (all analyses) and brain volume (FC, FDC analyses). As seen in Figure 3a, FD was significantly lower in multiple regions, including: the corpus callosum, cerebral peduncle, internal and external capsule, corona radiata, cingulum and tapetum (see Figure 2 for labelled regions). Similar WM structures also showed

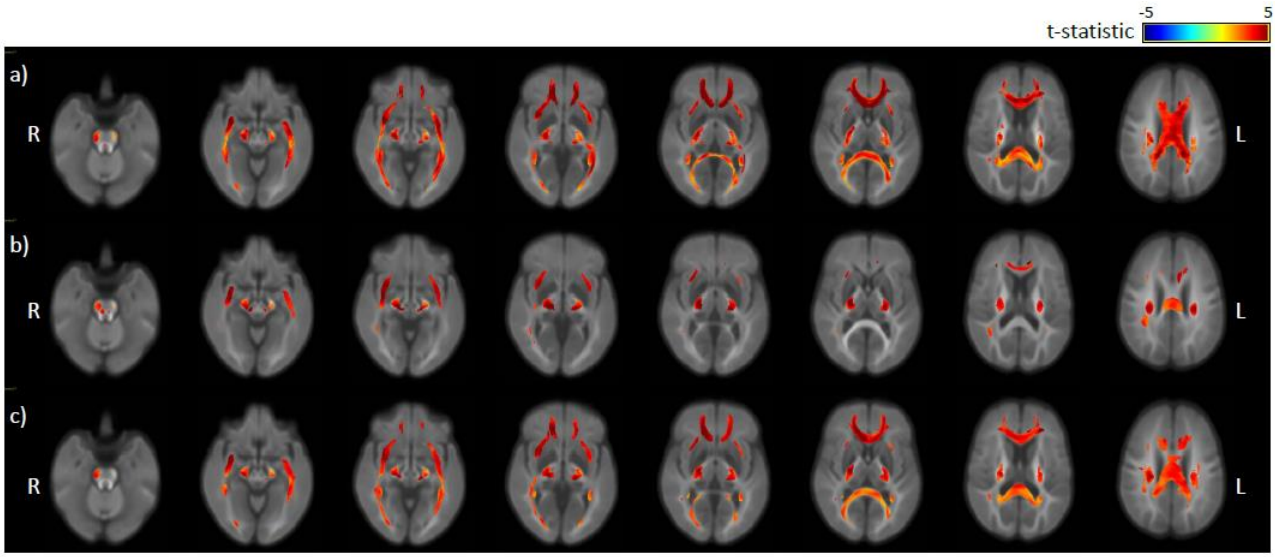


Figure 3. Fixels showing significant differences in the fibre density (FD), fibre-bundle cross-section (FC) and fibre density and bundle cross-section (FDC) of the moderate-severe TBI and control groups, controlling for age and sex (all analyses) and brain volume (FC and FDC), and colour coded by effect size (t-statistic, thresholded at p <.05):
(a) FD;
(b) FC;
(c) FDC

lower FC, but the affected regions tended to be smaller (Figure 3b). Finally, FDC was reduced in a number of regions, including the corpus callosum, internal and external capsule and cingulum (Figure 3c). Thus, more serious TBIs resulted in altered micro- and macro-structure in multiple important WM tracts approximately seven months after sustaining an injury: changes that could not be attributed to age, sex or brain volume.

When the un-thresholded effect size maps for both the mild and moderate-severe groups were compared (see Supplementary Figures), the pattern of injury appeared to be quite consistent, but with considerably larger effects found following more severe injury. This suggests that similar brain regions are affected by TBIs of all severities.

Reaction time

Table 2 displays the reaction times for the TBI (all TBI) and control groups. The reaction times for the compatible and incompatible tasks were both significantly slower in the TBI group,

Table 2. Reaction time data for the traumatic brain injury and control groups

cognitive test	TBI			controls					
	N	*mean*	*SD*	*N*	*mean*	*SD*	*Hedges' g*	*t*	*p*
4-choice compatible RT task	154	464.7	94.3	103	437.20	90.63	-0.30	-2.33	.021
4-choice incompatible RT task	152	700.4	198.9	103	638.13	173.76	-0.33	-2.58	.010

Note. RT = reaction time; N = number of participants; SD = standard deviation; *t* = t-test

Table 3. Reaction time data for the mild TBI, moderate-severe TBI and control groups

cognitive test	mild TBI		moderate-severe TBI		controls			mild TBI vs controls		moderate-severe vs controls		mild TBI vs moderate-severe	
	mean	*SD*	*mean*	*SD*	*mean*	*SD*	*Welch's F*	*Hedges' g*	*p*	*Hedges' g*	*p*	*Hedges' g*	*p*
4-choice compatible RT task	453.0	83.3	517.5	121.6	437.20	90.63	$F(2, 69.91) = 5.36$, $p = .007$	-0.18	.365	-0.82	.007	-0.70	.031
4-choice incompatible RT task	685.8	195.2	768.1	205.6	638.13	173.76	$F(2, 71.46) = 5.17$, $p = .008$	-0.26	.127	-0.72	.013	-0.42	.152

Note. TBI = traumatic brain injury; SD = standard deviation; RT = reaction time; 4-choice compatible RT task (N_{mild}=126, $N_{moderate\text{-}severe}$=28, $N_{controls}$=103); 4-choice incompatible RT task (N_{mild}=125, $N_{moderate\text{-}severe}$=27, $N_{controls}$=103)

with these differences equating to small effects (*g* = -.30 and -.33, respectively). Subgroup analyses (Table 3) revealed that, although the reaction times of the mild TBI group did not differ from the controls (*p* >.05, small effects), the moderate-severe TBI group was significantly slower on the both the compatible and incompatible tasks (large effects: *g* = -.82 and -.72, respectively).

The association between reaction time and fixel findings was also examined. No statistically significant associations were found, suggesting that reaction time is not related to fixel findings. Further analysis showed that age was strongly and significantly related to both the compatible and incompatible reaction time tasks (*r* = -.58 and -.57, respectively; see Table 4).

Discussion

This study undertook a FBA of diffusion-weighted data to examine micro- and macro-structural changes in the WM of adults who had sustained mild, moderate and severe TBIs on average seven months earlier. As a whole, the TBI group (all TBI) showed evidence of altered tissue microstructure (lower FD) in the corpus callosum (genu, body) and forceps minor. Subgroup analyses additionally revealed that there was no evidence of altered WM in the mild TBI group: FD, FC and FDC were all unaffected. However, the WM micro- and macro-structure of the moderate to severe TBI group was altered (lower FD, FC, FDC) in multiple WM tracts, including the corpus callosum, corona radiata, and internal and external capsule. According to Raffelt et al. (2017), these changes indicate that there were fewer axons within these WM tracts and that they occupied a smaller cross-sectional area. The moderate to severe TBI group also had significantly

Table 4. Pearson *r* correlations (*p*-value) between reaction time and age

cognitive tests	age
4-choice compatible visual RT task	**-.58 (.000)**
4-choice incompatible visual RT task	**-.57 (.000)**

Note. 4-choice compatible visual RT task (*N* = 257); 4-choice incompatible visual RT task (*N* = 255)

slower reaction times than the controls, but the mild group did not. There was, however, no significant association between reaction times and fixel findings.

DTI has previously been used to examine WM changes following TBI and has identified many regions where there appears to be damage (for reviews, see Amyot et al., 2015; Niogi & Mukherjee, 2010; Shenton et al., 2012; Wallace et al., 2018a). However, DTI is limited by the fact that the measures obtained from it (FA, MD) are averaged across all of the fibre tracts that are contained within a voxel, making interpretation problematic when more than one fibre tract is present (Mori & Tournier, 2014). Although low FA values often occur when WM is damaged following a TBI, damage to a single fibre tract in a voxel that contains multiple tracts/populations may result in null findings if the other fibre tracts are undamaged. This, in turn, may be incorrectly interpreted as indicating a lack of damage because the information provided by FA is not tract-specific (Mori & Tournier, 2014; Raffelt et al., 2012). FBA provides an alternative method of analysing diffusion data that is able to overcome this considerable limitation. Specifically, changes can be attributed to individual WM fibre tracts in voxels that contain more than one tract (Raffelt et al., 2015). In addition, FBA is able to determine the specific ways in which the WM has been affected: namely, whether there are fewer axons that are less densely packed (FD), the tracts have a reduced cross-sectional area representing morphometric changes (FC), and/or there is a combination of both changes (FDC) (Mito et al., 2018; Raffelt et al., 2017). FBA may therefore provide more specific anatomical information than DTI.

The TBI group, as a whole, displayed lower FD in the corpus callosum (genu, body) and forceps minor, indicating that there were fewer axons contained within these fibre tracts. There were no differences in WM macrostructure (FC), or in the combined measure of micro- and macro-structure (FDC). Following mild TBI, there was no evidence of WM changes. These findings contrast with those of previous DTI studies, which report that mild TBI is associated with altered WM in multiple regions, including the corpus callosum, fornix, superior longitudinal fasciculus,

thalamic radiations, external and internal capsule, cingulum, and corona radiata (e.g., Grossman et al., 2012; Messe et al., 2012; Wallace et al., 2018a; Zhu et al., 2014). Although FBA is designed to be more sensitive to damage to individual WM tracts in areas where fibres cross (Raffelt et al., 2017), it may still be unable to detect the subtle damage that can occur following minor injuries. Alternatively, the mild participants may not have sustained WM damage as a consequence of their injuries, given that most had a GCS of 15 (63%). Indeed, this mild group did not differ significantly from the controls in terms of FA and MD in the five regions that were examined in a recent ROI study (genu, body & splenium of corpus callosum, fornix, superior longitudinal fasciculus) (see Wallace et al., 2020a). There was, however, a weak trend toward lower FA and higher MD in the mild TBI group, relative to controls (Wallace et al., 2020a).

As expected, the largest WM alterations were found in people who had sustained more serious injuries. Specifically, moderate to severe TBI led to micro- and macrostructural differences (lower FD, FC, FDC) in a large number of important WM tracts, including commissural fibres that connect equivalent regions in the two hemispheres (e.g., corpus callosum), association fibres that provide within-hemisphere connections (e.g., superior longitudinal fasciculus) and projection fibres that connect cortical and subcortical regions (e.g., internal capsule) (Aralasmak et al., 2006). People with more severe injuries also had considerably slower reaction times, but reaction times were not associated with fixel findings. It is possible that an association exists, however no significant relationship was found after the fixel data were corrected for age; it is therefore possible that any effect was confounded by age. Although the physical, psychological, behavioural and cognitive impairments experienced by people who suffer a TBI (Cristofori & Levin, 2015; Griffen & Hanks, 2014) may be the result of decreased fibre density in addition to alterations to the broader WM structure (i.e., fewer axons contained within WM tracts that have a reduced cross-sectional area), further research is needed to determine this.

Limitations

Although FBA was able detect damage to specific WM tracts in our TBI sample, group comparisons fail to consider individual differences in the extent and location of WM changes post-TBI (Hulkower et al., 2013). Given the heterogeneous nature of TBI damage, injury progression and recovery (Bigler & Stern, 2015; Hulkower et al., 2013), the utility of FBA now needs to be investigated with individual participants. However, a large normative FBA database would be needed in order to investigate individual differences in WM changes.

The current study examined participants on a single occasion, which meant that the progression of WM damage was not assessed, and the range of post-injury intervals was quite large (i.e., interval between injury and MRI). WM damage may initially manifest as a reduction in tissue microstructure (FD), but over time tissue macrostructure (FC) may be more affected due to WM degeneration and atrophy (Raffelt et al., 2017). WM degeneration can continue for years after a TBI (Hill et al., 2016). Therefore FC, which is thought to reflect accumulated axonal loss (Raffelt et al., 2017), may decrease progressively as this degeneration continues, however FC was not related to time post-injury in the current study. In addition, thin WM structures (e.g., fornix, anterior commissure) may not be accurately assessed using FBA; although microstructural changes (FD) can be detected in small structures, FC can be insensitive and any macrostructural changes may instead present as microstructural changes (FD) (Raffelt et al., 2017; Vaughan et al., 2017). This problem may be exacerbated by the large voxel size used to acquire the images ($2.5mm^3$), in addition to partial volume effects, which occur when there are two or more different types of tissue present within a single voxel (e.g., WM, grey matter, cerebrospinal fluid) (Raffelt et al., 2017; Vos et al., 2011). Image resolution may be improved by using smaller voxels, enabling thinner WM structures (e.g., fornix) to be examined more thoroughly (Raffelt et al., 2017), at the cost of increased scan time and reduced signal-to-noise.

Additionally, there was a group difference in age and sex and, although these variables were entered as covariates in the fixel analyses, it is possible that this method may not have

entirely accounted for these differences. Future studies should endeavour to use more closely matched controls. Lastly, the moderate (N = 15) and severe (n = 14) TBI samples were both small, making it necessary to combine them for the subgroup analysis. Given that more serious TBIs generally lead to greater WM damage (e.g., Castano-Leon et al., 2018), it is likely that the extent and, potentially, location of the changes to the WM may differ for moderate and severe TBIs. Unfortunately, it was not possible to examine whether this was the case.

Directions for future research

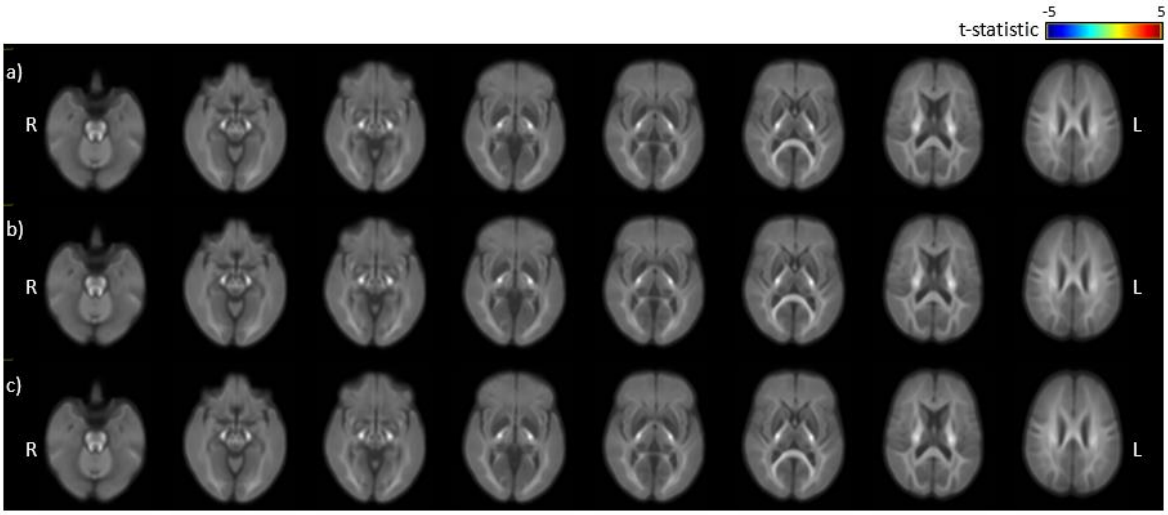
The reliability and generalisability of these findings now need to be evaluated in other TBI samples (e.g., different age groups, different post-injury periods). Most of the mild TBI group had a GCS of 15 (63%); other groups of mild participants with a wider range of GCS scores should be examined to determine whether FBA detects changes following these injuries. Additionally, larger samples of people with moderate and severe injuries are needed to determine whether there are differences in the pattern of WM changes following moderate and severe TBI. Furthermore, large-scale, longitudinal FBA studies are needed to examine the progression of micro- and macrostructural WM changes following TBI. These studies should assess whether FD, FC and FDC are differentially affected at earlier and/or later post-injury intervals, given that WM degeneration can continue for years after an injury (Hill et al., 2016). Finally, although the current study failed to find an association between FBA and reaction times, additional research is needed to determine whether FBA findings are related to other cognitive, behavioural and psychological outcomes.

Conclusions

This study examined whether micro- and/or macrostructural WM changes were detected using FBA, seven months after sustaining a TBI. Moderate to severe TBI led to WM damage that manifested as a reduction in the number of axons, together with broader structural changes (lower FD, FC, FDC) in multiple brain regions, including the corpus callosum, corona radiata,

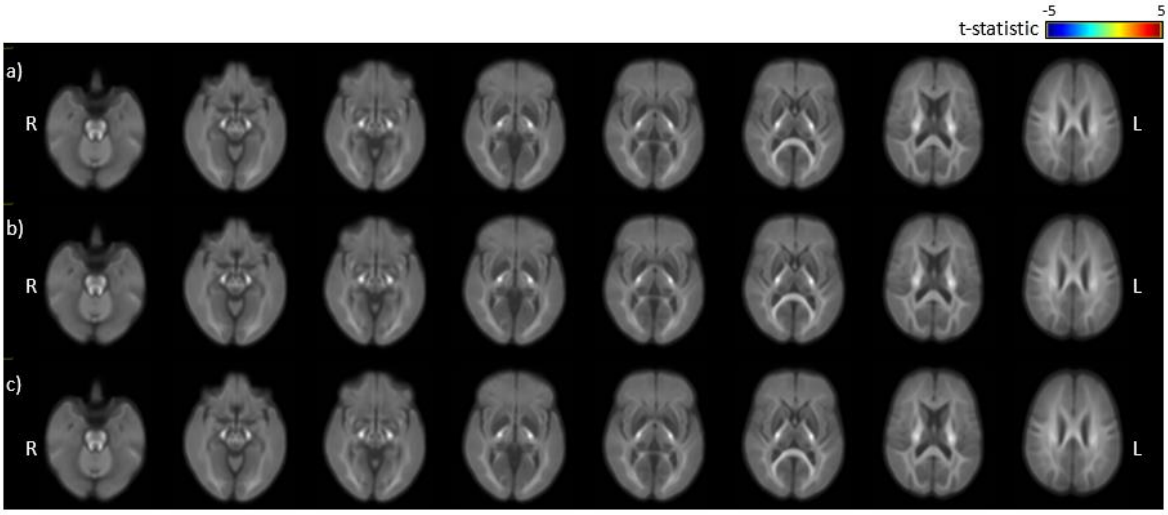
cerebral peduncle, and internal and external capsule. People with moderate to severe TBI also had slower reaction times, however no significant associations were found between reaction time and fixel findings. These findings have shown that moderate to severe TBI leads to a reduction in the number of axons within fibre tracts that have a reduced cross-sectional area. Although these WM changes may limit the ability of axons to relay information, the impact of these changes needs to be examined further.

6.3 Supplementary Material



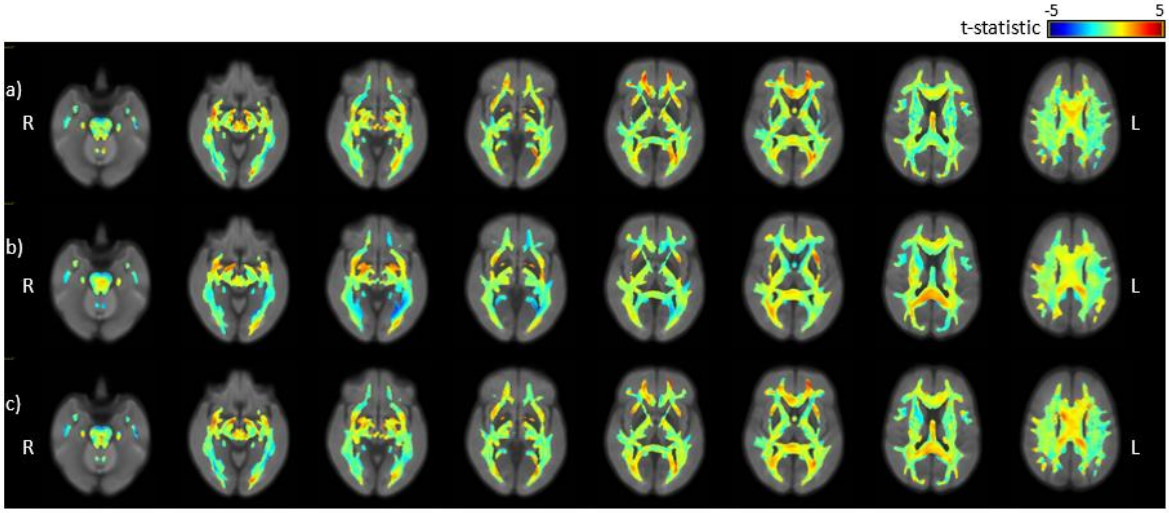
Supplementary Figure S1. Fixels showing significant differences in the fibre density (FD), fibre-bundle cross-section (FC) and fibre density and bundle cross-section (FDC) of the healthy and orthopaedic and control groups, controlling for age and sex (all analyses), and brain volume (FC and FDC) and colour coded by effect size (t-statistic, thresholded at p <.05):
(a) FD;
(b) FC;
(c) FDC

No statistically significant group differences were observed.

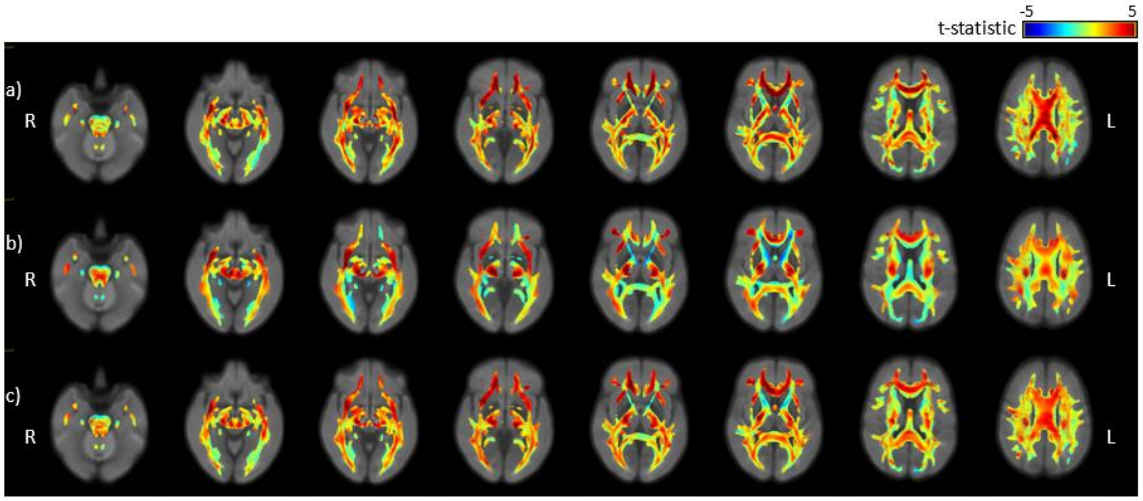


Supplementary Figure S2. Fixels showing significant differences in the fibre density (FD), fibre-bundle cross-section (FC) and fibre density and bundle cross-section (FDC) of the mild TBI and control groups, controlling for age and sex (all analyses), and brain volume (FC and FDC) and colour coded by effect size (t-statistic, thresholded at p<.05):
(a) FD;
(b) FC;
(c) FDC

No statistically significant group differences were observed.



Supplementary Figure S3. Fixels showing un-thresholded differences in the fibre density (FD), fibre-bundle cross-section (FC) and fibre density and bundle cross-section (FDC) of the mild TBI and control groups, controlling for age and sex (all analyses), and brain volume (FC and FDC) and colour coded by effect size (t-statistic):
(a) FD;
(b) FC;
(c) FDC



Supplementary Figure S4. Fixels showing un-thresholded differences in the fibre density (FD), fibre-bundle cross-section (FC) and fibre density and bundle cross-section (FDC) of the moderate-severe TBI and control groups, controlling for age and sex (all analyses), and brain volume (FC and FDC) and colour coded by effect size (t-statistic):
(a) FD;
(b) FC;
(c) FDC

CHAPTER 7: DISCUSSION

The overarching aim of this thesis was to examine WM changes and cognitive outcomes following adult TBI. Four studies were completed to address these aims: two meta-analyses, to synthesise and evaluate existing research, and two cross-sectional studies, to expand the findings from the meta-analyses and examine whether a new method of analysis could detect WM changes following TBI. This discussion summarises the findings from the four studies and their contribution to the broader TBI and DTI literature. The limitations of the thesis and suggestions for future research are also provided.

7.1 Summary of findings

Study 1: Meta-analysis – DTI findings following TBI

The first study (Chapter 3) involved a meta-analysis of research that used DTI to examine the location and extent of WM alterations following adult mild, moderate and severe TBI. Initial subgroup analyses indicated that the findings from different time-points (acute: ≤ 1 week, subacute: 1 week-3 months, chronic: > 3 months) and acquired using different scanner and acquisition parameters could be combined. However, the findings from mild and moderate to severe injuries could not justifiably be combined; thus, studies that examined the full spectrum of injury severity (mild to severe TBI) were excluded from further analysis. A total of 44 studies were included in the meta-analysis.

Overall, widespread WM changes were evident in both the mild and moderate to severe TBI groups, reflecting less directional (lower FA) and greater rates (higher MD) of diffusion, with larger changes found following more severe injuries. Following mild TBI, FA was lower and MD was higher in most brain regions (88% and 95% of brain regions, respectively). Moreover, 12% of regions displayed considerably less directional diffusion (lower FA; medium-large, significant

effects) and 47% displayed a greater rate of diffusion (higher MD; medium-large, significant effects). Moderate to severe TBI was examined less frequently but, again, almost all regions displayed WM damage: FA was lower in 92% of regions, and MD was higher in 100% of regions. Considerable WM damage (i.e., medium to large and significant effects) was found in 72% (FA findings) and 57% (MD findings) of regions. The brain regions that were most affected by TBI (lowest FA, highest MD) following mild and moderate to severe TBI were the CC, internal capsule, occipital white matter, centrum semiovale, fornix and thalamic radiations. These findings suggest that TBI leads to widespread WM changes that are detected even following more minor injuries, many of which are likely to go undetected using conventional neuroimaging (CT, MRI).

Study 2: Meta-analysis – Relationship between DTI findings and cognition following TBI

The second study (Chapter 4) meta-analysed 20 studies that examined the relationship between DTI findings and cognition following adult TBI in order to determine which brain regions were related to cognitive functioning following TBI. Initial subgroup analyses found that the timing of the DTI in relation to the cognitive testing (simultaneous vs delayed cognitive testing); magnet strength (1.5T, 3T); scanner brand (General Electric, Philips, Siemens); differences in *b*-values (<1000, ≥1000); and number of diffusion-weighted images (<30, ≥30, based on Dodd et al., 2014) did not lead to significantly different findings. In contrast, DTI performed in the subacute period (>1 week-3 months post-injury) resulted in significantly stronger correlations between FA and cognition than the acute and chronic period (>3 months post-injury). However, each interval resulted in positive, moderate to large correlations between FA and cognition. Thus, there was insufficient evidence to justify separating the findings by any of these variables. Unfortunately, the impact of injury severity could not be examined in subgroup analyses because there were too few participants in each subgroup (<80; see Huedo-Medina et al., 2006), which meant that findings may have differed between injury severities.

Cognition was categorised into seven domains and, overall, better cognitive performance in each of these domains was associated with higher FA and/or lower MD. In particular, higher FA

and/or lower MD in the CC, fornix, internal capsule, and superior longitudinal, arcuate and uncinate fasciculi were strongly related to the cognitive domains of memory and/or attention. Although this meta-analysis suggested that poorer cognitive performance was related to WM damage (lower FA, higher MD), most of the findings were based on single studies that had used relatively small samples (60% of studies had fewer than 26 participants), limiting the conclusions that could be drawn.

Study 3: White matter changes detected using DTI and their relationship to cognition

Study 3 (Chapter 5) examined whether the findings from Studies 1 and 2 were replicated in a considerably larger sample of people with TBI. To this end, large samples of people with mild, moderate and severe TBIs, and healthy and orthopaedic controls, underwent cognitive testing and MRI with DTI. The ROIs and cognitive domains were based on the findings from the two meta-analyses: the genu, body and splenium of the CC, fornix and superior longitudinal fasciculus and memory, attention and executive functioning. The effects of age, sex, education and the delay between injury and MRI were controlled for in the analyses.

Although the mild TBI group did not display WM changes or poorer cognitive performance relative to controls, moderate to severe TBI led to notable WM alterations (lower FA, higher MD) in all five ROIs and poorer memory, attention and executive functioning performance. Notably, however, DTI findings were not associated with cognitive performance following moderate to severe TBI.

Study 4: Fixel-based analysis of TBI

The final study (Chapter 6) was deigned to determine whether a very recently developed method of analysing diffusion-weighted data, known as FBA, could detect micro- and macro-structural WM changes in the same sample of TBI participants that were examined in Study 3. FBA is particularly promising because traditional methods used to analyse DTI (e.g., ROI analysis, used in Study 3) are inaccurate in voxels that contain more than one WM tract (i.e., crossing

fibres) and, instead, provide measures (e.g., FA, MD) that are averaged across all WM tracts in each voxel. FBA, on the other hand, is capable of differentiating between the different fibre orientations contained within a single voxel and can therefore attribute the fixel metrics to individual WM tracts.

This study found that, for the entire TBI group, within-voxel fibre density was lower in the genu and body of the CC and the forceps minor, reflecting altered tissue microstructure. A measure of fibre-bundle cross-section and a combined measure of tissue micro- and macro-structure were not altered in any region, suggesting that there were no macrostructural changes to the WM. Subgroup analyses revealed that mild TBI did not lead to any WM changes detected using FBA. In contrast, there were considerable micro- and macro-structural WM changes following moderate to severe TBI (lower FD, FC, FDC) affecting widespread tracts, including the CC, internal and external capsule and cingulum. Similarly, people had slower reaction times following moderate to severe, but not mild TBI. However, FBA findings were not related to reaction time. Thus, WM damage following moderate to severe TBI was characterised by a reduction in the number of axons in addition to a reduction in the cross-sectional area of WM tracts.

7.2 Summative findings from the four studies

Taken together, the findings from the four studies have shown that WM changes following a TBI are widespread; are larger following more severe injuries; may be related to cognitive functioning; and may be identified using FBA. These findings have highlighted the challenges associated with assessing the relationship between WM damage and cognitive impairment.

7.2.1 Widespread WM changes

The four studies have shown that TBI leads to WM damage that affects widespread brain regions. WM changes manifested as less uniform/directional (low FA), but a greater magnitude (high MD) of diffusion in Studies 1 and 3, which may result from demyelination, gliosis, or axonal degeneration (Amyot et al., 2015). The extent of the damage, however, varied between brain regions, suggesting that certain regions are more vulnerable to the effects of TBI. In particular, the CC, internal capsule, fornix, cerebral white matter, centrum semiovale, thalamic radiations, superior longitudinal, inferior longitudinal, and uncinate fasciculi showed considerable WM changes (Study 1). Although FA was examined more frequently than MD (see Hulkower et al., 2013), the magnitude of diffusion was affected (higher MD) in more brain regions following mild TBI; highlighting the importance of examining both FA and MD.

Widespread WM changes were also detected using FBA which, unlike DTI, provides tract-specific information (Study 4) (Raffelt et al., 2015; Raffelt et al., 2017). This analysis suggests that WM damage resulting from moderate to severe TBI manifests as a reduction in the density of axons (i.e., fewer axons within fibre tracts) in addition to reduced cross-sectional areas of WM tracts, reflecting morphologic changes that affect the broader structure of the WM, which may result from WM degeneration (Raffelt et al., 2015; Raffelt et al., 2017).

Regardless of the technique used to analyse the data (e.g., ROI, FBA), WM changes were more evident following more severe injuries (Studies 1, 3, 4). These findings provide support for much existing research that has suggested a dose-response relationship between TBI severity and the amount of WM damage. For instance, WM changes were identified in every examined brain region following moderate to severe TBI, but far fewer following mild TBI (e.g., Kraus et al., 2007; Matsushita et al., 2011) and severe TBI led to lower FA than moderate TBI (e.g., Castano-Leon et al., 2018).

In particular, the first meta-analysis (Study 1) found that 12% and 72% of regions showed significantly less directional (low FA) diffusion following mild and moderate to severe TBI, respectively. In addition, 47% and 57% of regions showed a greater magnitude/rate of diffusion (high MD) following mild and moderate to severe TBI, respectively. Further, effect sizes were considerably larger following more severe injuries. Even with the narrow focus of five ROIs in Study 3, effect sizes were far larger following moderate to severe TBI, with all five regions showing considerable WM damage, compared to a non-significant trend following mild TBI. Widespread micro- and macro-structural changes were also detected using FBA following moderate to severe, but not mild, TBI (Study 4).

Comparison between Studies 1 and 3: group comparisons

WM changes affecting the genu, body and splenium of the CC, the fornix and the SLF were examined in both the first meta-analysis (Study 1) and within a large TBI sample (Study 3), allowing for a direct comparison of the findings from Studies 1 and 3, as shown in Table 1. In both studies, there was a trend toward less directional diffusion (lower FA) following mild TBI, relative to controls, suggesting slight damage resulting from these minor injuries. Using an uncorrected significance level (i.e., not corrected for multiple comparisons; $p < .05$), both the genu of the CC and the fornix showed significantly lower FA in Study 3, compared to non-significant findings from Study 1. In contrast, significant WM changes were detected following moderate to severe TBI in both Studies 1 and 3, with all five regions displaying less directional diffusion (lower FA; large to very large effects). The region that was most affected by moderate to severe TBI in Study 3 was the genu of the CC (g =-1.44), while in the first meta-analysis (Study 1) it was the fornix that appeared to be most affected (g =-1.99).

An examination of the MD findings showed that mild TBI led to significantly greater magnitude of diffusion (higher MD) in all five regions in the meta-analysis and in two of five regions in Study 3, namely the genu and splenium of the CC ($p < .05$). More damage was detected in the splenium of the CC in both Studies 1 and 3 (g =-.60 and -.38, respectively). Moderate to

Table 1. Comparison of FA and MD group comparisons (Hedges' *g* effect sizes) from Studies 1 & 3

ROIs	mild TBI		moderate-severe TBI	
	study 1 (N_{TBI} provided in brackets)	study 3 (N_{TBI}=135)	study 1 (N_{TBI} provided in brackets)	study 3 (N_{TBI} =34)
		fractional anisotropy (FA)		
CC: genu	-.26 (671)	-.22*	-1.25** (122)	-1.44**
CC: body	-.18 (387)	-.22	-1.04** (113)	-1.03**
CC: splenium	-.28 (580)	-.25	-1.40** (133)	-1.17**
fornix	-.41 (209)	-.35*	-1.99** (26)	-.62**
SLF	-.24 (378)	-.00	-1.01** (55)	-.88**
		mean diffusivity (MD)		
CC: genu	-.34** (399)	-.28*	-.25 (81)	-1.12**
CC: body	-.41* (178)	-.28	-.51** (72)	-1.12**
CC: splenium	-.60** (378)	-.38*	-1.03** (103)	-1.16**
fornix	-.54* (66)	-.23	-.15 (6)	-.59**
SLF	-.59* (145)	-.50	-.48 (6)	-88**

Note. TBI = traumatic brain injury; ROIs = regions of interest; CC = corpus callosum; N_{TBI} = number of TBI participants; *p*-values not corrected for multiple comparisons; * p <.05 ** p <.01

severe TBI led to a considerably greater rate/magnitude of diffusion in all five regions in Study 3, while only two of five regions had higher MD in Study 1: the body and splenium of CC. It is worth noting that MD was examined less frequently by the meta-analysed studies: two of the non-significant findings from Study 1 (fornix and SLF) were based on single studies of only six participants. Again, the splenium of the CC showed the largest WM alterations (higher MD) in both Studies 1 and 3 (*g* =-1.03 and -1.16, respectively). This finding is consistent with those from conventional MRI studies, which have shown that this portion of the CC is more vulnerable to damage from TBI than both the genu and body (Gentry, Godersky, & Thompson, 1988; Shiramizu et al., 2008). The strain resulting from a TBI may affect the splenium to a greater extent because of its close proximity to the falx cerebri, a structure that prevents the lateral movement of the two hemispheres (Fitsiori et al., 2011; Shiramizu et al., 2008).

7.2.2 The relationship between DTI findings and cognition

This thesis has also shown that the WM changes that are identified using DTI are related to cognitive outcomes. In particular, the findings from Study 2 suggest that more directional and slower diffusion is associated with better cognitive performance, across most cognitive domains and in most brain regions. The size of these relationships ranged from negligible (FA: white matter and concept formation/reasoning, r = -.02) to very strong (FA: fornix and attention, r = .85). Memory, attention and executive functioning were most commonly examined, with memory and attention most strongly related to WM damage from a number of regions (i.e., poorer performance was related to lower FA and higher MD). These domains therefore remain the most promising to examine post-TBI (Cristofori & Levin, 2015; Dikmen et al., 2009; Rabinowitz & Levin, 2014).

Brain structures that were highlighted in the two meta-analyses and the FBA analysis as being particularly vulnerable to TBI and/or related to cognitive functioning appear to be the most promising for continued research. Unsurprisingly, the CC showed considerable damage (Studies 1, 3 and 4) and was strongly related to cognition (Study 2). This structure is the largest commissural tract that is responsible for interhemispheric communication and is extremely vulnerable to damage resulting from TBI (Rutgers et al., 2008; Shiramizu et al., 2008). In addition, projection tracts, such as the internal and external capsule, were consistently damaged (Studies 1 and 4), and related to cognitive functioning: MD in the internal and external capsule were strongly related to attention and memory, respectively (Study 2). The SLF, a primary association tract that connects the frontal lobe and the temporoparieto-occipital regions (Aralasmak et al., 2006), also showed considerable damage that was associated with attention (Ptak, 2012; Voets et al., 2017). These regions appear to be most promising for continued research. Specifically, longitudinal studies may elucidate whether early examination of these structures predicts long-term cognitive outcomes.

Comparison between studies 2 and 3: correlation between DTI findings and cognition

It was not possible to directly compare the findings from Studies 2 and 3 regarding the relationship between DTI and cognitive findings, because Study 3 only examined this relationship in the moderate to severe TBI group. Although the second meta-analysis (Study 2) showed that directional and slow diffusion (high FA, low MD) in almost every examined region was associated with better cognitive performance, no significant relationships were found in Study 3 (strict significance level was adopted to compensate for multiple comparisons). It is possible that differences in the choice of cognitive test, the time post-injury that people were examined, and/or demographic variables led to these discrepant findings. Additional research should now examine large samples of people with TBI using a range of cognitive tests to determine whether, and to what extent, WM changes are related to cognitive outcomes.

7.2.3 Region of interest and fixel-based analyses: comparison

Although this thesis has shown that DTI can identify substantial WM changes that may to be related to post-injury cognitive functioning, the potential for DTI to provide a sensitive evaluation of WM integrity following TBI has been hampered by the problem of crossing fibres (Mori & Tournier, 2014; Raffelt et al., 2015). Specifically, FA and MD do not provide tract-specific information and, therefore, these measures cannot be used to infer WM integrity, particularly in regions of the brain where fibres cross (i.e., up to 90% of all voxels; Jeurissen et al., 2013). For instance, if a single fibre tract is damaged in a voxel that contains multiple fibre populations, FA may be higher, which could lead to the erroneous conclusion that the WM is healthy or has recovered (Mori & Tournier, 2014; Raffelt et al., 2012). This limitation can be overcome by using FBA, which is a recently developed technique that is used to analyse diffusion-weighted data. This technique can attribute damage to an individual WM tract in voxels that contain more than one tract and, furthermore, identifies whether WM alterations are the result of less densely packed

axons (FD), fibre bundles with a reduced cross-sectional area (morphometric changes) (FC), and/or a combination of both (FDC) (Mito et al., 2018; Raffelt et al., 2017; Raffelt et al., 2015).

It was not possible to do a direct comparison between the findings from traditional DTI analyses (i.e., ROI analysis) and the newer FBA, because FBA provides information for the whole brain, while ROI analysis (used in Study 3) provides regionally-specific information. However, it was possible to broadly compare the findings obtained from these two techniques in the five regions that were examined using ROI analysis in Study 3, as displayed in Table 2.

People with mild TBIs did not display significant WM changes when examined using ROI analysis (Study 3), despite a non-significant trend towards lower FA and higher MD (Study 3), suggesting slight damage. Similarly, there were no statistically significant differences detected using FBA following mild TBI (Study 4), despite this method potentially providing greater anatomical information about WM structure. In addition, no cognitive impairments were identified in this sample (Studies 3 and 4). These findings contrast with those of a number of studies that have reported WM changes following mild TBI (see reviews by Hulkower et al., 2013; Shenton et al., 2012), in particular in the CC (e.g., Inglese et al., 2005; Kumar, Gupta, et al., 2009; Matsushita et al., 2011; Miles et al., 2008), fornix (e.g., Singh, Jeong, Hwang, Sungkarat, & Gruen, 2010) and SLF (e.g., Geary et al., 2010; Kraus et al., 2007). As highlighted previously, these findings may reflect the fact that group analyses may overlook the heterogeneous damage that may result from TBIs. Alternatively, it is possible that any WM alterations and/or cognitive impairments had recovered by the time of the examination (mean of 7 months post-injury). As noted, WM damage has been shown to partially resolve over time and cognitive impairments are mostly recovered six months following mild TBI (e.g., Arfanakis et al., 2002; Cristofori & Levin, 2015; Grossman et al., 2013; Mayer et al., 2010). Large-scale, longitudinal studies are required to follow people with mild TBIs from soon after an injury to months and years post-injury to determine if these minor injuries do lead to WM damage and cognitive problems and, if so, when they recover.

Table 2. White matter changes following moderate to severe TBI detected using ROI analysis (study 3) and FBA (study 4)

	study 3 (region of interest analysis)		study 4 (fixel-based analysis)		
	FA	MD	FD	FC	FDC
CC genu	✓	✓	✓	✓	✓
CC body	✓	✓	✓	✓	✓
CC splenium	✓	✓	✓	✓	✓
fornix	✓	✓	×	×	×
SLF	✓	✓	✓	✓	✓

As expected, more serious injuries resulted in notable WM damage in all five regions, reflecting less directional (lower FA), but greater rates of diffusion (higher MD), as seen in the ROI analysis (Study 3). WM damage was also detected using FBA in widespread regions — changes that manifested as less densely packed axons in addition to reduced cross-sectional areas of WM tracts (Mito et al., 2018; Raffelt et al., 2017). The CC (genu, body, splenium) and SLF were affected but, interestingly, the fornix was not, in opposition to the ROI findings. This discrepant finding needs to be resolved in future studies. Although it would appear that FBA may provide more specific information about the structure of the WM, further research is needed to assess the utility of FBA in the examination of TBI.

The widespread WM changes that were detected following moderate to severe TBI using FBA are similar to those that have been found using DTI, however, it is likely that the FBA findings provide greater anatomical specificity (Mito et al., 2018). Indeed, FBA may provide a biomarker of tract-specific WM damage resulting from TBI that warrants further research (Gajamange et al., 2018).

7.3 Limitations

Limitations that are specific to each study were presented in the relevant chapters (3-6), but there are some overall limitations that are worth noting. In terms of the meta-analyses, there

are a number of variables that may have affected the findings but could not be examined. For instance, studies in the meta-analyses used differing definitions and criteria to categorise TBI severity, which makes comparing and interpreting findings from different studies difficult (see Carroll, Cassidy, Holm, Kraus, & Coronado, 2004). Some studies classified severity based on participants' DAI grading (e.g., Chang & Jang, 2010; Hong et al., 2012; Seo et al., 2012), and others just provided a severity category, without providing details of how this was determined.

Indeed, TBI classification remains extremely challenging (Hawryluk & Manley, 2015) and currently relies on the physical mechanism of injury (how the TBI was sustained; e.g., head hitting an object, acceleration/deceleration forces etc.) and/or severity of clinical symptoms, rather than more advanced techniques (e.g., molecular biomarkers, objective neuroimaging) that may allow for precise, targeted interventions and outcome prediction (Hawryluk & Manley, 2015; Saatman et al., 2008). The clinical course and prognoses of TBIs of different severities vary considerably and classification is therefore important to ensure appropriate clinical care is provided (Hawryluk & Manley, 2015). Of note, there are a number of large, international and interdisciplinary studies that have been developed recently to provide invaluable data about TBIs. These large-scale projects emphasise common data elements and better classification of TBIs is a primary goal (Hawryluk & Bullock, 2016). These studies include the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT; Maas et al., 2013), Transforming Research and Clinical Knowledge in TBI (TRACK-TBI; Yue et al., 2013) and Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI; Maas et al., 2015).

Despite subgroup analyses not providing sufficient evidence to separate the findings by most methodological variables, it was not possible to examine the effect of all variables (e.g., injury severity in the second meta-analysis). This was because there were fewer than 20 studies and 80 participants in each subgroup and, based on Huedo-Medina and colleagues (2006), there is insufficient power to test for heterogeneity if there are fewer than 20 studies and/or 80 participants in each subgroup. As noted, different acquisition parameters (e.g., b-values, voxel

size, number of diffusion-weighted images) were used by the studies included in the meta-analyses, in addition to differences in pre- and post-processing of data (e.g., software) and analysis techniques which may have contributed to heterogeneous findings, however examination of these variables was beyond the scope of the meta-analyses.

At present there is no consensus regarding the definition of 'acute', 'subacute' and 'chronic' which may negatively impact attempts to assess the progression of TBI damage. The current thesis used arbitrary cut offs for acute (≤ 1 week), subacute (>1 week to ≤ 3months; Amyot et al., 2015) and chronic (> 3 months) periods, but definitions vary in the literature. These time points must be defined, based on clinical or theoretical grounds, in order to accurately assess and document the progression of TBI damage and/or recovery.

Studies 3 and 4 would have benefitted from equal numbers of people with mild, moderate and severe TBIs, despite the sample being representative of the epidemiology of TBI (approximately 80% mild, 10% moderate and 10% severe, see Faul & Coronado, 2015). Although the initial sample size used in Studies 3 and 4 was considerably larger than that used in the majority of TBI imaging research, the primary findings were from the moderate to severe group, which had a sample size not much greater than those used in other studies (Study 3: $N_{moderate-severe}$=31, Study 4: $N_{moderate-severe}$=29).

7.4 Future research

Throughout this thesis, three main areas for future research have been identified. Firstly, there is a paucity of longitudinal studies in the DTI and TBI literature. Although many longitudinal studies have examined cognitive outcomes following TBI (e.g., Himanen et al., 2006; Marsh, 2019) very few longitudinal studies have used DTI to examine TBI. Large-scale, longitudinal studies following TBI participants for years after injury with regular testing (e.g., cognitive, emotional, behavioural, physical, quality of life, advanced neuroimaging) would provide invaluable information about injury progression and recovery after TBI. In particular, such studies would

help to elucidate the WM and cognitive changes that are specific to the acute and hyper-acute post-injury periods; previous studies examining these periods have found inconsistencies regarding specific DTI changes (e.g., Bazarian et al., 2007; Huisman et al., 2004; Shenton et al., 2012). Furthermore, the progression of WM and cognitive changes, particularly following mild TBI, could be examined in longitudinal studies. Historically, mild TBI has led to controversy, with some researchers believing long-term post-concussion symptoms are the result of psychological or psychiatric factors, rather than neurological damage (see Arciniegas et al., 2005; Dwyer & Katz, 2018). Overall, the complex nature of WM and cognitive changes resulting from DAI are not fully understood.

Secondly, in order to determine whether DTI and/or FBA have clinical utility, these techniques need to be able to identify damage in individual patients. The majority of studies utilise group analyses that may primarily reflect more advanced pathology in few participants and/or minimise heterogeneous, but less severe, damage in others (Ware et al., 2017). Whether these techniques are appropriate for single subject analyses remains to be determined. Several studies have examined this; Yuh et al. (2014) found that low FA modestly predicted unfavourable outcome at three- and six-months post-injury in individual mild TBI patients. In another study, Ware et al., (2017) compared individuals with moderate to severe TBI to a normative control group and found significant variability in the location and extent of DAI. Further, this damage was related to processing speed. More recently, work has examined whether DTI can be used to diagnose DAI in the spinothalamic tract in individual mild TBI patients (Jang & Lee, 2019). However, as noted by Douglas et al. (2018), there is currently not enough evidence to suggest that DTI can diagnose mild TBI in individuals.

Current research is examining the use of big data in the diagnosis and understanding of TBI pathophysiology (e.g., Newcombe, 2019). Big data analyses involve processing and analysing extremely large volumes of complex data (i.e., structured and unstructured data) — data that are already produced during brain imaging — using specialised programs and techniques (e.g.,

artificial intelligence, machine learning) to identify trends and associations that would be missed using current data analysis techniques (Agoston & Langford, 2017). In addition, the development of normative imaging databases would allow for single-subject investigations using machine learning, potentially leading to improved diagnosis and prognosis (Douglas et al., 2018). Indeed, longitudinal studies that compare post-injury scans to either pre-injury data (which are rarely available) or normative data would allow for an examination of individual differences in the magnitude and location of WM alterations/damage (Hulkower et al., 2013; Niogi & Mukherjee, 2010). Single subject analyses may lead to improvements in the way we identify and assess those more likely to exhibit problems following a TBI, in order to allocate people to rehabilitation programs (e.g., cognitive and/or skills training, group therapy) and decrease the levels of disability in the community.

Finally, this research has shown that FBA can detect tract-specific WM changes following moderate to severe TBI. Additional research is now needed to evaluate the reliability and generalisability of these findings. These studies, in addition to longitudinal studies, could determine whether FBA findings differ over time as WM changes progress, considering that WM degeneration can occur for years following injury (Hill et al., 2016). Initial analyses did not find evidence linking reaction time and FBA findings. Although it is possible that problems resulting from TBI may be due to fewer axons contained within WM tracts with decreased cross-section areas, future research should examine whether FBA findings are related to cognitive outcomes and whether early FBA can be used to predict long term cognitive, functional and behavioural outcomes.

7.5 Conclusions

This thesis has shown that DTI can identify widespread WM changes following TBIs, particularly moderate to severe injuries. Further, these WM changes may be related to cognitive outcomes, however the relationships were not consistent across all studies, highlighting the need

for additional research. These findings pave the way for future work to examine whether early DTI can predict long-term cognitive outcomes and identify individuals likely to have long term cognitive problems. Such research will be instrumental to tailoring rehabilitation programs to allocate scarce resources, with the goal of reducing the levels of TBI-related disability in the community.

Importantly, this research has shown that tract-specific WM damage can be identified following more severe TBI using the very recently developed FBA. This damage is widespread and manifests as decreased density of axons in addition to a reduced cross-sectional area of WM tracts, reflecting morphologic changes affecting the broader WM structure. Whether FBA findings are related to post-injury cognitive functioning remains to be determined. Further research needs to be conducted examining large-scale, longitudinal data and studies are required to examine whether these techniques (DTI, FBA) are appropriate for single-subject analyses, to make these techniques viable for clinical settings.

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. doi:10.1111/j.1365-2559.1989.tb03040.x

Agoston, D. V., & Langford, D. (2017). Big Data in traumatic brain injury; promise and challenges. *Concussion, 2*(4), Cnc45. doi:10.2217/cnc-2016-0013

Ahmed, S., Bierley, R., Sheikh, J. I., & Date, E. S. (2000). Post-traumatic amnesia after closed head injury: a review of the literature and some suggestions for further research. *Brain Injury, 14*(9), 765-780. doi:10.1080/026990500421886

Albrecht, J. S., Liu, X., Smith, G. S., Baumgarten, M., Rattinger, G. B., Gambert, S. R., . . . Zuckerman, I. H. (2015). Stroke incidence following traumatic brain injury in older adults. *Journal of Head Trauma Rehabilitation, 30*(2), E62-67. doi:10.1097/htr.0000000000000035

Amyot, F., Arciniegas, D. B., Brazaitis, M. P., Curley, K. C., Diaz-Arrastia, R., Gandjbakhche, A., . . . Stocker, D. (2015). A Review of the Effectiveness of Neuroimaging Modalities for the Detection of Traumatic Brain Injury. *Journal of Neurotrauma, 32*(22), 1693-1721. doi:10.1089/neu.2013.3306

Andersson, J. L. R., & Sotiropoulos, S. N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *NeuroImage, 125*, 1063-1078. doi:10.1016/j.neuroimage.2015.10.019

Aoki, Y., Inokuchi, R., Gunshin, M., Yahagi, N., & Suwa, H. (2012). Diffusion tensor imaging studies of mild traumatic brain injury: A meta-analysis. *Journal of Neurology, Neurosurgery and Psychiatry, 83*(9), 870-876. doi:10.1136/jnnp-2012-302742

Aralasmak, A., Ulmer, J. L., Kocak, M., Salvan, C. V., Hillis, A. E., & Yousem, D. M. (2006). Association, commissural, and projection pathways and their functional deficit reported in literature. *Journal of Computer Assisted Tomography, 30*(5), 695-715. doi:10.1097/01.rct.0000226397.43235.8b

Arbour, R. B. (2013). Traumatic brain injury: pathophysiology, monitoring, and mechanism-based care. *Critical Care Nursing Clinics of North America, 25*(2), 297-319. doi:10.1016/j.ccell.2013.02.010

Arciniegas, D. B., Anderson, C. A., Topkoff, J., & McAllister, T. W. (2005). Mild traumatic brain injury: A neuropsychiatric approach to diagnosis, evaluation, and treatment. *Neuropsychiatric Disease and Treatment, 1*(4), 311-327.

Arenth, P. M., Russell, K. C., Scanlon, J. M., Kessler, L. J., & Ricker, J. H. (2014). Corpus callosum integrity and neuropsychological performance after traumatic brain injury: A diffusion tensor imaging study. *Journal of Head Trauma Rehabilitation, 29*(2), E1-E10. doi:10.1097/HTR.0b013e318289ede5

Arfanakis, K., Haughton, V. M., Carew, J. D., Rogers, B. P., Dempsey, R. J., & Meyerand, M. E. (2002). Diffusion tensor MR imaging in diffuse axonal injury. *AJNR American Journal of Neuroradiology, 23*(5), 794-802.

Ashman, T. A., Gordon, W. A., Cantor, J. B., & Hibbard, M. R. (2006). Neurobehavioral consequences of traumatic brain injury. *Mount Sinai Journal of Medicine, 73*(7), 999-1005.

Asken, B. M., DeKosky, S. T., Clugston, J. R., Jaffee, M. S., & Bauer, R. M. (2017). Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): a systematic critical review. *Brain Imaging and Behavior*. doi:10.1007/s11682-017-9708-9

Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., & Gee, J. C. (2011). A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage, 54*(3), 2033-2044. doi:10.1016/j.neuroimage.2010.09.025

Azouvi, P., Arnould, A., Dromer, E., & Vallat-Azouvi, C. (2017). Neuropsychology of traumatic brain injury: An expert overview. *Revue Neurologique, 173*(7-8), 461-472. doi:10.1016/j.neurol.2017.07.006

Baek, S. O., Kim, O. L., Kim, S. H., Kim, M. S., Son, S. M., Cho, Y. W., . . . Jang, S. H. (2013). Relation between cingulum injury and cognition in chronic patients with traumatic brain injury; diffusion tensor tractography study. *NeuroRehabilitation, 33*(3), 465-471. doi:10.3233/NRE-130979

Bandak, F. A., Ling, G., Bandak, A., & De Lanerolle, N. C. (2015). Injury biomechanics, neuropathology, and simplified physics of explosive blast and impact mild traumatic brain injury. *Handbook of Clinical Neurology, 127*, 89-104. doi:10.1016/b978-0-444-52892-6.00006-4

Barker-Collo, S., & Feigin, V. L. (2008). Memory deficit after traumatic brain injury: How big is the problem in New Zealand and what management strategies are available? *New Zealand Medical Journal, 121*(1268).

Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal, 66*(1), 259-267.

Basso, A., Previgliano, I., Duarte, J. M., & Ferrari, N. (2001). Advances in management of neurosurgical trauma in different continents. *World Journal of Surgery, 25*(9), 1174-1178. doi:10.1007/s00268-001-0079-3

Bay, E. H., Blow, A. J., & Yan, X. E. (2012). Interpersonal relatedness and psychological functioning following traumatic brain injury: implications for marital and family therapists. *Journal of Marital and Family Therapy, 38*(3), 556-567. doi:10.1111/j.1752-0606.2011.00231.x

Bazarian, J. J., Cernak, I., Noble-Haeusslein, L., Potolicchio, S., & Temkin, N. (2009). Long-term neurologic outcomes after traumatic brain injury. *Journal of Head Trauma Rehabilitation, 24*(6), 439-451. doi:10.1097/HTR.0b013e3181c15600

Bazarian, J. J., Zhong, J., Blyth, B., Zhu, T., Kavcic, V., & Peterson, D. (2007). Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. *Journal of Neurotrauma, 24*(9), 1447-1459. doi:10.1089/neu.2007.0241

Belanger, H. G., Curtiss, G., Demery, J. A., Lebowitz, B. K., & Vanderploeg, R. D. (2005). Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. *Journal of the International Neuropsychological Society, 11*(3), 215-227. doi:10.1017/s1355617705050277

Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., . . . Johnson, S. C. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *NeuroImage, 42*(2), 503-514. doi:10.1016/j.neuroimage.2008.04.254

Bigler, E. D. (2007). Anterior and middle cranial fossa in traumatic brain injury: relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. *Neuropsychology, 21*(5), 515-531. doi:10.1037/0894-4105.21.5.515

Bigler, E. D. (2008). Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *Journal of the International Neuropsychological Society, 14*(1), 1-22. doi:10.10170S135561770808017X

Bigler, E. D., Abildskov, T. J., Goodrich-Hunsaker, N. J., Black, G., Christensen, Z. P., Huff, T., . . . Max, J. E. (2016). Structural Neuroimaging Findings in Mild Traumatic Brain Injury. *Sports Medicine and Arthroscopy Review, 24*(3), e42-e52. doi:10.1097/JSA.0000000000000119

Bigler, E. D., & Bazarian, J. J. (2010). Diffusion tensor imaging: A biomarker for mild traumatic brain injury? *Neurology, 74*(8), 626-627. doi:10.1212/WNL.0b013e3181d3e43a

Bigler, E. D., & Maxwell, W. L. (2011). Neuroimaging and neuropathology of TBI. *NeuroRehabilitation, 28*(2), 63-74. doi:10.3233/nre-2011-0633

Bigler, E. D., & Snyder, J. L. (1995). Neuropsychological outcome and quantitative neuroimaging in mild head injury. *Archives of Clinical Neuropsychology, 10*(2), 159-174. doi:10.1016/0887-6177(94)E0003-8

Bigler, E. D., & Stern, Y. (2015). Traumatic brain injury and reserve. *Handbook of Clinical Neurology, 128*, 691-710. doi:10.1016/b978-0-444-63521-1.00043-1

Blyth, B. J., & Bazarian, J. J. (2010). Traumatic alterations in consciousness: traumatic brain injury. *Emergency Medicine Clinics of North America, 28*(3), 571-594. doi:10.1016/j.emc.2010.03.003

Bohnen, N., Zutphen, W. V., Twijnstra, A., Wijnen, G., Bongers, J., & Jolles, J. (1994). Late outcome of mild head injury: Results from a controlled postal survey. *Brain Injury, 8*(8), 701-708. doi:10.3109/02699059409151024

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2009). *Introduction to Meta-analysis*. NJ, USA: John Wiley & Sons, Ltd.

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods, 1*(2), 97-111. doi:10.1002/jrsm.12

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009). Subgroup Analyses. In *Introduction to Meta-Analysis* (pp. 149-186): John Wiley & Sons, Ltd.

Boyles, A. L., Harris, S. F., Rooney, A. A., & Thayer, K. A. (2011). Forest Plot Viewer: A new graphing tool. *Epidemiology, 22*(5), 746-747.

Brandstack, N., Kurki, T., Hiekkanen, H., & Tenovuo, O. (2011). Diffusivity of normal-appearing tissue in acute traumatic brain injury. *Clinical Neuroradiology, 21*(2), 75-82. doi:10.1007/s00062-011-0058-5

Brazinova, A., Rehorcikova, V., Taylor, M. S., Buckova, V., Majdan, M., Psota, M., . . . Synnot, A. (2015). Epidemiology of traumatic brain injury in Europe: a living systematic review. *Journal of Neurotrauma*. doi:10.1089/neu.2015.4126

Brody, A. S., Frush, D. P., Huda, W., Brent, R. L., DiPietro, M. A., Applegate, K. E., . . . Stolic, A. (2007). Radiation risk to children from computed tomography. *Pediatrics, 120*(3), 677-682. doi:10.1542/peds.2007-1910

Bruns, J., Jr., & Hauser, W. A. (2003). The epidemiology of traumatic brain injury: a review. *Epilepsia, 44 Suppl 10*, 2-10. doi:10.1046/j.1528-1157.44.s10.3.x

Carroll, L. J., Cassidy, J. D., Holm, L., Kraus, J., & Coronado, V. G. (2004). Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *Journal of Rehabilitation Medicine*(43 Suppl), 113-125. doi:10.1080/16501960410023877

Castano-Leon, A. M., Cicuendez, M., Navarro, B., Munarriz, P. M., Cepeda, S., Paredes, I., . . . Lagares, A. (2018). What can we learn from diffusion tensor imaging from a large traumatic brain injury cohort? White matter integrity and its relationship with outcome. *Journal of Neurotrauma*. doi:10.1089/neu.2018.5691

Castriotta, R. J., & Murthy, J. N. (2011). Sleep disorders in patients with traumatic brain injury: a review. *CNS Drugs, 25*(3), 175-185. doi:10.2165/11584870-000000000-00000

Chan, R. C., Shum, D., Toulopoulou, T., & Chen, E. Y. (2008). Assessment of executive functions: review of instruments and identification of critical issues. *Archives of Clinical Neuropsychology, 23*(2), 201-216. doi:10.1016/j.acn.2007.08.010

Chang, M. C., & Jang, S. H. (2010). Corpus callosum injury in patients with diffuse axonal injury: A diffusion tensor imaging study. *NeuroRehabilitation, 26*(4), 339-345. doi:10.3233/NRE-2010-0571

Chang, M. C., Kim, S. H., Kim, O. L., Bai, D. S., & Jang, S. H. (2010). The relation between fornix injury and memory impairment in patients with diffuse axonal injury: A diffusion tensor imaging study. *NeuroRehabilitation, 26*(4), 347-353. doi:10.3233/NRE-2010-0572

Chen, X. H., Johnson, V. E., Uryu, K., Trojanowski, J. Q., & Smith, D. H. (2009). A lack of amyloid β plaques despite persistent accumulation of amyloid β in axons of long-term survivors of

traumatic brain injury. *Brain Pathology, 19*(2), 214-223. doi:10.1111/j.1750-3639.2008.00176.x

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet Neurology, 7*(12), 1139-1151. doi:10.1016/S1474-4422(08)70259-X

Christensen, B. K., Colella, B., Inness, E., Hebert, D., Monette, G., Bayley, M., & Green, R. E. (2008). Recovery of cognitive function after traumatic brain injury: a multilevel modeling analysis of Canadian outcomes. *Archives of Physical Medicine and Rehabilitation, 89*(12), S3-S15. doi:10.1016/j.apmr.2008.10.002

Christensen, J. (2015). The Epidemiology of Posttraumatic Epilepsy. *Seminars in Neurology, 35*(3), 218-222. doi:10.1055/s-0035-1552923

Chua, K. S., Ng, Y. S., Yap, S. G., & Bok, C. W. (2007). A brief review of traumatic brain injury rehabilitation. *Annals of the Academy of Medicine of Singapore, 36*(1), 31-42.

Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*(1), 155-159.

Cohen, R. A. (2014). Introduction. In R. A. Cohen (Ed.), *The Neuropsychology of Attention* (pp. 3-10). Boston, MA: Springer US.

Corrigan, J. D., Selassie, A. W., & Orman, J. A. (2010). The epidemiology of traumatic brain injury. *Journal of Head Trauma Rehabilitation, 25*(2), 72-80. doi:10.1097/HTR.0b013e3181ccc8b4

Crane, P. K., Gibbons, L. E., Dams-O'Connor, K., Trittschuh, E., Leverenz, J. B., Dirk Keene, C., . . . Larson, E. B. (2016). Association of traumatic brain injury with late-life neurodegenerative conditions and Neuropathologic findings. *JAMA Neurology, 73*(9), 1062-1069. doi:10.1001/jamaneurol.2016.1948

Cristofori, I., & Grafman, J. (2017). Executive Functions After Traumatic Brain Injury: From Deficit to Recovery. In *Executive Functions in Health and Disease* (pp. 421-443).

Cristofori, I., & Levin, H. S. (2015). Traumatic brain injury and cognition. *Handbook of Clinical Neurology, 128*, 579-611. doi:10.1016/B978-0-444-63521-1.00037-6

D'Souza, M. M., Trivedi, R., Singh, K., Grover, H., Choudhury, A., Kaur, P., . . . Tripathi, R. P. (2015). Traumatic brain injury and the post-concussion syndrome: A diffusion tensor tractography study. *Indian Journal of Radiology and Imaging, 25*(4), 404-414. doi: 10.4103/0971-3026.169445

Dean, P. J. A., Sato, J. R., Vieira, G., McNamara, A., & Sterr, A. (2015). Multimodal imaging of mild traumatic brain injury and persistent postconcussion syndrome. *Brain and Behavior, 5*(1). doi:10.1002/brb3.292

Demery, J. A., Larson, M. J., Dixit, N. K., Bauer, R. M., & Perlstein, W. M. (2010). Operating characteristics of executive functioning tests following traumatic brain injury. *Clinical Neuropsychologist, 24*(8), 1292-1308. doi:10.1080/13854046.2010.528452

Dewan, M. C., Rattani, A., Gupta, S., Baticulon, R. E., Hung, Y. C., Punchak, M., . . . Park, K. B. (2018). Estimating the global incidence of traumatic brain injury. *Journal of Neurosurgery*, 1-18. doi:10.3171/2017.10.Jns17352

Dick, F. D., De Palma, G., Ahmadi, A., Scott, N. W., Prescott, G. J., Bennett, J., . . . Felice, A. (2007). Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. *Occupational and Environmental Medicine, 64*(10), 666-672. doi:10.1136/oem.2006.027003

Dikmen, S. S., Corrigan, J. D., Levin, H. S., MacHamer, J., Stiers, W., & Weisskopf, M. G. (2009). Cognitive outcome following traumatic brain injury. *Journal of Head Trauma Rehabilitation, 24*(6), 430-438. doi:10.1097/HTR.0b013e3181c133e9

Dikmen, S. S., Corrigan, J. D., Levin, H. S., MacHamer, J., Stiers, W., & Weisskopf, M. G. (2009). Cognitive outcome following traumatic brain injury. *Journal of Head Trauma Rehabilitation, 24*(6), 430-438. doi:10.1097/HTR.0b013e3181c133e9

Dixon, K. J. (2017). Pathophysiology of Traumatic Brain Injury. *Physical Medicine and Rehabilitation Clinics of North America, 28*(2), 215-225. doi:10.1016/j.pmr.2016.12.001

Dodd, A. B., Epstein, K., Ling, J. M., & Mayer, A. R. (2014). Diffusion tensor imaging findings in semi-acute mild traumatic brain injury. *Journal of Neurotrauma, 31*(14), 1235-1248. doi:10.1089/neu.2014.3337

Douet, V., & Chang, L. (2014). Fornix as an imaging marker for episodic memory deficits in healthy aging and in various neurological disorders. *Front Aging Neurosci, 6*, 343. doi:10.3389/fnagi.2014.00343

Douglas, D. B., Iv, M., Douglas, P. K., Anderson, A., Vos, S. B., Bammer, R., . . . Wintermark, M. (2015). Diffusion Tensor Imaging of TBI: Potentials and Challenges. *Topics in Magnetic Resonance Imaging, 24*(5), 241-251. doi:10.1097/rmr.0000000000000062

Douglas, D. B., Muldermans, J. L., & Wintermark, M. (2018). Neuroimaging of brain trauma. *Current Opinion in Neurology*. doi:10.1097/wco.0000000000000567

Draper, K., & Ponsford, J. (2008). Cognitive functioning ten years following traumatic brain injury and rehabilitation. *Neuropsychology, 22*(5), 618-625. doi:10.1037/0894-4105.22.5.618

Dwyer, B., & Katz, D. I. (2018). Chapter 17 - Postconcussion syndrome. *Handbook of Clinical Neurology, 158*, 163-178. doi:10.1016/B978-0-444-63954-7.00017-3

Eierud, C., Craddock, R. C., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., & LaConte, S. M. (2014). Neuroimaging after mild traumatic brain injury: review and meta-analysis. *NeuroImage: Clinical, 4*, 283-294. doi:10.1016/j.nicl.2013.12.009

Einarsen, C. E., van der Naalt, J., Jacobs, B., Follestad, T., Moen, K. G., Vik, A., . . . Skandsen, T. (2018). Moderate Traumatic Brain Injury: Clinical Characteristics and a Prognostic Model of 12-Month Outcome. *World Neurosurgery, 114*, e1199-e1210. doi:10.1016/j.wneu.2018.03.176

Ellis, P. D. (2010). *The Essential Guide to Effect Sizes: Statistical Power, Meta-Analysis, and the Interpretation of Research Results*. United Kingdom: University Press, Cambridge.

Engel, L., Chui, A., Goverover, Y., & Dawson, D. R. (2019). Optimising activity and participation outcomes for people with self-awareness impairments related to acquired brain injury: an interventions systematic review. *Neuropsychological Rehabilitation, 29*(2), 163-198. doi:10.1080/09602011.2017.1292923

Erez, A. B. H., Rothschild, E., Katz, N., Tuchner, M., & Hartman-Maeir, A. (2009). Executive functioning, awareness, and participation in daily life after mild traumatic brain injury: A preliminary study. *American Journal of Occupational Therapy, 63*(5), 634-640. doi:10.5014/ajot.63.5.634

Evans, C. C., Sherer, M., Nick, T. G., Nakase-Richardson, R., & Yablon, S. A. (2005). Early impaired self-awareness, depression, and subjective well-being following traumatic brain injury. *Journal of Head Trauma Rehabilitation, 20*(6), 488-500. doi:10.1097/00001199-200511000-00002

Faul, M., & Coronado, V. (2015). Epidemiology of traumatic brain injury. *Handbook of Clinical Neurology, 127*, 3-13. doi:10.1016/b978-0-444-52892-6.00001-5

Faul, M., Xu, L., Wald, M. M., & Coronado, V. G. (2010). *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002 - 2006*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for INjury Prevention and Contol.

Fife, T. D., & Giza, C. (2013). Posttraumatic vertigo and dizziness. *Seminars in Neurology, 33*(3), 238-243. doi:10.1055/s-0033-1354599

Filley, C. M., & Kelly, J. P. (2018). White Matter and Cognition in Traumatic Brain Injury. *Journal of Alzheimer's disease : JAD, 65*(2), 345-362. doi:10.3233/JAD-180287

Fisher, L. B., Pedrelli, P., Iverson, G. L., Bergquist, T. F., Bombardier, C. H., Hammond, F. M., . . . Zafonte, R. (2016). Prevalence of suicidal behaviour following traumatic brain injury: Longitudinal follow-up data from the NIDRR Traumatic Brain Injury Model Systems. *Brain Injury, 30*(11), 1311-1318. doi:10.1080/02699052.2016.1195517

Fitsiori, A., Nguyen, D., Karentzos, A., Delavelle, J., & Vargas, M. I. (2011). The corpus callosum: White matter or terra incognita. *British Journal of Radiology, 84*(997), 5-18. doi:10.1259/bjr/21946513

Fortin, J. P., Parker, D., Tunc, B., Watanabe, T., Elliott, M. A., Ruparel, K., . . . Shinohara, R. T. (2017). Harmonization of multi-site diffusion tensor imaging data. *NeuroImage, 161*, 149-170. doi:10.1016/j.neuroimage.2017.08.047

Frencham, K. A., Fox, A. M., & Maybery, M. T. (2005). Neuropsychological studies of mild traumatic brain injury: a meta-analytic review of research since 1995. *Journal of Clinical and Experimental Neuropsychology, 27*(3), 334-351. doi:10.1080/13803390490520328

Frey, L. C. (2003). Epidemiology of Posttraumatic Epilepsy: A Critical Review. *Epilepsia, 44*(SUPPL. 10), 11-17. doi:10.1046/j.1528-1157.44.s10.4.x

Froeling, M., Pullens, P., & Leemans, A. (2016). DTI analysis methods: Region of interest analysis. In *Diffusion Tensor Imaging: A Practical Handbook* (pp. 175-182). New York: Springer.

Gajamange, S., Raffelt, D., Dhollander, T., Lui, E., van der Walt, A., Kilpatrick, T., . . . Kolbe, S. (2018). Fibre-specific white matter changes in multiple sclerosis patients with optic neuritis. *NeuroImage: Clinical, 17*, 60-68. doi:10.1016/j.nicl.2017.09.027

Gardner, A., Kay-Lambkin, F., Stanwell, P., Donnelly, J., Williams, W. H., Hiles, A., . . . Jones, D. K. (2012). A systematic review of diffusion tensor imaging findings in sports-related concussion. *Journal of Neurotrauma, 29*(16), 2521-2538. doi:10.1089/neu.2012.2628

Geary, E. K., Kraus, M. F., Pliskin, N. H., & Little, D. M. (2010). Verbal learning differences in chronic mild traumatic brain injury. *Journal of the International Neuropsychological Society, 16*(3), 506-516. doi:10.1017/S135561771000010X

Gentry, L. R., Godersky, J. C., & Thompson, B. (1988). MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. *American Journal of Roentgenology, 150*(3), 663-672. doi:10.2214/ajr.150.3.663

Geytenbeek, M., Fleming, J., Doig, E., & Ownsworth, T. (2017). The occurrence of early impaired self-awareness after traumatic brain injury and its relationship with emotional distress and psychosocial functioning. *Brain Injury, 31*(13-14), 1791-1798. doi:10.1080/02699052.2017.1346297

Gill, I. J., Mullin, S., & Simpson, J. (2014). Psychosocial and psychological factors associated with post-traumatic stress disorder following traumatic brain injury in adult civilian populations: a systematic review. *Brain Injury, 28*(1), 1-14. doi:10.3109/02699052.2013.851416

Goeke, J. M. (2017). Postconcussion syndrome: Neuropsychological evaluation and management. *Psychiatric Annals, 47*(2), 92-96. doi:10.3928/00485713-20170106-01

Goldstein, A., & Mesfin, F. B. (2017). Neuroanatomy, Corpus Callosum. In *StatPearls*. Treasure Island (FL): StatPearls Publishing.

Gorgoraptis, N., Zaw-Linn, J., Feeney, C., Tenorio-Jimenez, C., Niemi, M., Malik, A., . . . Sharp, D. J. (2019). Cognitive impairment and health-related quality of life following traumatic brain injury. *NeuroRehabilitation, 44*(3), 321-331. doi:10.3233/NRE-182618

Goverover, Y., Genova, H., Smith, A., Chiaravalloti, N., & Lengenfelder, J. (2017). Changes in activity participation following traumatic brain injury. *Neuropsychological Rehabilitation, 27*(4), 472-485. doi:10.1080/09602011.2016.1168746

Greenfield, J. G., Love, S., Louis, D. N., & Ellison, D. W. (2008). *Greenfield's Neuropathology* (8 ed.). London: Hodden Arnold.

Griffen, J., & Hanks, R. (2014). Cognitive and Behavioral Outcomes from Traumatic Brain Injury. In M. Sherer & A. M. Sander (Eds.), *Handbook on the Neuropsychology of Traumatic Brain Injury* (pp. 25-45). New York, NY: Springer New York.

Grossman, E. J., Ge, Y. L., Jensen, J. H., Babb, J. S., Miles, L., Reaume, J., . . . Inglese, M. (2012). Thalamus and Cognitive Impairment in Mild Traumatic Brain Injury: A Diffusional Kurtosis Imaging Study. *Journal of Neurotrauma, 29*(13), 2318-+. doi:10.1089/neu.2011.1763

Grossman, E. J., Jensen, J. H., Babb, J. S., Chen, Q., Tabesh, A., Fieremans, E., . . . Grossman, R. I. (2013). Cognitive impairment in mild traumatic brain injury: A longitudinal diffusional kurtosis and perfusion imaging study. *American Journal of Neuroradiology, 34*(5), 951-957. doi:10.3174/ajnr.A3358

Gu, L., Li, J., Feng, D. F., Cheng, E. T., Li, D. C., Yang, X. Q., & Wang, B. C. (2013). Detection of white matter lesions in the acute stage of diffuse axonal injury predicts long-term cognitive impairments: A clinical diffusion tensor imaging study. *Journal of Trauma and Acute Care Surgery, 74*(1), 242-247. doi:10.1097/TA.0b013e3182684fe8

Guenette, J. P., Shenton, M. E., & Koerte, I. K. (2018). Imaging of Concussion in Young Athletes. *Neuroimaging Clinics of North America, 28*(1), 43-53. doi:10.1016/j.nic.2017.09.004

Haberg, A. K., Olsen, A., Moen, K. G., Schirmer-Mikalsen, K., Visser, E., Finnanger, T. G., . . . Eikenes, L. (2015). White matter microstructure in chronic moderate-to-severe traumatic brain injury: Impact of acute-phase injury-related variables and associations with outcome measures. *Journal of Neuroscience Research, 93*(7), 1109-1126. doi:10.1002/jnr.23534

Hawryluk, G. W., & Bullock, M. R. (2016). Past, Present, and Future of Traumatic Brain Injury Research. *Neurosurgery Clinics of North America, 27*(4), 375-396. doi:10.1016/j.nec.2016.05.002

Hawryluk, G. W., & Manley, G. T. (2015). Classification of traumatic brain injury: past, present, and future. *Handbook of Clinical Neurology, 127*, 15-21. doi:10.1016/b978-0-444-52892-6.00002-7

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. London: Academic Press Inc. Ltd.

Hendrickson, R. C., Schindler, A. G., & Pagulayan, K. F. (2018a). Untangling PTSD and TBI: Challenges and Strategies in Clinical Care and Research. *Current Neurology and Neuroscience Reports, 18*(12), 106. doi:10.1007/s11910-018-0908-5

Hendrickson, R. C., Schindler, A. G., & Pagulayan, K. F. (2018b). Untangling PTSD and TBI: Challenges and Strategies in Clinical Care and Research. *Current Neurology and Neuroscience Reports, 18*(12), 106. doi:10.1007/s11910-018-0908-5

Hesdorffer, D. C., Rauch, S. L., & Tamminga, C. A. (2009). Long-term psychiatric outcomes following traumatic brain injury: a review of the literature. *Journal of Head Trauma Rehabilitation, 24*(6), 452-459. doi:10.1097/HTR.0b013e3181c133fd

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *Bmj, 327*(7414), 557-560. doi:10.1136/bmj.327.7414.557

Hill, C. S., Coleman, M. P., & Menon, D. K. (2016). Traumatic Axonal Injury: Mechanisms and Translational Opportunities. *Trends in Neurosciences, 39*(5), 311-324. doi:10.1016/j.tins.2016.03.002

Himanen, L., Portin, R., Isoniemi, H., Helenius, H., Kurki, T., & Tenovuo, O. (2006). Longitudinal cognitive changes in traumatic brain injury: A 30-year follow-up study. *Neurology, 66*(2), 187-192. doi:10.1212/01.wnl.0000194264.60150.d3

Holland, B. S., & Copenhaver, M. D. (1988). Improved Bonferroni-Type Multiple Testing Procedures. *Psychological Bulletin, 104*(1), 145-149. doi:10.1037/0033-2909.104.1.145

Holli, K. K., Wäljas, M., Harrison, L., Liimatainen, S., Luukkaala, T., Ryymin, P., . . . Dastidar, P. (2010). Mild Traumatic Brain Injury. Tissue Texture Analysis Correlated to Neuropsychological and DTI Findings. *Academic Radiology, 17*(9), 1096-1102. doi:10.1016/j.acra.2010.04.009

Holm, L., Cassidy, J. D., Carroll, L. J., & Borg, J. (2005). Summary of the WHO Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury. *Journal of Rehabilitation Medicine, 37*(3), 137-141. doi:10.1080/16501970510027321

Hong, J. H., Jang, S. H., Kim, O. L., Kim, S. H., Ahn, S. H., Byun, W. M., . . . Lee, D. H. (2012). Neuronal loss in the medial cholinergic pathway from the nucleus basalis of Meynert in patients with traumatic axonal injury: a preliminary diffusion tensor imaging study.

Journal of Head Trauma Rehabilitation, 27(3), 172-176. doi:10.1097/HTR.0b013e318217192d

Huedo-Medina, T. B., Sánchez-Meca, J., Marín-Martínez, F., & Botella, J. (2006). Assessing heterogeneity in meta-analysis: Q statistic or I2 Index? *Psychological Methods, 11*(2), 193-206. doi:10.1037/1082-989X.11.2.193

Huisman, T. A. (2010). Diffusion-weighted and diffusion tensor imaging of the brain, made easy. *Cancer Imaging, 10 Spec no A*, S163-171. doi:10.1102/1470-7330.2010.9023

Huisman, T. A., Schwamm, L. H., Schaefer, P. W., Koroshetz, W. J., Shetty-Alva, N., Ozsunar, Y., . . . Sorensen, A. G. (2004). Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *AJNR American Journal of Neuroradiology, 25*(3), 370-376.

Hulkower, M. B., Poliak, D. B., Rosenbaum, S. B., Zimmerman, M. E., & Lipton, M. L. (2013). A decade of DTI in traumatic brain injury: 10 years and 100 articles later. *AJNR American Journal of Neuroradiology, 34*(11), 2064-2074. doi:10.3174/ajnr.A3395

Hutchinson, E. B., Schwerin, S. C., Avram, A. V., Juliano, S. L., & Pierpaoli, C. (2018). Diffusion MRI and the detection of alterations following traumatic brain injury. *Journal of Neuroscience Research, 96*(4), 612-625. doi:10.1002/jnr.24065

Hyder, A. A., Wunderlich, C. A., Puvanachandra, P., Gururaj, G., & Kobusingye, O. C. (2007). The impact of traumatic brain injuries: a global perspective. *NeuroRehabilitation, 22*(5), 341-353.

Ilvesmaki, T., Luoto, T. M., Hakulinen, U., Brander, A., Ryymin, P., Eskola, H., . . . Ohman, J. (2014). Acute mild traumatic brain injury is not associated with white matter change on diffusion tensor imaging. *Brain: A Journal of Neurology, 137*(7), 1876-1882. doi: 10.1093/brain/awu095

Imperati, D., Colcombe, S., Kelly, C., Martino, A., Zhou, J., Castellanos, F. X., & Milham, M. P. (2011). Differential development of human brain white matter tracts. *PLoS ONE, 6*(8). doi:10.1371/journal.pone.0023437

Inglese, M., Makani, S., Johnson, G., Cohen, B. A., Silver, J. A., Gonen, O., & Grossman, R. I. (2005). Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *Journal of Neurosurgery, 103*(2), 298-303. doi:10.3171/jns.2005.103.2.0298

Iverson, G. L., Gardner, A. J., Terry, D. P., Ponsford, J. L., Sills, A. K., Broshek, D. K., & Solomon, G. S. (2017). Predictors of clinical recovery from concussion: A systematic review. *British Journal of Sports Medicine, 51*(12), 941-948. doi:10.1136/bjsports-2017-097729

James, S. L., Theadom, A., Ellenbogen, R. G., Bannick, M. S., Montjoy-Venning, W., Lucchesi, L. R., . . . Murray, C. J. L. (2019). Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology, 18*(1), 56-87. doi:10.1016/S1474-4422(18)30415-0

Jang, S. H., Kim, S. H., Kim, O. R., Byun, W. M., Kim, M. S., Seo, J. P., & Chang, M. C. (2013). Cingulum injury in patients with diffuse axonal injury: a diffusion tensor imaging study. *Neuroscience Letters, 543*, 47-51. doi:10.1016/j.neulet.2013.02.058

Jang, S. H., & Lee, H. D. (2019). Diagnostic approach to traumatic axonal injury of the spinothalamic tract in individual patients with mild traumatic brain injury. *Diagnostics, 9*(4). doi:10.3390/diagnostics9040199

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage, 62*(2), 782-790. doi:10.1016/j.neuroimage.2011.09.015

Jeurissen, B., Leemans, A., Tournier, J. D., Jones, D. K., & Sijbers, J. (2013). Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Human Brain Mapping, 34*(11), 2747-2766. doi:10.1002/hbm.22099

Jewsbury, P. A., Bowden, S. C., & Duff, K. (2017). The Cattell–Horn–Carroll model of cognition for clinical assessment. *Journal of Psychoeducational Assessment, 35*(6), 547-567. doi:10.1177/0734282916651360

Jewsbury, P. A., Bowden, S. C., & Strauss, M. E. (2016). Integrating the switching, inhibition, and updating model of executive function with the Cattell-Horn-Carroll model. *Journal of Experimental Psychology: General, 145*(2), 220-245. doi:10.1037/xge0000119

Johnson, S. B., Blum, R. W., & Giedd, J. N. (2009). Adolescent maturity and the brain: the promise and pitfalls of neuroscience research in adolescent health policy. *Journal of Adolescent Health, 45*(3), 216-221. doi:10.1016/j.jadohealth.2009.05.016

Johnson, V. E., Stewart, W., & Smith, D. H. (2013). Axonal pathology in traumatic brain injury. *Experimental Neurology, 246*, 35-43. doi:10.1016/j.expneurol.2012.01.013

Jones, D. K. (2010). Challenges and limitations of quantifying brain connectivity in vivo with diffusion MRI. *Imaging in Medicine, 2*(3), 341-355. doi:10.2217/iim.10.21

Jones, D. K., & Cercignani, M. (2010). Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR Biomed, 23*(7), 803-820. doi:10.1002/nbm.1543

Jones, D. K., Horsfield, M. A., & Simmons, A. (1999). Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. *Magnetic Resonance in Medicine, 42*(3), 515-525.

Jones, D. K., Knosche, T. R., & Turner, R. (2013). White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *NeuroImage, 73*, 239-254. doi:10.1016/j.neuroimage.2012.06.081

Jourdan, C., Bosserelle, V., Azerad, S., Ghout, I., Bayen, E., Aegerter, P., . . . Azouvi, P. (2013). Predictive factors for 1-year outcome of a cohort of patients with severe traumatic brain injury (TBI): results from the PariS-TBI study. *Brain Injury, 27*(9), 1000-1007. doi:10.3109/02699052.2013.794971

Julien, J., Joubert, S., Ferland, M. C., Frenette, L. C., Boudreau-Duhaime, M. M., Malo-Véronneau, L., & de Guise, E. (2017). Association of traumatic brain injury and Alzheimer disease onset: A systematic review. *Annals of Physical and Rehabilitation Medicine, 60*(5), 347-356. doi:10.1016/j.rehab.2017.03.009

Kanaan, R. A., Allin, M., Picchioni, M., Barker, G. J., Daly, E., Shergill, S. S., . . . McGuire, P. K. (2012). Gender differences in white matter microstructure. *PLoS ONE, 7*(6). doi:10.1371/journal.pone.0038272

Kasahara, K., Hashimoto, K., Abo, M., & Senoo, A. (2012). Voxel- and atlas-based analysis of diffusion tensor imaging may reveal focal axonal injuries in mild traumatic brain injury - comparison with diffuse axonal injury. *Magnetic Resonance Imaging, 30*(4), 496-505. doi:10.1016/j.mri.2011.12.018

Kelley, E., Sullivan, C., Loughlin, J. K., Hutson, L., Dahdah, M. N., Long, M. K., . . . Poole, J. H. (2014). Self-awareness and neurobehavioral outcomes, 5 years or more after moderate to severe brain injury. *Journal of Head Trauma Rehabilitation, 29*(2), 147-152. doi:10.1097/HTR.0b013e31826db6b9

Kennedy, M. R., Coelho, C., Turkstra, L., Ylvisaker, M., Moore Sohlberg, M., Yorkston, K., . . . Kan, P.-F. (2008). Intervention for executive functions after traumatic brain injury: A systematic review, meta-analysis and clinical recommendations. *Neuropsychological Rehabilitation, 18*(3), 257-299. doi:10.1080/09602010701748644

Kennedy, M. R., Wozniak, J. R., Muetzel, R. L., Mueller, B. A., Chiou, H. H., Pantekoek, K., & Lim, K. O. (2009). White matter and neurocognitive changes in adults with chronic traumatic brain injury. *Journal of the International Neuropsychological Society, 15*(1), 130-136. doi: 10.1017/s1355617708090024

Khan, F., Baguley, I. J., & Cameron, I. D. (2003). 4: Rehabilitation after traumatic brain injury. *The Medical Journal of Australia, 178*(6), 290-295.

Kim, J. H., Ahn, S. H., Cho, Y. W., Kim, S. H., & Jang, S. H. (2015). The relation between injury of the spinothalamocortical tract and central pain in chronic patients with mild traumatic brain injury. *Journal of Head Trauma Rehabilitation, 30*(6), 40-46. doi: 10.1097/htr.0000000000000121

Kinyanjui, B. (2016). Traumatic Brain Injury in Kenya: A Preliminary Review of the Literature. *Sage open, 6*(1), 2158244016638392. doi:10.1177/2158244016638392

Koerte, I. K., Hufschmidt, J., Muehlmann, M., Lin, A. P., & Shenton, M. E. (2016). Advanced neuroimaging of mild traumatic brain injury. In *Translational Research in Traumatic Brain Injury* (pp. 277-297).

Konigs, M., Engenhorst, P. J., & Oosterlaan, J. (2016). Intelligence after traumatic brain injury: meta-analysis of outcomes and prognosis. *European Journal of Neurology, 23*(1), 21-29. doi:10.1111/ene.12719

Kraus, M. F., Susmaras, T., Caughlin, B. P., Walker, C. J., Sweeney, J. A., & Little, D. M. (2007). White matter integrity and cognition in chronic traumatic brain injury: A diffusion tensor imaging study. *Brain: A Journal of Neurology, 130*(10), 2508-2519. doi:10.1093/brain/awm216

Kumar, R., Gupta, R. K., Husain, M., Chaudhry, C., Srivastava, A., Saksena, S., & Rathore, R. K. S. (2009). Comparative evaluation of corpus callosum DTI metrics in acute mild and moderate traumatic brain injury: Its correlation with neuropsychometric test. *Brain Injury, 23*(7-8), 675-685. doi:10.1080/02699050903014915

Kumar, R., Husain, M., Gupta, R. K., Hasan, K. M., Haris, M., Agarwal, A. K., . . . Narayana, P. A. (2009). Serial changes in the white matter diffusion tensor imaging metrics in moderate traumatic brain injury and correlation with neuro-cognitive function. *Journal of Neurotrauma, 26*(4), 481-495. doi:10.1089=neu.2008.0461

Kumar, R., Saksena, S., Husain, M., Srivastava, A., Rathore, R. K. S., Agarwal, S., & Gupta, R. K. (2010). Serial changes in diffusion tensor imaging metrics of corpus callosum in moderate traumatic brain injury patients and their correlation with neuropsychometric tests: A 2-Year follow-up study. *Journal of Head Trauma Rehabilitation, 25*(1), 31-42. doi:10.1097/HTR.0b013e3181bff331

Kutanzi, K. R., Lumen, A., Koturbash, I., & Miousse, I. R. (2016). Pediatric Exposures to Ionizing Radiation: Carcinogenic Considerations. *International Journal of Environmental Research and Public Health, 13*(11). doi:10.3390/ijerph13111057

Lahz, S., & Bryant, R. A. (1996). Incidence of chronic pain following traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 77*(9), 889-891.

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Front Psychol, 4*, 863. doi:10.3389/fpsyg.2013.00863

Lange, R. T., Iverson, G. L., Brubacher, J. R., Madler, B., & Heran, M. K. (2012). Diffusion tensor imaging findings are not strongly associated with postconcussional disorder 2 months following mild traumatic brain injury. *The Journal of Head Trauma Rehabilitation, 27*(3), 188-198. doi: 10.1097/HTR.0b013e318217f0ad

Langhorn, L., Sorensen, J. C., & Pedersen, P. U. (2010). A critical review of the literature on early rehabilitation of patients with post-traumatic amnesia in acute care. *Journal of Clinical Nursing, 19*(21-22), 2959-2969. doi:10.1111/j.1365-2702.2010.03330.x

Langlois, J. A., Rutland-Brown, W., & Wald, M. M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *Journal of Head Trauma Rehabilitation, 21*(5), 375-378. doi:10.1097/00001199-200609000-00001

Langlois Orman, J. A., Kraus, J. F., Zaloshnja, E., & Miller, T. (2011). Epidemiology. In J. M. Silver, T. W. McAllister, & S. C. Yudofsky (Eds.), *Textbook of Traumatic Brain Injury, Second Edition*. Arlington, VA: American Psychiatric Publishing, Inc.

Le Bihan, D. (1991). Molecular diffusion nuclear magnetic resonance imaging. *Magnetic Resonance Quarterly, 7*(1), 1-30.

Le, T. H., & Gean, A. D. (2009). Neuroimaging of traumatic brain injury. *Mount Sinai Journal of Medicine, 76*(2), 145-162. doi:10.1002/msj.20102

Lee, H. D., & Jang, S. H. (2015). Injury of the corticoreticular pathway in patients with mild traumatic brain injury: A diffusion tensor tractography study. *Brain Injury, 29*(10), 1219-1222. doi: 10.3109/02699052.2015.1045028

Lepage, C., de Pierrefeu, A., Koerte, I. K., Coleman, M. J., Pasternak, O., Grant, G., . . . Bouix, S. (2018). White matter abnormalities in mild traumatic brain injury with and without post-traumatic stress disorder: a subject-specific diffusion tensor imaging study. *Brain Imaging and Behavior, 12*(3), 870-881. doi:10.1007/s11682-017-9744-5

Lew, H. L., Lin, P. H., Fuh, J. L., Wang, S. J., Clark, D. J., & Walker, W. C. (2006). Characteristics and treatment of headache after traumatic brain injury: a focused review. *American Journal of Physical Medicine & Rehabilitation, 85*(7), 619-627. doi:10.1097/01.phm.0000223235.09931.c0

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment* (5th ed.). New York, NY: Oxford University Press.

Liao, C. C., Chang, H. C., Yeh, C. C., Chou, Y. C., Chiu, W. T., & Chen, T. L. (2012). Socioeconomic deprivation and associated risk factors of traumatic brain injury in children. *Journal of Trauma and Acute Care Surgery, 73*(5), 1327-1331. doi:10.1097/TA.0b013e31826fc87f

Ling, J. M., Pena, A., Yeo, R. A., Merideth, F. L., Klimaj, S., Gasparovic, C., & Mayer, A. R. (2012). Biomarkers of increased diffusion anisotropy in semi-acute mild traumatic brain injury: A longitudinal perspective. *Brain: A Journal of Neurology, 135*(4), 1281-1292. doi: 10.1093/brain/aws073

Lipsey, M. W., & Wilson, D. B. (2001). *Practical meta-analysis*. Thousand Oaks, CA: Sage Publications.

Lipton, M. L., Gellella, E., Lo, C., Gold, T., Ardekani, B. A., Shifteh, K., . . . Branch, C. A. (2008). Multifocal white matter ultrastructural abnormalities in mild traumatic brain injury with cognitive disability: A voxel-wise analysis of diffusion tensor imaging. *Journal of Neurotrauma, 25*(11), 1335-1342. doi: 10.1089/neu.2008.0547

Little, D., Kraus, M., Joseph, J., Geary, E., Susmaras, T., Zhou, X., . . . Gorelick, P. (2010). Thalamic integrity underlies executive dysfunction in traumatic brain injury. *Neurology, 74*(7), 558-564. doi:10.1212/WNL.0b013e3181cff5d5

Lo, C., Shifteh, K., Gold, T., Bello, J. A., & Lipton, M. L. (2009). Diffusion tensor imaging abnormalities in patients with mild traumatic brain injury and neurocognitive impairment. *Journal of Computer Assisted Tomography, 33*(2), 293-297. doi: 10.1097/RCT.0b013e31817579d1

Lucas, S., Hoffman, J. M., Bell, K. R., Walker, W., & Dikmen, S. S. (2012). Characterization of headache after traumatic brain injury. *Cephalalgia, 32*(8), 600-606. doi:10.1177/0333102412445224

Lumley, T., Diehr, P., Emerson, S., & Chen, L. (2002). The importance of the normality assumption in large public health data sets. *Annual Review of Public Health, 23*, 151-169. doi:10.1146/annurev.publhealth.23.100901.140546

Maas, A. I. R., Menon, D. K., Steyerberg, E. W., Citerio, G., Lecky, F., Manley, G. T., . . . Sorgner, A. (2015). Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI)A Prospective Longitudinal Observational Study. *Neurosurgery, 76*(1), 67-80. doi:10.1227/NEU.0000000000000575

Maas, A. I. R., Murray, G. D., Roozenbeek, B., Lingsma, H. F., Butcher, I., McHugh, G. S., . . . on behalf of the International Mission on Prognosis Analysis of Clinical Trials in Traumatic Brain Injury Study, G. (2013). Advancing the care for traumatic brain injury: summary results from the IMPACT studies and perspectives on future research. *Lancet Neurology, 12*(12), 1200-1210. doi:10.1016/S1474-4422(13)70234-5

Madden, D. J., Bennett, I. J., Burzynska, A., Potter, G. G., Chen, N. K., & Song, A. W. (2012). Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochimica et Biophysica Acta - Molecular Basis of Disease, 1822*(3), 386-400. doi:10.1016/j.bbadis.2011.08.003

Marsh, N. V. (2019). Cognitive functioning following traumatic brain injury: The first 5 years. *NeuroRehabilitation, 43*(4), 377-386. doi:10.3233/NRE-182457

Marshman, L. A., Jakabek, D., Hennessy, M., Quirk, F., & Guazzo, E. P. (2013). Post-traumatic amnesia. *Journal of Clinical Neuroscience, 20*(11), 1475-1481. doi:10.1016/j.jocn.2012.11.022

Maruta, J., Suh, M., Niogi, S. N., Mukherjee, P., & Ghajar, J. (2010). Visual tracking synchronization as a metric for concussion screening. *Journal of Head Trauma Rehabilitation, 25*(4), 293-305. doi:10.1097/HTR.0b013e3181e67936

Maruta, J., Palacios, E. M., Zimmerman, R. D., Ghajar, J., & Mukherjee, P. (2016). Chronic post-concussion neurocognitive deficits. I. Relationship with white matter integrity. *Frontiers in Human Neuroscience, 10*, 35. doi: 10.3389/fnhum.2016.00035

Mathias, J. L., Beall, J. A., & Bigler, E. D. (2004). Neuropsychological and information processing deficits following mild traumatic brain injury. *Journal of the International Neuropsychological Society, 10*(2), 286-297. doi:10.1017/s1355617704102117

Mathias, J. L., Bigler, E. D., Jones, N. R., Bowden, S. C., Barrett-Woodbridge, M., Brown, G. C., & Taylor, D. J. (2004). Neuropsychological and information processing performance and its relationship to white matter changes following moderate and severe traumatic brain injury: a preliminary study. *Applied Neuropsychology, 11*(3), 134-152. doi:10.1207/s15324826an1103_2

Mathias, J. L., Dennington, V., Bowden, S. C., & Bigler, E. D. (2013). Community versus orthopaedic controls in traumatic brain injury research: how comparable are they? *Brain Injury, 27*(7-8), 887-895. doi:10.3109/02699052.2013.793398

Mathias, J. L., & Mansfield, K. M. (2005). Prospective and declarative memory problems following moderate and severe traumatic brain injury. *Brain Injury, 19*(4), 271-282. doi:10.1080/02699050400005028

Mathias, J. L., & Wheaton, P. (2007). Changes in attention and information-processing speed following severe traumatic brain injury: a meta-analytic review. *Neuropsychology, 21*(2), 212-223. doi:10.1037/0894-4105.21.2.212

Mathias, J. L., & Wheaton, P. (2015). Contribution of brain or biological reserve and cognitive or neural reserve to outcome after TBI: A meta-analysis (prior to 2015). *Neuroscience and Biobehavioral Reviews, 55*, 573-593. doi:10.1016/j.neubiorev.2015.06.001

Matsushita, M., Hosoda, K., Naitoh, Y., Yamashita, H., & Kohmura, E. (2011). Utility of diffusion tensor imaging in the acute stage of mild to moderate traumatic brain injury for detecting white matter lesions and predicting long-term cognitive function in adults. *Journal of Neurosurgery, 115*(1), 130-139. doi:10.3171/2011.2.jns101547

Mayer, A. R., Ling, J., Mannell, M. V., Gasparovic, C., Phillips, J. P., Doezema, D., . . . Yeo, R. A. (2010). A prospective diffusion tensor imaging study in mild traumatic brain injury. *Neurology, 74*(8), 643-650. doi:10.1212/WNL.0b013e3181d0ccdd

McInnes, K., Friesen, C. L., MacKenzie, D. E., Westwood, D. A., & Boe, S. G. (2017). Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. *PLoS ONE, 12*(4), e0174847. doi:10.1371/journal.pone.0174847

McKee, A. C., & Daneshvar, D. H. (2015). The neuropathology of traumatic brain injury. *Handbook of Clinical Neurology, 127*, 45-66. doi:10.1016/b978-0-444-52892-6.00004-0

Mena, J. H., Sanchez, A. I., Rubiano, A. M., Peitzman, A. B., Sperry, J. L., Gutierrez, M. I., & Puyana, J. C. (2011). Effect of the modified glasgow coma scale score criteria for mild traumatic brain injury on mortality prediction: Comparing classic and modified glasgow coma scale score model scores of 13. *Journal of Trauma - Injury, Infection and Critical Care, 71*(5), 1185-1193. doi:10.1097/TA.0b013e31823321f8

Menon, D. K., & Ercole, A. (2017). Chapter 14 - Critical care management of traumatic brain injury. *Handbook of Clinical Neurology, 140*, 239-274. doi:10.1016/B978-0-444-63600-3.00014-3

Menon, D. K., Schwab, K., Wright, D. W., & Maas, A. I. (2010). Position statement: definition of traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 91*(11), 1637-1640. doi:10.1016/j.apmr.2010.05.017

Messe, A., Caplain, S., Paradot, G., Garrigue, D., Mineo, J. F., Soto Ares, G., . . . Lehericy, S. (2010). Diffusion tensor imaging and white matter lesions at the subacute stage in mild traumatic brain injury with persistent neurobehavioral impairment. *Human Brain Mapping, 32*(6), 999-1011. doi: 10.1002/hbm.21092

Messe, A., Caplain, S., Pelegrini-Issac, M., Blancho, S., Montreuil, M., Levy, R., . . . Benali, H. (2012). Structural integrity and postconcussion syndrome in mild traumatic brain injury patients. *Brain Imaging and Behavior, 6*(2), 283-292. doi:10.1007/s11682-012-9159-2

Miles, L., Grossman, R. I., Johnson, G., Babb, J. S., Diller, L., & Inglese, M. (2008). Short-term DTI predictors of cognitive dysfunction in mild traumatic brain injury. *Brain Injury, 22*(2), 115-122. doi:10.1080/02699050801888816

Miller, G. A., & Chapman, J. P. (2001). Misunderstanding analysis of covariance. *Journal of Abnormal Psychology, 110*(1), 40-48. doi:10.1037//0021-843X.110.1.40

Mito, R., Raffelt, D., Dhollander, T., Vaughan, D. N., Tournier, J. D., Salvado, O., . . . Connelly, A. (2018). Fibre-specific white matter reductions in Alzheimer's disease and mild cognitive impairment. *Brain, 141*(3), 888-902. doi:10.1093/brain/awx355

Mittenberg, W., Tremont, G., Zielinski, R. E., Fichera, S., & Rayls, K. R. (1996). Cognitive-behavioral prevention of postconcussion syndrome. *Archives of Clinical Neuropsychology, 11*(2), 139-145. doi:10.1016/0887-6177(95)00006-2

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cognitive Psychology, 41*(1), 49-100. doi:10.1006/cogp.1999.0734

Moenninghoff, C., Kraff, O., Maderwald, S., Umutlu, L., Theysohn, J. M., Ringelstein, A., . . . Schlamann, M. (2015). Diffuse axonal injury at ultra-high field MRI. *PLoS ONE, 10*(3). doi:10.1371/journal.pone.0122329

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med, 6*(7), e1000097. doi:10.1371/journal.pmed.1000097

Montenigro, P. H., Corp, D. T., Stein, T. D., Cantu, R. C., & Stern, R. A. (2015). Chronic traumatic encephalopathy: historical origins and current perspective. *Annual Review of Clinical Psychology, 11*, 309-330. doi:10.1146/annurev-clinpsy-032814-112814

Mori, S., & Tournier, J. D. (2014). Chapter 8 - Moving Beyond DTI: High Angular Resolution Diffusion Imaging (HARDI). In *Introduction to Diffusion Tensor Imaging (Second Edition)* (pp. 65-78). San Diego: Academic Press.

Moshourab, R. A., Schafer, M., & Al-Chaer, E. D. (2015). Chronic pain in neurotrauma: Implications on spinal cord and traumatic brain injury. In F. H. Kobeissy (Ed.), *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects*. Boca Raton (FL): Taylor & Francis.

Motzkin, J. C., & Koenigs, M. R. (2015). Post-traumatic stress disorder and traumatic brain injury. *Handbook of Clinical Neurology, 128*, 633-648. doi:10.1016/b978-0-444-63521-1.00039-x

Mueller, B. A., Lim, K. O., Hemmy, L., & Camchong, J. (2015). Diffusion MRI and its role in neuropsychology. *Neuropsychology Review, 25*(3), 250-271. doi:10.1007/s11065-015-9291-z

Mukherjee, P., Berman, J. I., Chung, S. W., Hess, C. P., & Henry, R. G. (2008). Diffusion Tensor MR Imaging and Fiber Tractography: Theoretic Underpinnings. *American Journal of Neuroradiology, 29*(4), 632-641. doi:10.3174/ajnr.A1051

National, Vital, Statistics, & System. (2009). National Center for Health Statistics. Centers for Disease Control and Prevention.

Newcombe, V. (2019). Neuroimaging of TBI, moving towards ‘big data’ and precision management. *Journal of the Neurological Sciences, 405*, 39-40. doi:10.1016/j.jns.2019.10.107

Newcombe, V., Chatfield, D., Outtrim, J., Vowler, S., Manktelow, A., Cross, J., . . . Menon, D. (2011). Mapping traumatic axonal injury using diffusion tensor imaging: Correlations with functional outcome. *PLoS ONE, 6*(5). doi:10.1371/journal.pone.0019214

Newcombe, V., Das, T., & Cross, J. J. (2013). Diffusion imaging in neurological disease. *Journal of Neurology, 260*(1), 335-342. doi:10.1007/s00415-012-6769-y

Nichols, T. E., Das, S., Eickhoff, S. B., Evans, A. C., Glatard, T., Hanke, M., . . . Yeo, B. T. (2017). Best practices in data analysis and sharing in neuroimaging using MRI. *Nature Neuroscience, 20*(3), 299-303. doi:10.1038/nn.4500

Niogi, S. N., & Mukherjee, P. (2010). Diffusion tensor imaging of mild traumatic brain injury. *Journal of Head Trauma Rehabilitation, 25*(4), 241-255. doi:10.1097/HTR.0b013e3181e52c2a

Noggle, C. A. (2011). Arcuate Fasciculus. In S. Goldstein & J. A. Naglieri (Eds.), *Encyclopedia of Child Behavior and Development* (pp. 141-141). Boston, MA: Springer US.

Nordstrom, A., Edin, B. B., Lindstrom, S., & Nordstrom, P. (2013). Cognitive function and other risk factors for mild traumatic brain injury in young men: nationwide cohort study. *Bmj, 346*, f723. doi:10.1136/bmj.f723

Novack, T. A., Alderson, A. L., Bush, B. A., Meythaler, J. M., & Canupp, K. (2000). Cognitive and functional recovery at 6 and 12 months post-TBI. *Brain Injury, 14*(11), 987-996. doi:10.1080/02699050050191922

Oehr, L., & Anderson, J. (2017). Diffusion-Tensor Imaging Findings and Cognitive Function Following Hospitalized Mixed-Mechanism Mild Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *Archives of Physical Medicine and Rehabilitation, 98*(11), 2308-2319. doi:10.1016/j.apmr.2017.03.019

Orwin, R. G. (1983). A fail-safe N for effect size in meta-analysis. *Journal of Educational Statistics, 8*(2), 157-159. doi:10.2307/1164923

Osborn, A. J., Mathias, J. L., & Fairweather-Schmidt, A. K. (2014). Depression following adult, non-penetrating traumatic brain injury: a meta-analysis examining methodological variables and sample characteristics. *Neuroscience and Biobehavioral Reviews, 47*, 1-15. doi:10.1016/j.neubiorev.2014.07.007

Osborn, A. J., Mathias, J. L., & Fairweather-Schmidt, A. K. (2016). Prevalence of anxiety following adult traumatic brain injury: A meta-analysis comparing measures, samples and postinjury intervals. *Neuropsychology, 30*(2), 247-261. doi:10.1037/neu0000221

Owens, J. A., Spitz, G., Ponsford, J. L., Dymowski, A. R., & Willmott, C. (2018). An investigation of white matter integrity and attention deficits following traumatic brain injury. *Brain Injury*, 1-8. doi:10.1080/02699052.2018.1451656

Palacios, E. M., Fernandez-Espejo, D., Junque, C., Sanchez-Carrion, R., Roig, T., Tormos, J. M., . . . Vendrell, P. (2011). Diffusion tensor imaging differences relate to memory deficits in diffuse traumatic brain injury. *BMC Neurology, 11*(24). doi:10.1186/1471-2377-11-24

Palacios, E. M., Sala-Llonch, R., Junque, C., Fernandez-Espejo, D., Roig, T., Tormos, J. M., . . . Vendrell, P. (2013). Long-term declarative memory deficits in diffuse TBI: Correlations with cortical thickness, white matter integrity and hippocampal volume. *Cortex, 49*(3), 646-657. doi:10.1016/j.cortex.2012.02.011

Palacios, E. M., Sala-Llonch, R., Junque, C., Roig, T., Tormos, J. M., Bargallo, N., & Vendrell, P. (2012). White matter integrity related to functional working memory networks in traumatic brain injury. *Neurology, 78*(12), 852-860. doi:10.1212/WNL.0b013e31824c465a

Palacios, E. M., Sala-Llonch, R., Junque, C., Roig, T., Tormos, J. M., Bargallo, N., & Vendrell, P. (2013). White matter/gray matter contrast changes in chronic and diffuse traumatic brain injury. *Journal of Neurotrauma, 30*(23), 1991-1994. doi:10.1089/neu.2012.2836

Palmer, H. S., Garzon, B., Xu, J., Berntsen, E. M., Skandsen, T., & Haberg, A. K. (2010). Reduced fractional anisotropy does not change the shape of the hemodynamic response in survivors of severe traumatic brain injury. *Journal of Neurotrauma, 27*(5), 853-862. doi: 10.1089/neu.2009.1225

Pannek, K., Fripp, J., George, J., Boyd, R., Colditz, P., & Rose, S. (2017). *Automatic detection of volumes affected by subvolume movement.* . Paper presented at the ISMRM 25th Annual Meeting & Exhibition, Honolulu, HI, USA.

Pannek, K., Fripp, J., George, J. M., Fiori, S., Colditz, P. B., Boyd, R. N., & Rose, S. E. (2018). Fixel-based analysis reveals alterations is brain microstructure and macrostructure of preterm-born infants at term equivalent age. *NeuroImage: Clinical, 18*, 51-59. doi:10.1016/j.nicl.2018.01.003

Park, N. W., Moscovitch, M., & Robertson, I. H. (1999). Divided attention impairments after traumatic brain injury. *Neuropsychologia, 37*(10), 1119-1133. doi:10.1016/S0028-3932(99)00034-2

Pase, M. P., & Stough, C. (2014). An evidence-based method for examining and reporting cognitive processes in nutrition research. *Nutrition Research Reviews, 27*(2), 232-241. doi:10.1017/S0954422414000158

Pinto, P. S., Meoded, A., Poretti, A., Tekes, A., & Huisman, T. A. (2012). The unique features of traumatic brain injury in children. review of the characteristics of the pediatric skull and brain, mechanisms of trauma, patterns of injury, complications, and their imaging findings–part 2. *Journal of Neuroimaging, 22*(2), e18-41. doi:10.1111/j.1552-6569.2011.00690.x

Pinto, P. S., Poretti, A., Meoded, A., Tekes, A., & Huisman, T. A. (2012). The unique features of traumatic brain injury in children. Review of the characteristics of the pediatric skull and brain, mechanisms of trauma, patterns of injury, complications and their imaging findings--part 1. *Journal of Neuroimaging, 22*(2), e1-e17. doi:10.1111/j.1552-6569.2011.00688.x

Plassman, B. L., & Grafman, J. (2015). Traumatic brain injury and late-life dementia. *Handbook of Clinical Neurology, 128*, 711-722. doi:10.1016/b978-0-444-63521-1.00044-3

Ponsford, J. (2013). Factors contributing to outcome following traumatic brain injury. *NeuroRehabilitation, 32*(4), 803-815. doi:10.3233/NRE-130904

Ponsford, J., Bayley, M., Wiseman-Hakes, C., Togher, L., Velikonja, D., McIntyre, A., . . . Tate, R. (2014). INCOG recommendations for management of cognition following traumatic brain injury, Part II: Attention and information processing speed. *Journal of Head Trauma Rehabilitation, 29*(4), 321-337. doi:10.1097/HTR.0000000000000072

Ponsford, J., Downing, M. G., Olver, J., Ponsford, M., Acher, R., Carty, M., & Spitz, G. (2014). Longitudinal follow-up of patients with traumatic brain injury: outcome at two, five, and ten years post-injury. *Journal of Neurotrauma, 31*(1), 64-77. doi:10.1089/neu.2013.2997

Ponsford, J., & Kinsella, G. (1992). Attentional deficits following closed-head injury. *Journal of Clinical and Experimental Neuropsychology, 14*(5), 822-838. doi:10.1080/01688639208402865

Prigatano, G. P., & Borgaro, S. R. (2006). Neuropsychological testing after traumatic brain injury. *Neurology and Trauma, 2nd ed, Evans, RW (Ed), Oxford, New York*, 230-237.

Ptak, R. (2012). The frontoparietal attention network of the human brain: Action, saliency, and a priority map of the environment. *Neuroscientist, 18*(5), 502-515. doi:10.1177/1073858411409051

Rabinowitz, A. R., Hart, T., Whyte, J., & Kim, J. (2018). Neuropsychological recovery trajectories in moderate to severe traumatic brain injury: Influence of patient characteristics and diffuse axonal injury. *Journal of the International Neuropsychological Society, 24*(3), 237-246. doi:10.1017/S1355617717000996

Rabinowitz, A. R., & Levin, H. S. (2014). Cognitive sequelae of traumatic brain injury. *Psychiatric Clinics of North America, 37*(1), 1-11. doi:10.1016/j.psc.2013.11.004

Raffelt, D. A., Smith, R. E., Ridgway, G. R., Tournier, J. D., Vaughan, D. N., Rose, S., . . . Connelly, A. (2015). Connectivity-based fixel enhancement: Whole-brain statistical analysis of diffusion MRI measures in the presence of crossing fibres. *NeuroImage, 117*, 40-55. doi:10.1016/j.neuroimage.2015.05.039

Raffelt, D. A., Tournier, J. D., Fripp, J., Crozier, S., Connelly, A., & Salvado, O. (2011). Symmetric diffeomorphic registration of fibre orientation distributions. *NeuroImage, 56*(3), 1171-1180. doi:10.1016/j.neuroimage.2011.02.014

Raffelt, D. A., Tournier, J. D., Rose, S., Ridgway, G. R., Henderson, R., Crozier, S., . . . Connelly, A. (2012). Apparent Fibre Density: a novel measure for the analysis of diffusion-weighted magnetic resonance images. *NeuroImage, 59*(4), 3976-3994. doi:10.1016/j.neuroimage.2011.10.045

Raffelt, D. A., Tournier, J. D., Smith, R. E., Vaughan, D. N., Jackson, G., Ridgway, G. R., & Connelly, A. (2017). Investigating white matter fibre density and morphology using fixel-based analysis. *NeuroImage, 144*, 58-73. doi:10.1016/j.neuroimage.2016.09.029

Roberts, R. M., Mathias, J. L., & Rose, S. E. (2014). Diffusion tensor imaging (DTI) findings following pediatric non-penetrating TBI: A meta-analysis. *Developmental Neuropsychology, 39*(8), 600-637. doi:10.1080/87565641.2014.973958

Roberts, R. M., Mathias, J. L., & Rose, S. E. (2016). Relationship Between Diffusion Tensor Imaging (DTI) Findings and Cognition Following Pediatric TBI: A Meta-Analytic Review. *Developmental Neuropsychology, 41*(3), 176-200. doi:10.1080/87565641.2016.1186167

Rosen, H. J., & Viskontas, I. V. (2008) Chapter 3 Cortical neuroanatomy and cognition. *Handbook of Clinical Neurology, 88*, 41-60. doi:10.1016/S0072-9752(07)88003-1

Rosenthal, J. A. (1996). Qualitative descriptors of strength of association and effect size. *Journal of Social Service Research, 21*(4), 37-59. doi:10.1300/J079v21n04_02

Rothstein, H. R., Sutton, A. J., & Borenstein, M. (2006). *Publication bias in meta-analysis: Prevention, assessment and adjustments*: John Wiley & Sons.

Ruff, R. M., Iverson, G. L., Barth, J. T., Bush, S. S., & Broshek, D. K. (2009). Recommendations for diagnosing a mild traumatic brain injury: a National Academy of Neuropsychology education paper. *Archives of Clinical Neuropsychology, 24*(1), 3-10. doi:10.1093/arclin/acp006

Rugg-Gunn, F. J., Symms, M. R., Barker, G. J., Greenwood, R., & Duncan, J. S. (2001). Diffusion imaging shows abnormalities after blunt head trauma when conventional magnetic resonance imaging is normal. *Journal of Neurology, Neurosurgery, and Psychiatry, 70*(4), 530-533. doi:10.1136/jnnp.70.4.530

Russell, W. R., & Smith, A. (1961). Post-traumatic amnesia in closed head injury. *Archives of Neurology, 5*, 4-17.

Rutgers, D. R., Fillard, P., Paradot, G., Tadie, M., Lasjaunias, P., & Ducreux, D. (2008). Diffusion tensor imaging characteristics of the corpus callosum in mild, moderate, and severe traumatic brain injury. *AJNR American Journal of Neuroradiology, 29*(9), 1730-1735. doi:10.3174/ajnr.A1213

Saatman, K. E., Duhaime, A.-C., Bullock, R., Maas, A. I. R., Valadka, A., & Manley, G. T. (2008). Classification of Traumatic Brain Injury for Targeted Therapies. *Journal of Neurotrauma, 25*(7), 719-738. doi:10.1089/neu.2008.0586

Santiago, L. A., Oh, B. C., Dash, P. K., Holcomb, J. B., & Wade, C. E. (2012). A clinical comparison of penetrating and blunt traumatic brain injuries. *Brain Injury, 26*(2), 107-125. doi:10.3109/02699052.2011.635363

Schmahmann, J. D., & Pandya, D. N. (2006). *Fiber Pathways of the Brain*. New York, United States: Oxford University Press.

Schretlen, D. J., & Shapiro, A. M. (2003). A quantitative review of the effects of traumatic brain injury on cognitive functioning. *International Review of Psychiatry, 15*(4), 341-349. doi:10.1080/09540260310001606728

Schwab, K. A., Gudmudsson, L. S., & Lew, H. L. (2015). Long-term functional outcomes of traumatic brain injury. *Handbook of Clinical Neurology, 128*, 649-659. doi:10.1016/b978-0-444-63521-1.00040-6

Scott, G., Hellyer, P. J., Ramlackhansingh, A. F., Brooks, D. J., Matthews, P. M., & Sharp, D. J. (2015). Thalamic inflammation after brain trauma is associated with thalamo-cortical

white matter damage. *Journal of Neuroinflammation, 12*, 224. doi: 10.1186/s12974-015-0445-y

Seo, J. P., Kim, O. L., Kim, S. H., Chang, M. C., Kim, M. S., Son, S. M., & Jang, S. H. (2012). Neural injury of uncinate fasciculus in patients with diffuse axonal injury. *NeuroRehabilitation, 30*(4), 323-328. doi:10.3233/nre-2012-0762

Shenton, M. E., Hamoda, H. M., Schneiderman, J. S., Bouix, S., Pasternak, O., Rathi, Y., . . . Zafonte, R. (2012). A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging and Behavior, 6*(2), 137-192. doi:10.1007/s11682-012-9156-5

Sherer, M., Bergloff, P., Levin, E., High Jr, W. M., Oden, K. E., & Nick, T. G. (1998). Impaired awareness and employment outcome after traumatic brain injury. *Journal of Head Trauma Rehabilitation, 13*(5), 52-61. doi:10.1097/00001199-199810000-00007

Sherer, M., Sander, A. M., Maestas, K. L., Pastorek, N. J., Nick, T. G., & Li, J. (2015). Accuracy of self-reported length of coma and posttraumatic amnesia in persons with medically verified traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 96*(4), 652-658. doi:10.1016/j.apmr.2014.10.024

Shiramizu, H., Masuko, A., Ishizaka, H., Shibata, M., Atsumi, H., Imai, M., . . . Matsumae, M. (2008). Mechanism of injury to the corpus callosum, with particular reference to the anatomical relationship between site of injury and adjacent brain structures. *Neurologia Medico-Chirurgica, 48*(1), 1-6. doi:10.2176/nmc.48.1

Shrout, P. E., & Rodgers, J. L. (2018) Psychology, Science, and Knowledge Construction: Broadening Perspectives from the Replication Crisis. *Annual Review of Psychology, 69*, 487-510. doi:10.1146/annurev-psych-122216-011845.Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., . . . Rostrup, E. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: A longitudinal study. *Brain: A Journal of Neurology, 131*(2), 559-572. doi:10.1093/brain/awm294

Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., . . . Rostrup, E. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: A longitudinal study. *Brain: A Journal of Neurology, 131*(2), 559-572. doi: 10.1093/brain/awm294

Singh, K., Morse, A. M., Tkachenko, N., & Kothare, S. V. (2016). Sleep disorders associated with traumatic brain injury - A review. *Pediatric Neurology, 60*, 30-36. doi:10.1016/j.pediatrneurol.2016.02.013

Singh, M., Jeong, J., Hwang, D., Sungkarat, W., & Gruen, P. (2010). Novel diffusion tensor imaging methodology to detect and quantify injured regions and affected brain pathways in traumatic brain injury. *Magnetic Resonance Imaging, 28*(1), 22-40. doi:10.1016/j.mri.2009.05.049

Smajic, J. (2019). Neurological damage in trauma. In F. F. Ökten (Ed.), *Trauma, Anesthesia and Intensive Care book of proceedings and abstracts* (pp. 61-69). İzmir, Turkey.

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., . . . Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage, 31*(4), 1487-1505. doi:10.1016/j.neuroimage.2006.02.024

Smits, M., Houston, G. C., Dippel, D. W., Wielopolski, P. A., Vernooij, M. W., Koudstaal, P. J., . . . van der Lugt, A. (2011). Microstructural brain injury in post-concussion syndrome after minor head injury. *Neuroradiology, 53*(8), 553-563. doi: 10.1007/s00234-010-0774-6

Snell, D. L., Macleod, A. S., & Anderson, T. (2016). Post-concussion syndrome after a mild traumatic brain injury: A minefield for clinical practice. *Journal of behavioral and brain science, 6*(06), 227. doi:10.4236/jbbs.2016.66023

Soble, J. R., Critchfield, E. A., & O'Rourke, J. J. F. (2017). Neuropsychological Evaluation in Traumatic Brain Injury. *Physical Medicine and Rehabilitation Clinics of North America, 28*(2), 339-350. doi:10.1016/j.pmr.2016.12.009

Spreen, O., & Straus, E. (1998). *Compendium of neuropsychological tests*. New York: Oxford University Press.

Starkstein, S. E., & Pahissa, J. (2014). Apathy following traumatic brain injury. *Psychiatric Clinics of North America, 37*(1), 103-112. doi:10.1016/j.psc.2013.10.002

Stocchetti, N., & Zanier, E. R. (2016). Chronic impact of traumatic brain injury on outcome and quality of life: a narrative review. *Critical Care, 20*. doi:10.1186/s13054-016-1318-1

Strauss, S., Hulkower, M., Gulko, E., Zampolin, R. L., Gutman, D., Chitkara, M., . . . Lipton, M. L. (2015). Current Clinical Applications and Future Potential of Diffusion Tensor Imaging in Traumatic Brain Injury. *Topics in Magnetic Resonance Imaging, 24*(6), 353-362. doi:10.1097/rmr.0000000000000071

Sullivan, E. V., & Pfefferbaum, A. (2006). Diffusion tensor imaging and aging. *Neuroscience and Biobehavioral Reviews, 30*(6), 749-761. doi:10.1016/j.neubiorev.2006.06.002

Suri, A. K., & Lipton, M. L. (2018). Chapter 21 - Neuroimaging of brain trauma in sports. *Handbook of Clinical Neurology, 158*, 205-216. doi:10.1016/B978-0-444-63954-7.00021-5

Sussman, E. S., Pendharkar, A. V., Ho, A. L., & Ghajar, J. (2018). Chapter 3 - Mild traumatic brain injury and concussion: terminology and classification. *Handbook of Clinical Neurology, 158*, 21-24. doi:10.1016/B978-0-444-63954-7.00003-3.

Szczupak, M., Hoffer, M. E., Murphy, S., & Balaban, C. D. (2016). Posttraumatic dizziness and vertigo. *Handbook of Clinical Neurology, 137*, 295-300. doi:10.1016/b978-0-444-63437-5.00021-2

Tagliaferri, F., Compagnone, C., Korsic, M., Servadei, F., & Kraus, J. (2006). A systematic review of brain injury epidemiology in Europe. *Acta Neurochirurgica, 148*(3), 255-268; discussion 268. doi:10.1007/s00701-005-0651-y

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet, 2*(7872), 81-84.

Tollard, E., Galanaud, D., Perlbarg, V., Sanchez-Pena, P., Le Fur, Y., Abdennour, L., . . . Puybasset, L. (2009). Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: Preliminary results. *Critical Care Medicine, 37*(4), 1448-1455. doi: 10.1097/CCM.0b013e31819cf050

Tomarken, A. J., & Serlin, R. C. (1986). Comparison of anova Alternatives Under Variance Heterogeneity and Specific Noncentrality Structures. *Psychological Bulletin, 99*(1), 90-99. doi:10.1037/0033-2909.99.1.90

Toothaker, L. E. (1993). *Multiple comparison procedures*. London: Sage Publications.

Tournier, J. D., Calamante, F., & Connelly, A. (2007). Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained super-resolved spherical deconvolution. *NeuroImage, 35*(4), 1459-1472. doi:10.1016/j.neuroimage.2007.02.016

Tournier, J. D., Calamante, F., & Connelly, A. (2012). MRtrix: Diffusion tractography in crossing fiber regions. *International Journal of Imaging Systems and Technology, 22*(1), 53-66. doi:10.1002/ima.22005

Tournier, J. D., Calamante, F., Gadian, D. G., & Connelly, A. (2004). Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *NeuroImage, 23*(3), 1176-1185. doi:10.1016/j.neuroimage.2004.07.037

Tournier, J. D., Smith, R. E., Raffelt, D. A., Tabbara, R., Dhollander, T., Pietsch, M., . . . Connelly, A. (2019). MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. *bioRxiv*, 551739. doi:10.1101/551739

Trevena, L., & Cameron, I. (2011). Traumatic brain injury - long term care of patients in general practice. *Australian Family Physician, 40*(12), 956-961.

Tukey, J. W. (1977). *Exploratory data analysis* (Vol. 2). Boston, Massachusetts: Addison-Wesley.

Ubukata, S., Ueda, K., Sugihara, G., Yassin, W., Aso, T., Fukuyama, H., & Murai, T. (2015a). Corpus Callosum Pathology as a Potential Surrogate Marker of Cognitive Impairment in Diffuse Axonal Injury. *Journal of Neuropsychiatry and Clinical Neurosciences, 28*(2), 97-103. doi:10.1176/appi.neuropsych.15070159

Ubukata, S., Ueda, K., Sugihara, G., Yassin, W., Aso, T., Fukuyama, H., & Murai, T. (2015b). Corpus Callosum Pathology as a Potential Surrogate Marker of Cognitive Impairment in Diffuse Axonal Injury. *The Journal of Neuropsychiatry and Clinical Neurosciences, 28*(2), 97-103. doi:10.1176/appi.neuropsych.15070159

Uchino, A., Takase, Y., Nomiyama, K., Egashira, R., & Kudo, S. (2006). Acquired lesions of the corpus callosum: MR imaging. *European Radiology, 16*(4), 905-914. doi:10.1007/s00330-005-0037-9

Van Hecke, W., & Emsell, L. (2016). Strategies and Challenges in DTI Analysis. In *Diffusion Tensor Imaging* (pp. 153-173): Springer.

Vandenbroucke, J. P., von Elm, E., Altman, D. G., Gotzsche, P. C., Mulrow, C. D., Pocock, S. J., . . . Egger, M. (2007). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology, 18*(6), 805-835. doi:10.1097/EDE.0b013e3181577511

Vanderploeg, R. D., Belanger, H. G., & Curtiss, G. (2009). Mild traumatic brain injury and posttraumatic stress disorder and their associations with health symptoms. *Archives of Physical Medicine and Rehabilitation, 90*(7), 1084-1093. doi:10.1016/j.apmr.2009.01.023

Vanderploeg, R. D., Curtiss, G., Luis, C. A., & Salazar, A. M. (2007). Long-term morbidities following self-reported mild traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology, 29*(6), 585-598. doi:10.1080/13803390600826587

Vaughan, D. N., Raffelt, D., Curwood, E., Tsai, M. H., Tournier, J. D., Connelly, A., & Jackson, G. D. (2017). Tract-specific atrophy in focal epilepsy: Disease, genetics, or seizures? *Annals of Neurology, 81*(2), 240-250. doi:10.1002/ana.24848

Veeramuthu, V., Narayanan, V., Kuo, T. L., Delano-Wood, L., Chinna, K., Bondi, M. W., . . . Ramli, N. (2015). Diffusion tensor imaging parameters in mild traumatic brain injury and Its correlation with early neuropsychological impairment: A longitudinal study. *Journal of Neurotrauma, 32*(19), 1497-1509. doi: 10.1089/neu.2014.3750

Voelbel, G. T., Genova, H. M., Chiaravalotti, N. D., & Hoptman, M. J. (2012). Diffusion tensor imaging of traumatic brain injury review: Implications for neurorehabilitation. *NeuroRehabilitation, 31*(3), 281-293. doi:10.3233/NRE-2012-0796

Voets, N. L., Bartsch, A., & Plaha, P. (2017). Brain white matter fibre tracts: a review of functional neuro-oncological relevance. *Journal of Neurology, Neurosurgery, and Psychiatry, 88*(12), 1017-1025. doi:10.1136/jnnp-2017-316170

Vos, S. B., Jones, D. K., Viergever, M. A., & Leemans, A. (2011). Partial volume effect as a hidden covariate in DTI analyses. *NeuroImage, 55*(4), 1566-1576. doi:10.1016/j.neuroimage.2011.01.048

Wada, T., Asano, Y., & Shinoda, J. (2012). Decreased fractional anisotropy evaluated using tract-based spatial statistics and correlated with cognitive dysfunction in patients with mild traumatic brain injury in the chronic stage. *AJNR American Journal of Neuroradiology, 33*(11), 2117-2122. doi:10.3174/ajnr.A3141

Waljas, M., Lange, R. T., Hakulinen, U., Huhtala, H., Dastidar, P., Hartikainen, K., . . . Iverson, G. L. (2014). Biopsychosocial outcome after uncomplicated mild traumatic brain injury. *Journal of Neurotrauma, 31*(1), 108-124. doi: 10.1089/neu.2013.2941

Wallace, E. J., Mathias, J. L., & Ward, L. (2018a). Diffusion tensor imaging changes following mild, moderate and severe adult traumatic brain injury: a meta-analysis. *Brain Imaging and Behavior, 12*(6), 1607-1621. doi:10.1007/s11682-018-9823-2

Wallace, E. J., Mathias, J. L., & Ward, L. (2018b). The relationship between diffusion tensor imaging findings and cognitive outcomes following adult traumatic brain injury: A meta-analysis. *Neuroscience and Biobehavioral Reviews, 92*, 93-103. doi:10.1016/j.neubiorev.2018.05.023

Wammes, J. D., Good, T. J., & Fernandes, M. A. (2017). Autobiographical and episodic memory deficits in mild traumatic brain injury. *Brain and Cognition, 111*, 112-126. doi:10.1016/j.bandc.2016.11.004

Wang, Z., Wu, W., Liu, Y., Wang, T., Chen, X., Zhang, J., . . . Chen, R. (2016). Altered cerebellar white matter integrity in patients with mild traumatic brain injury in the acute stage. *PLoS ONE, 11*(3). doi:10.1371/journal.pone.0151489

Wardlaw, J. M., Brindle, W., Casado, A. M., Shuler, K., Henderson, M., Thomas, B., . . . Hernandez, M. C. V. (2012). A systematic review of the utility of 1.5 versus 3 Tesla magnetic resonance brain imaging in clinical practice and research. *European Radiology, 22*(11), 2295-2303. doi:10.1007/s00330-012-2500-8

Ware, J. B., Hart, T., Whyte, J., Rabinowitz, A. R., Detre, J. A., & Kim, J. (2017). Inter-Subject Variability of Axonal Injury in Diffuse Traumatic Brain Injury. *Journal of Neurotrauma*. doi:10.1089/neu.2016.4817

Wechsler, D. (1997). *Wechsler Memory Scale* (Third ed.). San Antonio: Psychological Corporation.

Weil, Z. M., Corrigan, J. D., & Karelina, K. (2016). Alcohol abuse after traumatic brain injury: Experimental and clinical evidence. *Neuroscience and Biobehavioral Reviews, 62*, 89-99. doi:10.1016/j.neubiorev.2016.01.005

Welch, B. L. (1951). On the comparison of several mean values: An alternative approach. *Biometrika, 38*, 330-336. doi:10.2307/2332579

Wheble, J. L. C., & Menon, D. K. (2016). TBI—The most complex disease in the most complex organ: The CENTER-TBI trial—A commentary. *Journal of the Royal Army Medical Corps, 162*(2), 87-89. doi:10.1136/jramc-2015-000472

Whitaker-Lea, W. A., & Valadka, A. B. (2017). Acute Management of Moderate-Severe Traumatic Brain Injury. *Physical Medicine and Rehabilitation Clinics of North America, 28*(2), 227-243. doi:10.1016/j.pmr.2016.12.002

WHO. (2006). *Neurological Disorders: Public Health Challenges*. Geneva: Wold Health Organization.

Wilde, E. A., Bouix, S., Tate, D. F., Lin, A. P., Newsome, M. R., Taylor, B. A., . . . York, G. (2015). Advanced neuroimaging applied to veterans and service personnel with traumatic brain injury: state of the art and potential benefits. *Brain Imaging and Behavior, 9*(3), 367-402. doi:10.1007/s11682-015-9444-y

Wilde, E. A., Hunter, J. V., & Bigler, E. D. (2014). Neuroimaging in traumatic brain injury. In W. B. Barr (Ed.), *Handbook on the Neuropsychology of Traumatic Brain Injury* (pp. 111-136). New York, NY, USA: Springer.

Wilde, E. A., Ware, A. L., Li, X., Wu, T. C., McCauley, S. R., Barnes, A., . . . Levin, H. (2019). Orthopedic Injured versus Uninjured Comparison Groups for Neuroimaging Research in Mild Traumatic Brain Injury. *Journal of Neurotrauma, 36*(2), 239-249. doi:10.1089/neu.2017.5513

Wilde, E. A., Li, X., Hunter, J. V. M., Narayana, P. A., Hasan, K. M., Biekman, B., . . . Levin, H. S. (2016). Loss of consciousness is related to white matter injury in mild traumatic brain injury. *Journal of Neurotrauma, 33*(22) 2000-2010. doi: 10.1089/neu.2015.4212

Williams, G., Morris, M. E., Schache, A., & McCrory, P. R. (2009). Incidence of gait abnormalities after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 90*(4), 587-593. doi:10.1016/j.apmr.2008.10.013

Williams, W. M., Rapport, L. J., Millis, S. R., & Hanks, R. A. (2014). Psychosocial outcomes after traumatic brain injury: life satisfaction, community integration, and distress. *Rehabilitation Psychology, 59*(3), 298-305. doi:10.1037/a0037164

Wise, E. K., Mathews-Dalton, C., Dikmen, S. S., Temkin, N., Machamer, J., Bell, K., & Powell, J. M. (2010). Impact of traumatic brain injury on participation in leisure activities. *Archives of Physical Medicine and Rehabilitation, 91*(9), 1357-1362. doi:10.1016/j.apmr.2010.06.009

Xiong, K. L., Zhu, Y. S., Zhang, L., Yin, Z. Y., Zhang, J. N., Qiu, M. G., & Zhang, W. G. (2014). White matter integrity and cognition in mild traumatic brain injury following motor vehicle accident. *Brain Research, 1591*, 86-92. doi:10.1016/j.brainres.2014.10.030

Xu, J., Rasmussen, I. A., Lagopoulos, J., & Haberg, A. (2007). Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. *Journal of Neurotrauma, 24*(5), 753-765. doi: 10.1089/neu.2006.0208

Yao, S., Song, J., Gao, L., Yan, Y., Huang, C., Ding, H., . . . Xu, G. (2015). Thalamocortical sensorimotor circuit damage associated with disorders of consciousness for diffuse axonal injury patients. *Journal of the Neurological Sciences, 356*(1-2), 168-174. doi: 10.1016/j.jns.2015.06.044

Yue, J. K., Vassar, M. J., Lingsma, H. F., Cooper, S. R., Okonkwo, D. O., Valadka, A. B., . . . Sinha, T. K. (2013). Transforming research and clinical knowledge in traumatic brain injury pilot: Multicenter implementation of the common data elements for traumatic brain injury. *Journal of Neurotrauma, 30*(22), 1831-1844. doi:10.1089/neu.2013.2970

Yuh, E. L., Cooper, S. R., Mukherjee, P., Yue, J. K., Lingsma, H. F., Gordon, W. A., . . . Track-Tbi, I. (2014). Diffusion Tensor Imaging for Outcome Prediction in Mild Traumatic Brain Injury: A TRACK-TBI Study. *Journal of Neurotrauma, 31*(17), 1457-1477. doi:10.1089/neu.2013.3171

Zhang, K., Johnson, B., Pennell, D., Ray, W., Sebastianelli, W., & Slobounov, S. (2010). Are functional deficits in concussed individuals consistent with white matter structural alterations: Combined FMRI & DTI study. *Experimental Brain Research, 204*(1), 57-70. doi: 10.1007/s00221-010-2294-3

Zhu, G. W., Wang, F., & Liu, W. G. (2009). Classification and prediction of outcome in traumatic brain injury based on computed tomographic imaging. *Journal of International Medical Research, 37*(4), 983-995. doi:10.1177/147323000903700402

Zhu, J., Ling, J., & Ding, N. (2019). Association between Diffusion Tensor Imaging Findings and Cognitive Outcomes Following Mild Traumatic Brain Injury: A PRISMA-Compliant Meta-Analysis. *ACS Chem Neurosci, 10*(12), 4864-4869. doi:10.1021/acschemneuro.9b00584

Zhu, Y., Li, Z., Bai, L., Tao, Y., Sun, C., Li, M., . . . Zhang, M. (2014). Loss of microstructural integrity in the limbic-subcortical networks for acute symptomatic traumatic brain injury. *BioMed Research International, 2014*. doi:10.1155/2014/548392