MINNA WÄLJAS

Biopsychosocial Outcome After Mild Traumatic Brain Injury

ACADEMIC DISSERTATION
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To my family

ABSTRACT

Mild traumatic brain injury (MTBI) is caused by either direct or indirect biomechanical force to the head. In most cases, the disturbance of brain function from MTBI appears to be related to dysfunction of brain metabolism rather than to structural damage. Yet, MTBI falls on a broad spectrum, from very mild neurometabolic changes in the brain with rapid recovery to permanent structural brain damage. Many patients with MTBI experience subjective deficits in cognitive functioning despite the lack of macroscopic abnormalities on conventional neuroimaging (magnetic resonance imaging, MRI; computed tomography, CT). Despite extensive research, it is still unclear why some individuals recover faster than others after this injury. Poor long-term outcome from MTBI is not well understood and remains controversial. The aim of this thesis was to examine biopsychosocial outcome from adult MTBI.

Participants were 129 MTBI patients consecutively admitted to the Emergency Department of Tampere University Hospital, Finland. At three weeks post injury, magnetic resonance imaging (MRI) including diffusion tensor imaging (DTI) of the whole brain was undertaken. An extensive neuropsychological examination was conducted for each patient one month and one year following MTBI. Two separate healthy control groups were also recruited from the community for the study: (a) a neuroimaging control group (n = 30), and (b) a neuropsychological control group (n = 36).

In sum, this study showed that most patients with MTBI recover fully. The vast majority of this cohort returned to work within two months (91.7%). Four weeks following injury, patients with MTBI reported more post-concussion symptoms than healthy controls but did not perform more poorly than healthy controls on cognitive testing. Return to work during the first four weeks following MTBI was strongly predicted by a combination of age, multiple bodily injuries, intracranial abnormality on day-of-injury CT, and fatigue ratings. Classic injury severity variables (i.e., duration of unconsciousness, Glascow Coma Scale scores, and duration of post traumatic amnesia) were not associated with length of time to return to work. Patients with MTBI were significantly more likely to show multifocal areas of diminished white matter on DTI compared to control subjects. However, white matter changes were not associated

with functional outcome. MTBI patients with multifocal white matter changes did not show evidence of worse symptoms, cognitive impairment, or slower return to work compared to MTBI patients with broadly normal white matter.

TIIVISTELMÄ

Lievä traumaattinen aivovamma on monimutkainen patofysiologinen prosessi, joka vaikuttaa aivoihin. Lievä aivovamma on seurausta päähan kohdistuneesta suorasta tai välillisestä biomekaanisesta voimasta. Useimmissa tapauksissa lievään aivovammaan liittyy toimintahäiriö aivojen aineenvaihdunnassa, mutta ei rakenteellisia vaurioita aivoissa. Lievä traumaattinen aivovamma on kuitenkin laajakirjoinen vamma, jonka seuraukset voivat vaihdella lievästä aivojen aineenvaihdunnan muutoksesta pysyviin rakenteellisiin aivovaurioihin. Kokonaistilanteen arviointia komplisoi se että potilaiden kokemilla subjektiivisilla oireilla sekä neuropsykologisilla tutkimuslöydöksillä on heikko korrelaatio perinteisten kuvantamislöydösten (magneettikuvaus, MRI; tietokonekerroskuvaus, CT) kanssa. Monet lievän aivovamman saaneet potilaat kokevat oireita vaikka aivokuvantamisen perusteella ei voida todeta makroskooppisia poikkeavuuksia aivoissa. Laajasta tutkimustyöstä huolimatta pitkäkestoista oireilua lievän aivovamman jälkeen ei vielä ymmärretä hyvin. On edelleenkin kiistanalaista miksi joillekin potilaille kehittyy hankala oirekirjo lievänäkin pidetyn aivovamman jälkeen. Opinnäytetyön tavoitteena oli arvioida lievän aivovamman jälkeiseen oirekuvaan liittyviä biopsykososiaalisia tekijöitä.

Tutkimukseen rekrytoitiin Tampereen yliopistollisen sairaalan ensiavusta perättäinen sarja lievän aivovamman saaneita potilaita. Tutkimusaineisto koostui 129 lievän aivovamman saaneesta potilaasta. Lisäksi rekrytoitiin kaksi erillistä verrokkiryhmää (a) aivokuvantamisen kontrolliryhmä (n=30), ja (b) neuropsykologisen tutkimuksen kontrolliryhmä (n=36). Kaikille potilaille tehtiin välittömästi trauman toteamisen jälkeen monileike CT-kuvaus ja n. 3 viikkoa trauman jälkeen MRI-kuvaus (sisältäen diffuusiotensorikuvauksen). Potilaille tehtiin laaja neuropsykologinen tutkimus yhden kuukauden ja yhden vuoden kuluttua vammasta.

Tutkimuksen perusteella suurin osa lievän aivovamman saaneista potilaista toipui täysin. Valtaosa kohortin potilaista palasi töihin kahden kuukauden kuluessa vammasta (91,7%). Klassiset vammamuutujat (tajuttomuuden kesto, Glascow Coma Scale pistemäärä sekä posttraumaattisen muistiaukon pituus) eivät ennustaneet sairasloman pituutta. Sen sijaan sairasloman pituutta ennustivat voimakkaasti ikä, liitännäisvammat, kallonsisäinen poikkeavuus CT-kuvauksessa ja subjektiivinen väsyvyyden arvio.

Lievän aivovamman saaneet potilaat raportoivat enemmän aivovamman jälkeisiä oireita kuin terveet verrokit, mutta eivät kuitenkaan suoriutuneet verrokkeja heikommin kognitiivisissa testeissä.

Diffuusiotensorikuvauksella todettiin lievän aivovamman saaneilla potilailla merkitsevästi enemmän laaja-alaisia muutoksia valkeassa aivoaineessa kontrolliryhmään verrattuna. Muutokset valkeassa aivoaineessa eivät kuitenkaan olleet yhteydessä toimintakykyyn: potilailla, joilla todettiin laaja-alaisia valkean aivoaineen muutoksia lievän aivovamman seurauksena, ei todettu enemmän oireita, kognitiivisia häiriöitä tai työhönpaluun hidastumista terveisiin kontrollihenkilöihin verrattuna.

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LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original articles, referred to in the text by their Roman numerals (I–IV). In addition, some previously unpublished results are included in the thesis.

I Wäljas, M., Iverson, G.L., Hartikainen, K., Liimatainen, S., Dastidar, P., Soimakallio, S., Jehkonen, M. & Öhman, J. (2012). *Reliability, Validity, and Clinical Usefulness of the BNI Fatigue Scale in Mild Traumatic Brain Injury*. *Brain Injury*;26(7-8):972-978.

II Wäljas, M., Iverson, G.L., Lange, R.T., Liimatainen, S., Hartikainen, K., Dastidar, P., Soimakallio, S. & Öhman, J. (2014). *Return to Work Following Mild Traumatic Brain Injury*. Journal of Head Trauma Rehabilitation, Nov 20. [Epub ahead of print].

III Wäljas, M., Lange, R.T., Hakulinen, U., Huhtala, H., Hartikainen, K., Dastidar, P., Soimakallio, S., Öhman, J. & Iverson, G.L. (2014). *Biopsychosocial Outcome After Uncomplicated Mild Traumatic Brain Injury*. Journal of Neurotrauma;31(1):108-124.

IV Wäljas, M., Lange, R.T., Dastidar, P., Huhtala, H., Liimatainen, S., Hartikainen, K., & Öhman, J., Iverson, G.L. (2014). *A Prospective Biopsychosocial Study of the Persistent Post-Concussion Symptoms Following Mild Traumatic Brain Injury*. Journal of Neurotrauma. Submitted.

LIST OF ABBREVIATIONS

ACR	Anterior corona radiata
ADC	Apparent diffusion coefficient
AUDIT	Alcohol Use Identification Test
BDI-II	Beck Depression Inventory Second Edition
BNI-FS	Barrow Neurological Institute Fatigue Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
CC	Corpus callosum
CNS	Central nervous system
CST	Cortical-spinal tract
CT	Computed tomography
DAI	Diffuse axonal injury
DTI	Diffusion tensor imaging
EEG	Electroencephalography
EQ-5D	EuroQuol Five Dimensions
FA	Fractional Anisotopy
FIS	Fatigue Impact Scale
FLAIR	Fluid attenuation inversion recovery
FMRI	Functional magnetic resonance imaging
FSE	Fast spin echo
FWSTMT	Four Word Short Term Memory Test
GCS	Glasgow Coma Scale
GRE	Gradient echo
IC	Internal capsule
LOC	Loss of consciousness
MRI	Magnetic resonance imaging
MTBI	Mild traumatic brain injury
PCA	Principal components analysis
PCD	Postconcussional disorder

PCS	Postconcussional syndrome
PCR	Posterior corona radiate
PPCS	Persistent post-concussion syndrome
PTA	Posttraumatic amnesia
RAVLT	Rey Auditory Verbal Learning Test
ROCFT	Rey Osterrieth Complex Figure Test
ROI	Region of interest
SE	Spin echo
SD	Standard deviation
T	Tesla
TA	Texture analysis
TAUH	Tampere University Hospital
TBI	Traumatic brain injury
TBSS	Tract based spatial statistics
TE	Echo time
TMT	Trail Making Test
TR	Repetition time
TSE	Turbo spin echo/Fast spin echo
T1	Longitudinal relaxation time
T2	Transverse relaxation time
T2*	Effective transverse relaxation time
VAS	Visual analogue scale
VBA	Voxel-based analysis
WAIS-III	Wechsler Adult Intelligence Scale Third Edition
WBA	Whole brain analysis
WHO	World Health Organization
WM	White matter
3D	Three-dimensional

1 INTRODUCTION

Mild traumatic brain injury (MTBI) is one of the most common neurologic disorders, one of the most common neurological conditions seen in accident and emergency departments, and a substantial public health problem. It is estimated that direct and indirect costs of TBI are approximately $60 billion per year in the United States (Powell et al., 1996; Marr & Coronado, 2002; Langlois et al., 2004). In Western countries a head trauma occurs approximately every 15 seconds (Signoretti et al., 2010). MTBI accounts for 95% of all head injuries. Children aged 0–4 years, adolescents aged 15–19 years, and adults aged 65 years and older are most likely to sustain a TBI (Centers for Disease Control and Prevention, 2003). Sports-related concussions occur with the greatest frequency in the pediatric and young adult age ranges (Giza and DiFiori, 2011). The general incidence of TBI in industrialized countries is frequently stated to be 200 per 100,000 population per annum (Bruns & Hauser, 2003). Recently, it has been estimated that the average crude annual TBI incidence rate in Finland is 137/100,000 (Numminen, 2011). However, most of the mild brain injuries are not treated at hospitals and therefore results based on hospital case record may greatly underestimate the real incidence of MTBI. It has been estimated that as many as 25 percent of all TBIs have no contact with the health care system at any level following injury (McCrea, 2008, p. 3) and as many as 75% of all MTBI cases are not hospitalized (Cassidy et al., 2004).

Slow or incomplete recovery from MTBI is poorly understood and there is still controversy in the literature whether a single episode of MTBI can result in long-term residual effects. Most patients appear to recover fully within days, weeks, or months after injury (Ruff et al., 2009). MTBI can cause wide range of changes in cognitive, somatic, and affective functioning. These impairments are most often subtle, temporary in nature, and resolve by 1–3 months (Holm et al., 2005; Iverson, 2005). It is widely acknowledged that a subgroup of patients who have suffered MTBI may have poorer clinical outcome than might be predicted on the basis of initial injury characteristics or conventional neuroradiological imaging techniques. The vast majority of the MTBI patients do not have visible impairments in brain macrostructure after a head injury. However, studies using advanced neuroimaging, such as diffusion tensor imaging, have shown that there may be subtle abnormalities in brain areas which appear normal on conventional imaging and this compromised microstructural white matter integrity

may be associated with impaired neurocognitive functioning after TBI (Garnett et al., 2000). Conventional neuroimaging methods underestimate the extent of white matter damage after TBI (Arfanakis et al., 2002) and widespread white matter abnormalities may persist in some patients classified as having sustained a MTBI (Kinnunen et al., 2011). Further, recent magnetic resonance spectroscopy neuroimaging studies suggest that abnormalities in brain function after concussion exist beyond the point of observed clinical recovery of 7 to 10 days (Vagnozzi et al., 2008; Prichep et al., 2012). Without an accurate and reliable biomarker of injury, it has been difficult for clinicians and researchers to properly define MTBI (Bigler & Bazarian, 2010). This has fueled efforts to find objective physiological correlates of persistent cognitive and neuropsychiatric symptoms by using novel neuroimaging techniques.

Limited understanding of white matter pathology in MTBI is primarily due to the low sensitivity of conventional neuroimaging to identify pathological changes in MTBI (Zappalà et al., 2012). Advances in neuroimaging that include electroencephalography (EEG), functional magnetic resonance imaging (fMRI), resting-state functional connectivity, magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) offer promise in aiding research into better understanding the complexities and nuances of MTBI (Slobounov et al., 2012). Recently, DTI has been used to investigate white matter abnormalities noninvasively in vivo and many studies have demonstrated the utility of DTI in identifying white matter changes secondary to TBI (Arfanakis et al., 2002; Belanger et al., 2007; Hou et al., 2007; Kraus et al., 2007; Mao et al., 2007; Wilde et al., 2008). Diffusion tensor imaging findings hold considerable promise as a potential magnetic resonance imaging (MRI) biomarker in MTBI patients with otherwise normal imaging and may assist in classification and tracking of MTBI and its effects (Bigler & Bazarian, 2010; Mayer et al., 2010: Zappalà et al., 2012). However, little is known about whether the TBI-related diffusion changes correlate with long-term recovery and clinical outcome.

The purpose of this study was to examine biopsychosocial outcome from adult MTBI. In part, the present thesis was designed to address significant gaps in the literature relating DTI and functional outcome following MTBI. It is the first study to examine the relation between DTI findings and multiple outcome measures (i.e., post-concussion symptoms, cognition, mental health, and return to work) in a large sample of patients with MTBIs.

2 REVIEW OF THE LITERATURE

2.1 Mild Traumatic Brain Injury

Leading causes of civilian MTBI include falls, motor vehicle accidents (MVA), sports, and assaults (Bazarian et al., 2005). In war zones, blasts are an important cause of MTBI among military personnel (Warden, 2006). Despite decades of research, there is no uniformly accepted definition of MTBI. Due to the lack of a universally agreed definition, MTBI remains challenging to diagnose (Ruff et al., 2009). Heterogenous diagnostic criteria weaken both clinical decision-making and also have a negative impact on research on MTBI. Classification of MTBI is based on initial injury characteristics, namely duration of unconsciousness (LOC), Glasgow Coma Scale (GCS) score, and duration of posttraumatic amnesia (PTA) (Rees, 2003; Iverson et al., 2012). Terms such as mild head injury, minor head injury, mild closed head injury, mild head trauma, concussion, and mild brain injury are sometimes used interchangeably (Iverson, 2005; Anderson et al., 2006). The term "concussion" is used commonly in sports medicine, whereas the term mild traumatic brain injury is used more commonly in general medical contexts (Belanger & Vanderploeg, 2005; Anderson et al., 2006). However, mild TBI is considered as a more comprehensive term, and it has been proposed that concussions be classified as a subset of MTBI (McCrory et al., 2009; Upshaw et al., 2012). In this study only the term mild traumatic brain injury and concussion are used.

2.1.1 Definition of Mild Traumatic Brain Injury

Traumatic brain injury is usually categorized as to severity into mild, moderate, and severe injury. These subgroups were initially based on scores on the Glasgow Coma Scale (GCS). Generally, brain injury is classified as severe if the GCS score is 8 or less, moderate if the GCS score is 9–12, and mild if the GCS score is 13–15 (Teasdale and Jennett, 1974). Historically, the definition of MTBI was not well defined, and several definitions of MTBI exist. However, there are few definitions of MTBI that have been used widely in scientific research.

A conceptual definition of MTBI, provided by the World Health Organization (WHO) Collaborating Center Task Force on Mild Traumatic Brain Injury (Carroll et al., 2004b) has been endorsed as reasonable for use in clinical practice and research (Iverson et al., 2012; Ruff et al., 2009). The WHO workgroup definition is derived from the definition provided by Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM) (Mild Traumatic Brain Injury Committee, 1993). According to The U.S. Department of Veterans Affairs (VA) and The Department of Defence (DoD) guidelines (2009), the ACRM definition is the most widely accepted criteria for MTBI. The WHO and ACRM definitions are very similar to the definition proposed by the Center for Disease Control (CDC) working group (National Center for Injury Prevention and Control, 2003).

All these above-mentioned definitions identify the same four diagnostic criteria for clinical identification of MTBI: (a) biomechanical force applied to the head; (b) loss of consciousness, if present, for less than 30 minutes; (c) Glasgow Coma Scale score between 13 and 15 after 30 minutes following injury; and (d) post-traumatic amnesia, if present, of less than 24 hours. There are only few definitional discrepancies between the WHO and ACRM definitions. In the ACRM definition one of the criteria is stated as "any alteration of mental state at the time of accident (dazed, disoriented, or confused)" whereas the word "dazed" was not used in the WHO definition. Furthermore, the ACRM definition indicates that neurologic signs "may or may not be transient" whereas the WHO definition refers only to "transient neurologic signs" (Ruff et al., 2009). In contrast, according to most recent international consensus group, concussion is defined as a "complex pathophysiological process affecting the brain induced by a traumatic biomechanical force" (McCroy et al., 2009). Definitions of MTBI, provided by the WHO, ACRM, and CDC are shown in detail below (see Tables 1–3).

Table 1. Diagnostic criteria for MTBI by WHO Collaborating Center Task Force

MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare.

These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury (Carroll et al., 2004b).

Table 2. Diagnostic criteria for MTBI by the American Congress of Rehabilitation Medicine

A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: (1) any period of loss of consciousness; (2) any loss of memory for events immediately before or after the accident; (3) any alteration in mental state at the time of the accident (e.g. feeling dazed, disorientated, confused); and (4) focal neurological deficit(s) that may or may not be transient. But where the severity of the injury does not exceed the following: (1) loss of consciousness of 30 minutes, (2) after 30 minutes, an initial Glasgow Coma Scale score of 13–15; and (3) posttraumatic amnesia not greater than 24 hours" (Mild Traumatic Brain Injury Committee, 1993).

Table 3. Diagnostic criteria for MTBI by Center for Disease Control working group

A case of MTBI is an occurrence of injury to the head resulting from blunt trauma or acceleration or deceleration forces with one or more of the following conditions attributable to the head injury during the surveillance period: (i) any period of observed or self-reported transient confusion, disorientation, or impaired consciousness; (ii) any period of observed or self-reported dysfunction of memory (amnesia) around the time of injury; (iii) observed signs of other neurological or neuropsychological dysfunction, such as seizures acutely following head injury; among infants and very young children: irritability, lethargy, or vomiting following head injury; symptoms among older children and adults such as headache, dizziness, irritability, fatigue, or poor concentration, when identified soon after injury, can be used to support diagnosis of mild TBI, but cannot be used to make the diagnosis in the absence of loss of consciousness or altered consciousness. Further research may provide additional guidance in this area; (iv) any period of observed or self-reported loss of consciousness lasting 30 minutes or less.

More severe brain injuries were excluded from the definition of MTBI and include one or more of the following conditions attributable to the injury: (i) loss of consciousness lasting longer than 30 minutes; (ii) posttraumatic amnesia lasting longer than 24 hours; (iii) penetrating craniocerebral injury" (National Center for Injury Prevention and Control, 2003).

In Finland, a working group set up by the Finnish Medical Society Duodecim has published a national Current Care guideline for adult brain injuries including definitions of injury severities (Aikuisiän aivovammat, Current Care Summary, 2008). The definition for MTBI is set out in Table 4.

Table 4. Diagnostic criteria for MTBI by Finnish Medical Society Current Care guideline

All of the following: Glasgow Coma Scale score of 13–15 after 30 minutes post-injury and during the surveillance period; posttraumatic amnesia lasting not longer than 24 hours; loss of consciousness lasting not longer than 30 minutes; no evidence of trauma-related intracranial findings in brain CT or MR imaging; no brain injury related neurosurgical procedures" (Aikuisiän aivovammat, Current Care Summary, 2008).

The most notable difference between the Finnish definition and those of WHO, ACRM, and CDC concerns neuroradiological findings: patients with visible trauma-related intracranial abnormalities are classified as having a moderate TBI.

Noteworthily, 81–92% of sport-related concussions are not accompanied by loss of consciousness (Daneshvar et al., 2011). In addition, most MTBIs are not associated with visible abnormalities on structural neuroimaging (Iverson, 2005). According to literature, the estimated prevalence of trauma-related neuroradiological abnormalities in MTBI ranges from 5% (GCS 15) to 30% (GCS 13) (Borg et al., 2004). The term complicated MTBI has been used to refer a subgroup of patients who have evidence of trauma-related intracranial abnormality (e.g., hemorrhage, contusion, or edema) and patients with negative neuroimaging are referred to as uncomplicated, respectively (Ruff, 2005; Williams, Levin, & Eisenberg, 1990; Iverson, 2006b). It has been suggested that a more precise gradation of brain injury severity would include a separate category for complicated MTBIs (Kashluba et al., 2008). TBI severity would then include mild, complicated mild, moderate, and severe injury groups (Kashluba et al., 2008). Recently, the U.S. Department of Defense has conceptualized complicated MTBI as "moderate" TBI (http://www.cdc.gov/nchs/data/icd/Sep08TBI.pdf).

2.1.2 Mechanism of Mild Traumatic Brain Injury

To determine the presence of MTBI, the first criterion is the trauma preceding the brain injury; there has to be a biomechanical force applied to the head. A definition of MTBI, provided by the WHO Collaborating Center Task Force on Mild Traumatic Brain Injury, states that "MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces" (Carroll et al., 2004b). Trauma may be blunt force, contact injury, or exposure to blast (VA/DoD clinical practice guideline, 2009). However, MTBI can be also produced by rotational forces, or acceleration or deceleration of the head without direct external impact to the head (Mild Traumatic Brain Injury Committee, 1993). Traditionally, TBI is divided into closed versus penetrating injuries. Head trauma is closed, if the skull remains intact, and penetrating if the skull and dura are penetrated by sharp objects. A new broader documentation has been recently proposed. Maas and collaborators (2011) recommend separating TBI into four categories: closed, penetrating, blast, and crush. According to Maas et al. (2011), crush injuries result from a slow mechanical force applied to the skull, and are therefore different from inertial forces (acceleration/deceleration) or impact traumas.

Most head impacts do not result in a MTBI (Crisco et al., 2010) and it is important to make a clear distinction between head injury and brain injury; both injuries can occur in combination but also separately. Head injury refers to an injury to any part of the head (e.g., scalp and skin abrasions, facial or dental injuries, bone fractures) whereas brain injury is defined as injury to the brain (Kay et al., 1992). It is possible to sustain

a head injury without the brain being injured and conversely, a brain injury can occur without any injury to the skull or head (Ruff, 2005).

2.1.3 Pathophysiology of Mild Traumatic Brain Injury

Mild traumatic brain injuries fall on broad spectrum: on the very mild end of the MTBI spectrum are concussions (usually sport-related) presumably characterized by rapidly resolving cellular changes in the brain and functional recovery within 24 hours. The pathophysiology of MTBI occurs on a spectrum from completely reversible to permanent structural and/or microstructural damage. On the uncomplicated end of the spectrum, MTBIs are associated with transient and presumably reversible neurometabolic derangements of cellular systems (Silverberg & Iverson, 2011). On the complicated end of the spectrum, MTBIs are characterized by macroscopic evidence of brain injury (contusion, hemorrhage, hematomas, swelling, etc). MTBI may also involve diffuse axonal injury (DAI) (Le & Gean, 2009), although this is difficult to detect with traditional CT and MRI scans (Arfanakis et al., 2002). Currently, there are no objective biological measures to determine the degree of severity of the neuropathology of MTBI (Signoretti et al., 2010).

Although a substantial minority of MTBI patients have trauma-related visible intracranial abnormalities, for the most part, the pathophysiology of MTBI is neurometabolic and mostly reversible (Iverson et al., 2012). Previously, it was assumed that symptoms associated with MTBI were due to destruction or shearing of neuronal axons. Recently, it has been demonstrated that most of the pathophysiology of MTBI induces neurons dysfunctional, but cells are not destroyed or axons "sheared" (McCrea, 2008 p. 53). There is compelling evidence that, even in absence of radiological and clinical abnormalities, the clinical manifestation of MTBI is due to a complex, sequential neurometabolic cascade that includes abrupt neuronal depolarization, release of excitatory neurotransmitters, ionic shifts, changes in glucose metabolism, altered cerebral blood flow, and impaired axonal function (Giza & Hovda, 2001; Signoretti et al., 2010). It has been argued, however, that the biochemical and molecular processes triggered by MTBI, are likely to be, at least in part, different from those present following severe injury (Signoretti et al., 2010).

Postinjury pathophysiological changes, namely persistent depression of glucose uptake, may last 2 to 4 weeks after injury in humans (Bergsneider et al., 2000). Based on positron emission tomography (PET) studies, it has been shown that metabolic recovery generally takes weeks to months after moderate to severe TBI (Bergsneider et al. 2001). Similar clinical studies using PET after MTBI have yet to be done (Giza & DiFiori,

2011) and the duration of vulnerability after a single MTBI remains unknown and possible biomarkers have yet to be determined (Prins et al., 2012). Studies of animals and humans show that following concussive brain injury, a vulnerable period to repeat injury exists (Giza & DiFiori, 2011). Metabolic alterations following MTBI create no morphological damage, but represent the pathological basis of the brain's vulnerability (Signoretti et al., 2010). Animal studies suggest that the effects of repeated injury are greatest within the first week following injury (Giza & DiFiori, 2011). The findings of Signoretti and co-workers indicate that the metabolic effects of two consecutive concussions occurring in temporal proximity can be dangerously additive and simulate the effects of a severe injury (Signoretti et al., 2010). Based on experimental animal studies, it has been shown that a second concussive event falling within temporal window of brain vulnerability has profound consequences on mitochondrial-related brain metabolism (Vagnozzi et al., 2007; Prins et al., 2012).

Animal research suggests that the timing and degree of metabolic disruption that occurs following mild head trauma differs as a function of the brain's developmental age (Cernak et al., 2010). Many authors have suggested that the pediatric brain is more vulnerable to traumatic injury (Kirkwood et al., 2006; Lovell & Fazio, 2008; Meehan et al., 2011) and pediatric patients may take longer to recover from MTBI (Meehan et al., 2011). However, substantial literature suggests that a single MTBI has no lasting cognitive sequelae in most children (Nadebaum et al., 2007; Babikian & Asarnow, 2009). Further, animal studies suggest that excessive premature activation, either through forced or voluntary exercise, is deleterious to the injured brain, leading to molecular, anatomical, and behavioral deficits and affecting adversely to recovery (Giza & DiFiori, 2011). Also human data indicate that premature activity may exacerbate postconcussive symptoms (Guskiewicz et al., 2003).

Few biochemical markers have been studied as to their relationship with MTBI. In their review study, Begaz and co-workers (2006) describe three biochemical markers that have been studied for their association with post-concussion symptoms in patients with MTBI: glial associated S100 proteins, neuron-specific enolase (NSE), and cleaved-Tau protein (CTP). Based their review, the S100 has been the most widely studied and most promising serum marker in mild TBI (Begaz et al., 2006). Nevertheless, the authors conclude that, to date, no biomarker has consistently demonstrated the ability to predict post-concussional syndrome following MTBI (Begaz et al., 2006).

2.1.4 Multiple Concussions

The literature on cumulative effects on cognitive functioning from one or two previous concussions is mixed. In their study with 867 male high school and university amateur athletes, Iverson and co-workers (2006) found no measurable effect for one or two previous concussions on athletes' preseason neuropsychological test performance or symptom reporting. Similarly, other studies have found no obvious cumulative effects of concussions on neuropsychological functioning or symptom reporting (Macciocchi et al. 2001; Moser and Schatz 2002). On the other hand, results from other studies suggest that the cumulative effects of multiple concussions may lead to chronic traumatic encephalopathy and prolonged functional impairment (Sim et al., 2008; Halstead et al, 2010; Gavett et al., 2011; Giza and DiFiori, 2011) There is some evidence of prolonged symptoms in youth athletes with a history of two or more previous concussions (Collins et al., 2002; Guskiewicz et al., 2003; Iverson et al., 2004; Moser et al., 2005). Also, it has been suggested that there is a subgroup of athletes for whom repetitive head impacts affect learning and memory at least on a temporary basis (McAllister et al., 2012).

An association has been reported between the number of previous concussions and the likelihood of a future concussion. In a large prospective cohort study (2,905 college football players), players reporting a history of three or more previous concussions were 3 times more likely to have an additional concussion than players with no concussion history (Guskiewicz et al., 2003). In addition, Levy and co-workers (2004) reported that professional football players were over 5 times more likely to sustain a second concussion compared to players who had never had a concussion. In humans, it has been shown that athletes who sustained a second concussion before full metabolic recovery took longer to recover based on magnetic resonance spectroscopy (Vagnozzi et al., 2008).

2.2 Diffusion Tensor Imaging in Mild Traumatic Brain Injury

It is widely acknowledged that a subgroup of patients who have sustained an MTBI may have poorer clinical outcome than might be predicted on the basis of conventional neuroradiological imaging techniques. Researchers have placed increasing effort on identifying objective physiological correlates of persistent cognitive and neurobehavioral symptoms by examining novel neuroimaging techniques. There is considerable interest in using diffusion tensor imaging (DTI) to investigate changes in white matter associated with MTBI (Niogi & Mukherjee, 2010; Sharp & Ham, 2011; Shenton et al., 2012). DTI is considered to be sensitive to subtle microstructural changes in the brain.

Although MRI is generally more sensitive than CT in detecting brain parenchymal damage, white matter fiber bundles are not visible using anatomical MRI. Thus, DTI is currently the only viable means to identify between-group differences in the diffusion of water when studying the integrity of white matter fibers in vivo (Bansal et al., 2007).

It has been suggested that measuring the degree of diffuse axonal injury (DAI) by utilizing DTI will greatly enhance prediction of functional outcome following MTBI (Maller et al., 2010). Presence of DAI is easily missed with conventional CT or MRI underestimating its extent following TBI (Maller et al., 2010). DAI is a key determinant of outcome following severe TBI and presence of DAI has been demonstrated neuropathologically in a small number of MTBI patients who died from unrelated causes (Sharp & Ham, 2011). In mild and moderate TBIs, DAI occurs most frequently in grey-white matter interfaces, particularly the internal capsule and frontotemporal regions including corpus callosum and anterior cingulate (Maller et al., 2010). Previous studies suggest that DAI is related to persistent postconcussive symptoms and transient deficits in cognitive performance following MTBI (Niogi et al., 2008b; Grossman et al., 2012).

The basic principles of diffusion MRI were introduced in the mid-1980s (Le Bihan et al., 2001), and after the mid-1990s DTI has increasingly been used in neuroscience (Mori & Zhang, 2006). DTI characterizes the three-dimensional (3D) spatial distribution of water diffusion in each MR imaging voxel (Basser & Pierpaoli, 1996). DTI examines the diffusion of water molecules throughout the brain. Water does not diffuse equally in all directions and this non-random type of water movement is referred to as anisotropic diffusion (Voelbel et al., 2012). For example, water in brain diffuses preferentially along axonal fiber bundles rather than perpendicular to these bundles because there are fewer obstacles to prevent movement along the fibers (Mori & Barker, 1999; Mori & Zhang, 2006). Further, water diffusion along white matter tracts is less random (more highly restricted) than in gray matter (Voelbel et al., 2012). In well organized and intact white matter fiber tracts the shape of water diffusion will occur preferentially along those tracts (i.e., more anisotropic), whereas in less organized fiber structures (i.e., gray matter, CSF, axonal loss, or demyelination) the shape of water diffusion will be more isotropic (Little & Holloway, 2007).

There are two major different approaches to examine microstructure damage from DTI data: voxelwise whole brain analysis (WBA) and region of interest (ROI) analysis. In addition, some studies have utilized quantitative tractography (Niogi & Mukherjee, 2010). WBA includes two kinds of studies, namely voxel-based analysis (VBA) and tract based spatial statistics (TBSS). These approaches are useful to investigate the overall changes in white matter. However, results from these different studies are

not interchangeable (Aoki et al., 2012). ROI analysis refers to a priori defined local approaches and is useful to investigate specific white matter tracts or areas.

From the tensor it is possible to derive some scalar indices that provide measurement of the (a) magnitude of diffusion or (b) directionality of the diffusion. There are five major DTI-derived invariants, including fractional anisotropy (FA), apparent diffusion coefficient (ADC), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) (Aoki et al., 2012). Brief descriptions of these DTI metrics are provided in Table 5.

Table 5. Overview of common diffusion tensor imaging measures

DTI measure	Description	Numerical value	Description of the values
FA	Quantifies the orientation and integrity of WM tracts: describes the degree of directionality of diffusion, and is calculated as a ratio of three eigenvalues (λ1, λ2, λ3)	0 to 1	0 = totally isotropic, i.e. random, multi-directional movement; 1 = highly anisotropic, i.e. movement in one particular direction
AD	Describes the magnitude of diffusion along the fiber orientation within the tract: reflects diffusivity parallel to axonal fibers and is related to pathology of axons		Corresponds to the primary eigenvalue in the diffusion tensor (λ1)
RD	Denotes the mean rate of diffusion orthogonal to the fiber orientation: reflects diffusivity perpendicular to axonal fibers and is related to myelin abnormalities		Calculated from the average of the second (λ2) and third (λ3) eigenvalues in the diffusion tensor
Trace value	Measure of total diffusivity in tissue: is the sum of the three diagonal elements of the tensor, which is equal to the sum of the three eigenvalues (λ1, λ2, λ3)		
MD /ADC	Overall average measure of diffusion: measures diffusion magnitude and rate of diffusion within cerebral tissue, describes the local magnitude of diffusion regardless of direction (i.e. is rotationally invariant), provides a measure of vasogenic or cytotoxic edema after white matter injury	mm^2/s	Average of three eigenvalues (λ1, λ2, λ3): obtained by dividing trace value by three, yields the averaged mean diffusivity (i.e. apparent diffusion coefficient)
Tractography	Reconstructs 3D streamlined information from the tensor field: allows for the visualization of networks in the body		

Abbreviations: AD=axial diffusivity, ADC=apparent diffusion coefficient, DTI=diffusion tensor imaging, FA=fractional anisotropy, RD=radial diffusivity, WM=white matter

In most studies, measures of FA and ADC are used (Niogi & Mukherjee, 2010). FA is a measure of the anisotropy of water diffusion in tissue and provides indirect information

about brain structure: decreased FA values may be a sensitive indicator of histologic abnormality. FA values around 1 are considered totally anisotropic; FA values around 0 are considered totally isotropic (Ducreux et al., 2005; Skoglund et al., 2008). As a marker of the directionality and coherence of axonal fibers, it has been postulated that FA reduction could represent structural damage, for example, axonal loss (Werring et al., 1999) and fiber degeneration (Matsui et al., 2007). Either an increase above or decrease below the normal FA range likely indicates white matter abnormality (Maruta et al., 2010).

ADC, then, is a measure of diffusion magnitude and rate of diffusion within cerebral tissue. A low ADC value indicates that the cortical white matter tracts are well organized, and a high ADC value indicates that these tracts are disorganized (Niogi & Mukherjee, 2010). Additionally, AD and RD have been examined in some studies in relation to MTBI (Bazarian et al., 2007; Wilde et al., 2008; Mayer et al., 2010). Based on animal studies, AD and RD are associated with different pathologies: AD corresponds to axonal pathology whereas RD denotes the extent of diffusion that is perpendicular to the direction of maximal diffusivity and measures myelin pathology (Song et al., 2003). Rotationally invariant (i.e. independent of the orientation of the tissue structures, for example the patient's body within the MR magnet) scalar measurements described above provide local information about anisotropy and diffusion direction. However, they don't provide global connectivity information between two points. To investigate connection paths in the brain tractography approaches have been developed. Fiber tracking is the most advanced application of DTI and this approach allows for the examination of brain connectivity through 3D visualization of WM networks (Le Bihan et al., 2001; Mori & Zhang, 2006).

Prior studies that have examined microstructural white matter integrity following MTBI using DTI have found differences in multiple brain regions relative to controls. Regions of the brain most commonly affected include the corpus callosum, internal and external capsule, centrum semiovale, and the corticospinal tract (Arfanakis et al., 2002; Inglese et al., 2005; Bazarian et al., 2007; Kraus et al., 2007; Wilde et al., 2008; Chu et al., 2010; Gardner, 2012). Some differences have also been reported in the frontal association pathways (anterior corona radiata, uncinate fasciculus, and superior longitudinal fasciculus, forceps minor) and commissural fibers of the corpus callosum (Niogi & Mukherjee, 2010). According to a recent review, the most commonly disrupted white matter tracts in MTBI are the genu and body of corpus callosum, internal capsule, and superior longitudinal fasciculus (Voelbel et al., 2012). In contrast, studies have failed to demonstrate any differences between MTBI patients and trauma controls in all DTI parameters at 4 weeks post-injury (Zhang et al., 2010) and 6–8 weeks post-injury (Lange et al., 2012).

The presence of DTI findings in MTBI patients remains controversial. In part, inconsistencies in research findings are due to current MRI technology constraints, timeframe of scanning, population characteristics, and study inclusion criteria (Zhang et al., 2010). As a general rule, it is widely accepted that FA values decrease and ADC values increase after moderate-to-severe TBI, and in the chronic stage of recovery following MTBI (Niogi & Mukherjee, 2010). Some studies, however, have reported increased FA values and decreased diffusivity (i.e., ADC or MD or RD) within 72 hours (Bazarian et al., 2007), 6 days (Wilde et al., 2008; Henry et al., 2011), and 21 days following MTBI (Mayer et al., 2010). It has been suggested that elevated or reduced FA values likely reflect different types of WM abnormalities. Further, it has been suggested that increased FA and decreased diffusivity values are evident only in the very acute phase after the injury (Wilde et al., 2008). These initial findings (increased FA, decreased diffusivity) might be due to inflammatory changes during the acute recovery phase (i.e., cytotoxic edema/ axonal swelling) rather than classic shear-strain lesions (Bazarian et al., 2007; Chu et al., 2010). There is evidence, however, that FA values might be increased and MD values decreased also in chronic stage after MTBI (6 months) (Henry et al., 2011).

Abnormalities in DTI metrics are not pathognomonic to TBI, but are indicative of changes in the microstructural integrity of WM pathways in the central nervous system (Voelbel et al., 2012). In addition, DTI changes are not diagnostic of DAI but can reflect other pathological processes such as demyelination, inflammation, and gliosis (Miles et al., 2008). It has been suggested that degradation of the myelin sheath is a likely candidate to cause changes in anisotropy detected by DTI (Niogi & Mukherjee, 2010).

2.2.1 Cognition and Diffusion Tensor Imaging

The relationship between DTI measures of white matter structure and cognitive function is not simple. It has been suggested that there may be subtle abnormalities in brain areas that can be detected by DTI (i.e., compromised microstructural white matter integrity) that may be associated with impaired neurocognitive functioning following MTBI (Garnett et al., 2000; Bazarian et al., 2007; Niogi et al., 2008a; Lipton et al., 2009; Lo et al., 2009). However, the clear relationship between observable neuropsychological deficits associated with MTBI and underlying structural and/ or functional deficits based upon current clinical brain imaging techniques has been challenging to establish (Zhang et al., 2010).

To date, there are only few DTI studies in MTBI that have examined the relationship between neuropsychological outcome with DTI metrics in adults with MTBI and that have (a) utilized a 3T MRI scanner and (b) used an ROI based approach in relation to post-concussive symptoms (see Aoki et al., 2012 for meta-analysis and Voelbel et al., 2012 for review). These studies are presented in Table 6. In part, inconsistencies can be explained by differences in patient sample characteristics and methodological differences in MRI acquisition (Maller et al., 2010). Previous studies have reported on small numbers of patients and/or addressed a limited range of outcome variables. In addition, the time frame in these studies varies considerably (from 72 hours to 12.4 years post injury) making the comparison of the results difficult and leading to differential diagnostic uncertainties.

Table 6. Summary of ROI-based DTI studies in MTBI with 3T MRI.

First Author (Year)	N MTBI	N Ctrls	Mean age of MTBI patients	Post-injury Interval	Setting	DTI metrics	Number of ROIs	DTI Software (ROI drawing method)	Type of Study	Neuropsych tests/ outcome measures	Main findings in relation to cognition
Kraus et al. (2007)	20 (+17 moderate-severe)	18	35.85 years SEM 2.1	≥ 6 months post injury (Mean 107 months post injury)	Subjects recruited from the University of Illinois Medical Center and via advertisements	FA, AD, RD	13	DTI Studio, (freehand)	ns	Tower of London, Stroop Colour–Word Test, Paced Auditory Serial Addition Test, Trail Making Test, Conners' Continuous Performance Test, Controlled Oral Word Association Test, Ruff Figural Fluency Test, Wechsler Test of Adult Reading, California Verbal Learning Test – Second Edition, Brief Visual Spatial Memory Test – Revised, Digit Span and Spatial Span from the Wechsler Memory Scales – Third Edition, and the Grooved Pegboard, Test of Memory Malingering, Dot Counting	The MTBI group showed reduced white matter integrity in the superior longitudinal fasciculus, sagittal stratum and corticospinal tract. Relationship between overall white matter load was more strongly related to the domains of executive and memory function than FA in individual ROIs. There was a modest negative correlation between FA in individual regions of interest with cognitive function.
Bazarian et al. (2007)	6	6	21.7 years, range 18–31 years	≤ 72 hours post injury 1-month PCS and self-report QOL assessment by telephone	Patients were recruited from Emergency Department of the University of Rochester School of Medicine	FA, Trace Values	5	Matlab, (freehand)	Prospective	ImPACT, a computer- based neurobehavioral test battery, Rivermead Post Concussion Questionnaire, EuroQol/EQ-5D (1 month post injury)	ROI analysis indicated a significant increase in FA in the posterior corpus callosum and a significant decrease in trace value in the left anterior internal capsule. In this study, DTI results were highly correlated with post-concussive symptoms and neurobehavioral tests.

First Author (Year)	N MTBI	N Ctrls	Mean age of MTBI patients	Post-injury Interval	Setting	DTI metrics	Number of ROIs	DTI Software (ROI drawing method)	Type of Study	Neuropsych tests/ outcome measures	Main findings in relation to cognition
Niogi et al. (2008a)	43	23	32.4 years range 17–61 years	Mean 16.9 months (range: 1–53 months)	Hospital Emergency Department	FA, ADC	6	DTI Studio, (ellipse)	Prospective	The Attention Network Task, The California Verbal Learning Test Second Edition	In both controls and MTBI patients, bilateral UF is associated with memory performance while integrity of the left ACR is associated with attentional control: damage to the UF is associated with decreased memory performance in MTBI patients
Niogi et al. (2008b)	34	26	28.3 years, range 17– 58 years	≥ 1 month post injury (range: 1–65 months)	ns	FA	39	DTI Studio, (ellipse)	Selected, patients with persistent PCS	The Attention Network Task	Significant correlation of the number of damaged white matter tracts and reaction times
Mayer et al. (2010)	22	21	27.45 ± 7.39 years	≤ 21 days post injury (3 to 5month follow-up, n = 10 MTBIs, 15 controls)	Patients recruited from University Emergency Department	FA, AD, RD	8	AFNI software package,(ns)	Prospective, unselected	Trail Making Test, Paced Auditory Serial Addition Test, Stroop Test, Wechsler Adult Intelligence Scale – Third Edition (digit span, letter number sequence, arithmetic, digits backward, digit symbol coding), Grooved Pegboard, Wisconsin Card Sorting Test, Controlled Oral Word Association, California Verbal Learning Test – Second Edition, State-Trait Anxiety Index, Beck Depression Inventory-Second Edition, Neurobehavioral Symptom Checklist, Neurobehavioral Symptom Checklist, The Wechsler Test of Adult Reading, Test of Memory and Malingering, Edinburgh Handedness Inventory	FA levels in the right hemisphere predicted variance in attentional deficits for the MTBI group. DTI results were more accurate in classifying MTBI patients from controls than cognitive assessment and conventional neuroimaging

First Author (Year)	N MTBI	N Ctrls	Mean age of MTBI patients	Post-injury Interval	Setting	DTI metrics	Number of ROIs	DTI Software (ROI drawing method)	Type of Study	Neuropsych tests/ outcome measures	Main findings in relation to cognition
Little et al. (2010)	12 (+ 12 moderate -severe)	12	31.2 years, SEM 2.71	55.5 months (Range 12–149 months)	Patients recruited via local newspaper	FA, Fiber Tracking	19 (specific interest in thalamus)	DTI Studio (ns)	Selected sample	Continuous Performance Test, Tower of London, Stroop test, Paced Auditory Serial Addition Test, Trail Making Test A and B, Controlled Oral Word Association Test, Ruff Unique Designs, Digit Span, Spatial Span, California Verbal Learning Test, Benton Visual Memory Test	FA in thalamus not significantly reduced in MTBI group in relation to controls. For the whole sample, FA values did not account for significant variance in cognitive function from cortico-cortico and corpus callosum regions. FA from thalamic seed voxels accounted for variance in cognitive functions.
Zhang et al. (2010)	15	15	21.3 ± 1.5 years	Mean 30 days ±2 days	Collegiate players from Pennsylvania State University	FA, ADC, Number of fibers, Fiber Tracking	7	MedINRIA (freehand)	ns	Hopkins Verbal Learning Test – Revised, Stroop test, Trail Making Tests, Symbol Digit Modalities Test, Reported Fatigue Scores, ImPACT	No significant differences between MTBI subjects and normal controls for all neuropsychologial variables. no consistent findings across brain imaging techniques (fMRI and DTI) were observed.
Grossman et al. (2012)	22	14	38.2 ± 11.7 years	Group 1 (n = 7) ≤ 1 year, (mean 0.18 years) Group 2 (n = 15) ≥ 1 year (mean 3.9 years)	MTBI patients recruited from hospital centers while receiving treatment for post-concussive symptoms	MD, FA, MK (a scalar index derived from DKI)	6 (specific interest in thalamus	Matlab, ImageJ, Rectangular	Prospective, selected	Weinberg Visual Cancellation Test, Stroop Test, Prioritization Form A and Form B, Controlled Oral Word Association Test, The HeadMinder Cognitive Stability Index (Attention and Concentration, Memory and Learning, Processing Speed , Response Speed)	Cognitive impairment was correlated with MK in the thalamus and the internal capsule

First Author (Year)	N MTBI	N Ctrls	Mean age of MTBI patients	Post-injury Interval	Setting	DTI metrics	Number of ROIs	DTI Software (ROI drawing method)	Type of Study	Neuropsych tests/ outcome measures	Main findings in relation to cognition
Lange et al. (2012)	60	34	30.8 ± 9.9 years	Mean 47 days, (SD = 6.3, range = 31–66)	Subjects recruited from the emergency department of Vancouver General Hospital	FA,MD	3 (specific interest in corpus callosum)	In-house developed software tools and Philips Healthcare analysis tool PRIDE	Prospective, consecutive	British Columbia Postconcussion Symptom Inventory, Test of Memory Malingering	There were no significant differences between MTBI and trauma control groups on all DTI measures. DTI findings were unrelated to post-concussion symptom reporting.

Abbreviations: ACR = anterior corona radiata, AD = axial diffusivity, ADC = apparent diffusion coefficient, CoC = Community Controls, DTI = diffusion tensor imaging, FA = fractional anisotropy, HC = Healthy Controls, QOL = quality of life, MD = mean diffusivity, MK = mean kurtosis, MRI = magnetic resonance imaging, ns = sot stated, PCS = post-concussion symptoms, RD = radial diffusivity, ROI = region of interest, SEM = standard error of measurement, TBI = traumatic brain injury, TC = Trauma Controls, UF = uncinate fasciculus,WM = white matter, DTIStudio (http://lbam.med.jhmi.edu/DTIuser/DTIuser.asp), MedINRIA software (http://www-sop.inria.fr/asclepios/software/MedINRIA/)

Kraus and associates (2007) examined the relationship between both white matter integrity and white matter load with neuropsychological functions. A total of 39 patients with closed head TBI (of which 20 were classified as having MTBI) were recruited and examined an average 8.9 years post injury. Subjects completed an extensive neuropsychological test battery; the MTBI group did not differ significantly from controls in any cognitive domain scores when compared to the controls. Further, the MTBI group showed no significant increases in RD in any ROI. However, the MTBI group showed reduced FA along the corticospinal tract, in the superior longitudinal fasciculus, and sagittal stratum. In their study, a 1 SD threshold below the control mean FA was used to indicate reduced anisotropy. The authors documented that the total number of regions with reduced FA (White Matter Load) was negatively associated with poorer performance on measures of attention, memory, and executive functions.

Bazarian et al. (2007) used both WBA and ROI methods. Six MTBI patients and six controls underwent DTI scanning, post-concussive symptom assessment, and neurobehavioral testing within 72 hours of injury. Both WBA and ROI methods detected decreased trace values in white matter voxels. In the ROI analysis, the MTBI group had significantly lower mean trace in the left anterior internal capsule and significantly higher maximum ROI specific median FA values in the posterior corpus callosum. These values were significantly correlated with post-concussive symptom scores and two neurobehavioral tests (visual motor speed and impulse control). However, abnormal DTI indices had the strongest clinical correlation not with cognitive dysfunction, but with post-concussive symptoms. According to the authors, the findings suggest the presence of axonal injury in the left anterior internal capsule and posterior corpus callosum (Bazarian et al., 2007).

Niogi and co-workers (2008a) examined with DTI measures which white matter tracts are primarily associated with the memory domain and attentional control. Their study consisted of 43 MTBI patients (23 controls) and the time since injury was in average 1.4 years. As a group, the MTBI patients did not differ from the normal control group in attentional control. However, individual patients within the MTBI cohort performed outside the normal range and also had anterior corona radiata bilateral average FA values below the normal range. In mild TBI subjects, FA of the uncinate fasciculus in both hemispheres correlated significantly with memory performance. In contrast, for both controls and MTBI patients, no significant correlations were found between structure and function using ADC.

In a related study, Niogi and co-workers (2008b) investigated the extent of microstructural injury in normal-appearing white matter in a cohort of 34 patients with isolated mild TBI in relation to cognitive performance. Based on their findings, 10 of 11 patients with uncomplicated MTBIs (no abnormalities on conventional

3T MRI) had evidence of microstructural white matter injury on DTI. In addition, the extent of microstructural white matter injury on DTI correlated with impaired cognitive reaction time, whereas the number of traumatic microhaemorrhages detected on conventional MRI did not.

Grossman and co-workers (2011) identified associations between the cognitive performance of MTBI patients with DTI measures in a group of 22 MTBI patients. The study sample was divided in two groups based on whether they were studied within or more than one year after injury. In addition to DTI measures, they also used diffusional kurtosis imaging (DKI), a recently developed noninvasive MRI technique that measures non-gaussian properties of water diffusion (Grossman et al., 2011). The MTBI group showed significantly lower mean kurtosis (MK) and FA and higher MD in the thalamus and the internal capsule. When cognitively-impaired patients were compared with cognitively-unimpaired patients, they showed significantly lower MK and FA in the thalamus and internal capsule. However, the difference for FA did not remain significant after Bonferroni correction. Changes detected in the thalamus and the internal capsule of patients were present during both ≤ 1 year and ≥ 1 year time intervals following injury, compared to controls, indicating that damage occurring in these regions might be sustained.

Little and co-workers (2010) conducted a study on 24 patients with a history of TBI (12 each of mild TBI and moderate to severe TBI) with specific interest on thalamocortical projection fibers and their association with impaired cognitive functioning. MTBI patients were examined average 4.5 years post-injury. The MTBI patients did not differ from controls in thalamic FA. In the TBI groups, there were no correlations between any cortical or corpus callosum ROIs with executive function, attention, or memory performance. However, for the total TBI sample, there was a relationship between the attention domain and FA in the genu of the corpus callosum. In addition, FA from the thalamic seed voxels accounted for variance in executive function, attention, and memory (Little et al., 2010).

Mayer and collaborators (2010) studied 22 unselected patients with MTBI within 21 days of injury. Besides neuroimaging, participants underwent an extensive battery of cognitive and behavioral tests. There were no differences between MTBI patients and controls in terms of AD. In contrast, MTBI patients demonstrated increased FA and reduced RD within the genu and several left hemisphere WM tracts compared to controls. Furthermore, FA levels in the right hemisphere predicted variance in attentional deficits for the MTBI group, and DTI measures were more accurate than neuropsychological results in classifying patients from controls. MTBI patients did not differ from controls on neuropsychological performance.

Zhang and others (2010) compared the DTI results of 15 MTBI patients and 15 control subjects 30 (±2 days) following sport-related MTBI. In this study, participants underwent both fMRI and DTI. In DTI, both WBA (TBSS) and ROI analysis were carried out. The MTBI group showed more variability (SD) of FA and ADC values in the genu and body of the corpus callosum. However, neither WBA nor ROI analysis showed significant alteration of WM integrity in MTBI subjects as evidenced by fractional anisotropy FA. In addition, no significant changes in FA or in number of fibers between groups were observed at all ROIs. In terms of diffusivity, decreased ADC at both left and right dorsolateral prefrontal cortex was detected in MTBI subjects compared to controls. Based on their results, the authors conclude that no consistent findings across advanced brain imaging techniques (fMRI and DTI) were observed (Zhang et al., 2010).

Lange and associates (2012) examined the association between post-concussion symptom reporting following MTBI in relation to possible loss of white matter integrity of the corpus callosum using DTI. A total of 60 patients underwent DTI of the corpus callosum at 6 to 8 weeks post injury. Participants also completed a post-concussion symptom checklist. The MTBI group reported a significantly greater number of total post-concussion symptoms compared with the trauma control group. However, DTI findings were unrelated to post-concussion symptom reporting. Contrary their initial hypothesis, the MTBI patient group did not have significantly lower FA, or higher MD, in the corpus callosum compared with the trauma controls.

In sum, DTI studies of MTBI have shown some inconsistency toward FA and ADC in relation to cognitive functions. Findings across studies vary greatly with both increases and decreases, or no differences, in FA and MD measures reported. MRI techniques and thresholds, time frame of scanning, and patient characteristics adopted in these studies differ considerably making the comparison of the results difficult.

2.3 Outcome After Mild Traumatic Brain Injury

There is significant individual variability in outcome following MTBI. The acute symptoms that may follow MTBI are often categorized according to following domains (a) physical, (b) behavioral/emotional, and (c) cognitive. Some of the more common symptoms in each category are presented in Table 7.

Table 7. Common symptoms associated with MTBI

Physical	Cognitive	Behavioural/emotional
Headache	Feeling mentally "foggy"	Irritability, aggression
Nausea	Feeling slowed down	Depression, sadness
Vomiting	Difficulty concentrating	Emotional lability
Balance problems	Difficulty remembering	Nervousness
Vertigo, dizziness	Forgetfulness	Anxiety
Visual problems	Confused	Apathy, lack of spontaneity
Fatigue	Answers questions slowly	
Sensitivity to light	Memory problems	
Sensitivity to noise		
Drowsiness		
Sleep less/more than usual		
Trouble falling asleep		
Numbness/Tingling		
Reduced alcohol tolerance		

Note: Based in part on International Statistical Classification of Diseases and Related health Problems, 10th ed, 1992, ICD-10 Diagnostic Criteria for Post-concussion Syndrome and Diagnostic and Statistical Manual of Mental Disorders, 4th ed. 1994, DSM-IV Research Criteria for Postconcussional Disorder, and Maruta et al., 2011.

A combination of the above-mentioned symptoms is most common. MTBI has an enormous adverse effect on balance, cognitive functioning, and symptoms in the first 24 hours postinjury (Iverson, 2012, p. 52). Symptoms are usually at their worst in the first 72 hours postinjury and a gradual symptom recovery occurs over period of 7 to 30 days in majority of cases (McCrea, 2008, p. 96; Iverson, 2012, p. 43). The resolution of post-concussion symptoms is much faster in young, healthy, athletes, who generally recover within 10 days (Macciocchi et al., 1996), whereas accident victims tend to have more protracted recovery periods (Ponsford et al., 2000). It is relatively uncommon for cognitive, psychological, or psychosocial symptoms to persist longer than 3 to 6 months following MTBI (Belanger et al., 2005; Belanger and Vanderploeg, 2005).

It is widely accepted that the prognosis of MTBI is good and poor late outcome requires explanation. The symptoms experienced following MTBI are nonspecific and these symptoms are common in various other medical and psychiatric conditions. Although most patients appear to recover fully within three months after injury, persistent symptoms are possible in a small number of cases (Binder et al., 1997). Despite extensive research, slow or incomplete recovery from MTBI is still poorly understood (McCrea, 2008; Ruff et al., 2009). A large body of evidence suggests that long term poor functional outcome following MTBI is associated with non-injury-related factors

such as demographic, psychosocial, medical, motivational, and other situational factors (Binder, 1997; Iverson et al., 2007; McCrea, 2008). Further, it has been suggested that access to compensation is the strongest predictor of MTBI outcome (Carroll et al., 2004a).

Traditional brain injury severity variables (e.g., duration of loss of consciousness, Glasgow Coma Score) (Van der Naalt et al., 1999a) or post-injury cognitive impairment have shown limited usefulness to predict outcome after MTBI (Hanlon et al., 1999; Ruffolo et al., 1999), especially because LOC and PTA are difficult to identify and verify outside of a research setting (Bigler & Bazarian, 2010). It has been suggested that post-concussion symptoms tend to be more common following MTBI than following moderate-to-severe TBI (Sigurdardottir et al., 2009). According to one study by Collins and co-workers (2002), posttraumatic amnesia was up to 10 times more predictive than loss of consciousness in predicting neurocognitive deficits following sport-related concussion. Further, in one study a symptom of "fogginess" was shown to be highly predictive of neurocognitive deficits and prolonged recovery following concussion (Iverson et al., 2004).

There have been inconsistent findings whether trauma-related lesions are likely to be responsible for the post-injury symptoms and if they may explain chronic difficulties experienced by some patients. Some studies have reported that MTBI patients with trauma-related intracranial abnormalities are more likely to have worse outcome compared to those with uncomplicated MTBIs (patients with no intracranial abnormalities) (Williams et al., 1990; Wilson et al., 1996; Van der Naalt et al., 1999b; Temkin et al., 2003; Iverson, 2006; Lange et al., 2009). Other studies, however, have not reported this association (Hofman et al., 2001; McCauley et al., 2001; Hughes et al., 2004).

2.3.1 Post-concussion Syndrome After Mild Traumatic Brain Injury

Following MTBI, a proportion of individuals report persisting symptoms that include a constellation of rather non-specific symptoms such as headache, cognitive dysfunction, dizziness, fatigue, and irritability – a condition that is widely called post-concussion syndrome. The distinguishing feature between postconcussive symptoms (typical symptoms following MTBI) and postconcussive syndrome is the duration of symptom persistence (Jotwani & Harmon, 2010).

The persistent post-concussion syndrome (PPCS) is one of the most controversial syndromes in medicine and psychology, and this construct has been the subject of debate since the end of the 19th century and still remains controversial (McCrea,

2008, p. 152). Previously the debate has been polarized around the psychological versus organic etiology of PPCS. Recently, the discussion is being replaced by a multifactorial biopsychosocial perspective, integrating biological, social, cognitive, affective, and behavioral factors emphasizing the complex multifactorial nature of condition (Wood, 2007; Iverson, 2012). There are three interrelated issues that hamper an understanding of the post-concussion syndrome: (a) lack of uniform diagnostic criteria; (b) lack of specificity of symptoms; and (c) lack of clarity over pathogenesis (Williams et al., 2010).

Currently, there are no consensus-based diagnostic guidelines for post-concussion syndrome. In research, the two most commonly used diagnostic terms are postconcussional syndrome (PCS) per the International Classification of Diseases-10th edition (World Health Organization, 1992) and postconcussional disorder (PCD) per the Diagnostic and Statistical Manual of Mental Disorders-IV (American Psychological Association, 1994). These two diagnostic sets have very different diagnostic thresholds: PCS (ICD-10) being more liberal and PCD (DSM-IV) being more restrictive. There are three core differences between the ICD-10 and DSM-IV diagnostic systems. ICD-10 diagnosis for PCS requires patients' self-reported symptoms to meet the diagnostic threshold, whereas DSM-IV criteria for PCD require the presence of cognitive difficulty on objective tests. Also, ICD-10 requires symptoms to be present for more than one month and DSM-IV requires symptoms to be present for more than three months. Further, DSM-IV, but not ICD-10, requires evidence of impairment in social and/or occupational functioning. PCS and PCD criteria are presented in Table 8 and 9. Differences between these two diagnostic systems result in significantly different incidence estimates. Based on previous studies, the prevalence rate of PCS (ICD-10) is 3 to 6 times greater than that of PCD (DSM-IV) at three months after MTBI (McCauley et al., 2001; Boake et al., 2005; McCauley et al., 2007).

Table 8. ICD-10 Diagnostic criteria for post-concussion syndrome

Note: The nosological status of this syndrome is uncertain, and criterion A of the introduction to this rubric is not always ascertainable. However, for those undertaking research into this condition, the following criteria are recommended:

A. The general criteria of F07 must be met. The general criteria for F07, Personality and Behavioral Disorders Due to Brain Disease, Damage and Dysfunction, are as follows:
   G1. Objective evidence (from physical and neurological examination and laboratory tests) and/or history, of cerebral disease, damage, or dysfunction.
   G2. Absence of clouding of consciousness and of significant memory deficit.
   G3. Absence of sufficient or suggestive evidence for an alternative causation of the personality or behavior disorder that would justify its placement in section F6 (Other Mental Disorders Due to Brain Damage and Dysfunction and to Physical Disease).

B. History of head trauma with loss of consciousness, preceding the onset of symptoms by a period of up to four weeks (objective EEG, brain imaging, or oculonystagmographic evidence for brain damage may be lacking).

C. At least three of the following:
   1. Complaints of unpleasant sensations and pains, such as headache, dizziness (usually lacking the features of true vertigo), general malaise and excessive fatigue, or noise intolerance.
   2. Emotional changes, such as irritability, emotional lability, both easily provoked or exacerbated by emotional excitement or stress, or some degree of depression and/or anxiety.
   3. Subjective complaints of difficulty in concentration and in performing mental tasks, and of memory complaints, without clear objective evidence (e.g. psychological tests) of marked impairment.
   4. Insomnia.
   5. Reduced tolerance to alcohol.
   6. Preoccupation with the above symptoms and fear of permanent brain damage, to the extent of hypochondriacal over-valued ideas and adoption of a sick role.

Table 9. DSM-IV Research criteria for postconcussional disorder

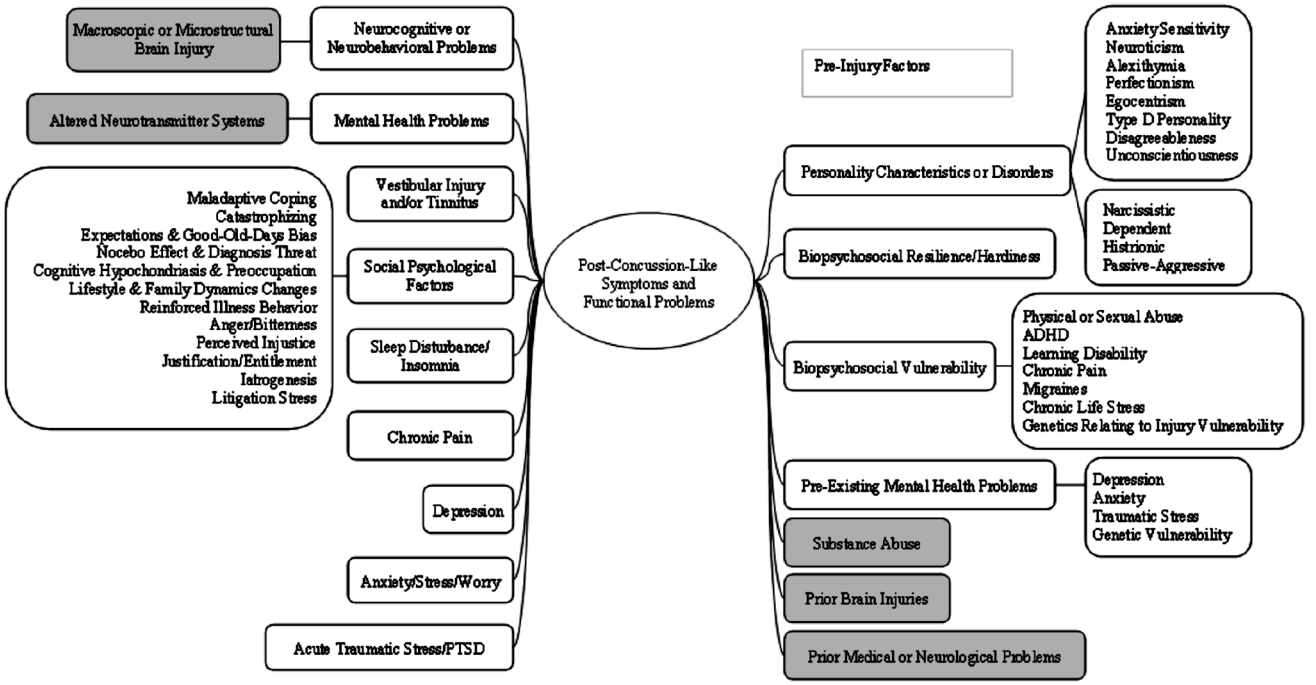
A.	A history of head trauma that has caused a significant cerebral concussion. *Note. The manifestations of concussion include loss of consciousness, post-traumatic amnesia, and less commonly, post-traumatic onset of seizures. Specific approaches for defining this criterion need to be refined by further research.*
B.	Evidence from neuropsychological testing or quantified cognitive assessment of difficulty in attention (concentrating, shifting focus of attention, performing simultaneous cognitive tasks) or memory (learning or recalling information).
C.	Three (or more) of the following occur shortly after the trauma and last at least 3 months: (1) becoming fatigued easily (2) disordered sleep (3) headache (4) vertigo or dizziness, (5) irritability or aggression on little or no provocation, (6) anxiety, depression, or affective liability (7) changes in personality (e.g., social or sexual inappropriateness) (8) apathy or lack of spontaneity.
D.	The symptoms in criteria B or C have their onset following head trauma or else represent a substantial worsening of preexisting symptoms.
E.	The disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning. In school age children, the impairment may be manifested by a significant worsening in school or academic performance dating from the trauma.
F.	The symptoms do not meet criteria for Dementia due to Head Trauma and are not better accounted for by another mental disorder (e.g., Amnestic Disorder due to Head Trauma, Personality Change Due to Head Trauma.

Considerable controversy exists regarding the origin of persistent, long-term post-concussive symptoms. It has been argued that the extent of the injury does not explain the patient's subjective problems (Bigler, 2001; Rees, 2003). Three major classes of factors contribute to the development of PPCS: pre-injury factors (e.g., gender, age, personality type, coping styles, personality, socioeconomic factors); injury factors (e.g., mechanism of injury, magnitude, and anatomic location of brain injury); and post injury factors (e.g., medications, hormonal milieu, plasticity) (Wood, 2004; Ruff, 2005; Garden et al., 2010). It has been suggested that organic factors are responsible for the origin of the post-concussion symptoms, but psychological factors and non-injury related factors are largely responsible for the persistence of symptom clusters (Wood, 2004; Daneshvar et al., 2011; Iverson & Lange, 2011; Iverson et al., 2012).

Some signs and symptoms of MTBI may not be present immediately, but may evolve over several hours to days after injury (Eckner & Kutcher, 2010). However, it has been argued that substantially delayed onset of symptoms is a rare occurence (McCrea et al., 2009), and the onset of new symptoms of PPCS after 6 weeks post-injury have no biologic precedent in uncomplicated MTBI (Rees, 2003). Post-concussive symptoms are non-specific to TBI and often endorsed by normal controls without brain injury

(Garden et al., 2010, Lange et al., 2012), patients with major depressive disorder (Iverson, 2006a), patients with chronic pain (Smith-Seemiller et al., 2003; Stålnacke, 2012), and personal injury claimants (Lees-Haley et al., 2001; Carroll et al., 2004a) with no history of brain injury.

Based on Silverberg's and Inverson's review (2011), both biological and psychosocial factors can contribute to PCS throughout its course. Their review of the research evidence suggests that a biopsychosocial conceptualization of the development and maintenance of the post-concussion syndrome best fits the data (Silverberg & Iverson, 2011). A theoretical biopsychosocial model is presented in Figure 1.



1 For example, hypertension, heart disease, cardiac surgery, diabetes, thyroid problems, and small vessel ischemic disease.
Note: Structural and/or microstructural damage to the brain is not necessary to cause or to maintain the symptoms comprising a post-concussion syndrome. Moreover, structural and/or microstructural damage, if present, is likely insufficient to causally maintain a persistent post-concussion syndrome. Assuming that a constellation of persistent symptoms are present (i.e., not exaggerated), there are many factors that could, singly or in combination, be the underlying cause of these symptoms. Notably, patients with chronic pain frequently report a constellation of symptoms that are post-concussion-like, and patients with depression are virtually guaranteed to report symptoms that mimic a post-concussion syndrome (in the absence of a history of head trauma).

Figure 1. A biopsychosocial conceptualization of poor outcome from mTBI.

The diagnostic situation is further complicated because premorbid or comorbid conditions such as pain, post-traumatic stress disorder (PTSD), and depression can mimic PPCS even in the absence of MTBI (Garden et al., 2010). Further, depending on the criteria set used in research, there are enormous differences in prevalence. Boake at al. (2005) found that only 11% of TBI patients (90% mild, 10% moderate) met PCD criteria whereas 64% of patients met PCS criteria.

Prior studies have repeatedly demonstrated that MTBI participants report significantly greater levels of postconcussive symptoms than normal controls (Beaupré et al., 2012; Lange et al., 2012). However, post-concussion symptoms are also common in the general population (Kashluba et al., 2006). Iverson and Lange (2003) examined the prevalence of post-concussion-like symptoms in a sample of 104 healthy, non-injured volunteers. Experiences of fatigue, poor concentration, irritability, temper problems, memory problems, and poor sleep were frequently reported by participants. Based on the frequency ratings of each symptom, 35.9% to 71.8% of the sample experienced one or more of the symptoms at least 1–2 times in the past two weeks. There was a strikingly high prevalence of mild post-concussion-like symptoms in a healthy population despite the absence of a head injury. The percentages of healthy participants who met ICD-10 criteria for PCS was 72.1%. In addition, this study demonstrated that post-concussion-like symptoms are highly associated with depressive symptomatology. Similarly, Garden and co-workers (2010) studied the endorsement of post-concussion-like symptoms in a nonhead injured sample, and found the level of endorsement of such symptoms was high. Of the total sample, 59.1% could be classified as having PCS (endorsed symptoms as a mild problem or greater on three out of the six ICD-10 Category C). The most frequently endorsed symptoms at mild or higher level were headache (83%), nervous/tense (77%), irritable (78%), and fatigue (82%).

Iverson (2006a) has shown that about 90% of patients with a depressive disorder (with no recent history of brain injury) meet PCS criteria for symptoms rated mild or greater. When using more exclusive criteria for PCS (symptoms rated moderate to severe), still more than 50% of the depression patients met criteria for the diagnosis. Similar findings have been reported recently by Lange and associates (2012). They found that over 50% of the trauma control group met ICD-10 criteria for post-concussion syndrome on the basis of symptoms endorsed at a mild level of greater. In sum, PPCS is not specific to MTBI. It has been argued that the use of the term PCS/PCD may even be misleading because it incorrectly suggests that the basis of symptom constellation is a brain injury (Meares et al., 2008).

It has been estimated that 10 to 20% of MTBI patients might develop PPCS and fall into a category sometimes called the "Miserable Minority" (Ruff, 2005). According to some studies, as many as 15% of people with a history of MTBI still suffer from symptoms

one year after injury (Rees, 2003; Carrol et al., 2004a). In a Scandinavian study, 40% of persons with MTBI fullfilled the criteria for a PCS at three months and 27.3% were PCS cases one year after the trauma (Sigurdardottir et al., 2009). This finding is in line with another Scandinavian study by Ingebrigtsen and co-workers (1998) in which a total of 40% of MTBI patients fulfilled the diagnostic criteria for post-concussion syndrome at three months after injury. An even greater annual incidence of disability was reported by Thornhill and co-workers (2000). In their study with a cohort of 362, they found that moderate to severe disability was present in 47% of patients at one year post-injury (Thornhill et al., 2000). The scientific basis for the commonly cited 10–20% rate of Miserable Minority (patients not recovering following MTBI by 6–12 months) is questionable and might be too high (Iverson, 2005; Iverson et al., 2007). Methodological issues, such as recruitment bias (small number of non-representative, methodologically-limited samples), and the criteria used to diagnose the disorder (PCS vs PCD), may lead to such overestimates (Iverson et al., 2007; Williams et al., 2010).

In contrast, it has been suggested that motivation to return to play may result in underreporting of symptoms after sport-related concussions (McCrea et al., 2009). Based on prospective samples, it is estimated that only a very small percentage (less than 5%) of civilian cases report persistent post-concussion symptoms 6 to 12 months after MTBI (Iverson eet al., 2007; McCrea et al., 2009). McCrea (2008, p. 165) states that depending on how restrictive the diagnostic criteria are of the disorder/syndrome, the estimate could be even lower than 1 percent of all MTBI patients.

Subjective symptom reporting remains an essential element in the diagnosis and evaluation of post-concussion symptoms following MTBI. In athletic settings, a number of standardized symptom checklist have been developed to diagnose and manage concussion, such as the Sport Concussion Assessment Tool (SCAT, SCAT2, and SCAT3), which is one of the most widely used sideline assessment tools (see Eckner and Kutcher, 2010 for review; Putukian, 2011; Dziemianowicz et al., 2012). The Military Acute Concussion Evaluation (MACE) has been used to assess individuals in combat situations (Coldren et al., 2010). In health care settings and research, the Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ) (King et al., 1995), Post-Concussion Symptom Score (PCSS) (Lowell and Collins, 1998), and Acute Concussion Evaluation (ACE) (Gioia and Collins, 2006) are the most widely used symptom checklists (Dziemianowicz et al., 2012).

It is widely accepted that the method of collecting symptoms can impact test results. Self-report of post-concussive symptoms by patients has been criticized as being unreliable. Studies show that a patient's self-report may be the result of simple malingering (Hall & Chapman, 2005), or recall biases such as the "good old days" bias (individuals to have a retrospective rosy view of the past and often underestimate problems pre-

injury) (Iverson et al., 2010). However, it has also been stated that self-report measures may be a better way of obtaining consistent results than, for example, interviewing. It has been reported that there is a significant difference in symptom reporting across interviewer gender; subjects endorse more symptoms when the interviewer is a woman (Krol et al., 2011). Also, it has been reported that patients endorse far more symptoms on a questionnaire than during the interview (Nolin et al., 2006; Iverson and Lange, 2011). The influence of interview method on symptom reporting following MTBI is striking. Iverson et al. (2010) compared interview-based, post-concussion symptom reporting to endorsement of symptoms on a questionnaire in a sample of 61 MTBI patients. During the clinical interview, patients spontaneously endorsed an average of 3.3 symptoms (SD = 1.9). In contrast, when given the questionnaire to complete, patients endorsed an average of 9.1 symptoms (SD = 3.2). In addition, it was common for patients to endorse symptoms as moderate or severe on the questionnaire, despite not spontaneously reporting those symptoms during the interview (Iverson et al., 2010).

2.3.1.1 Cognitive Sequel After Mild Traumatic Brain Injury

Based on meta-analyses of the literature, neuropsychological deficits are pronounced in the first week following injury but improve over time (Schretlen & Shapiro, 2003; Belanger et al., 2005; Frencham et al., 2005). Current literature suggests that there are no objectively measured cognitive deficits attributable to MTBI beyond 1–3 months following injury in the majority of cases (Holm et al., 2005; Iverson, 2005). Recovery rates vary by age and measures used (Dikmen et al., 2001). The overall effect of MTBI on cognitive functioning after the acute recovery period is considerably smaller than the effects of depression, bipolar disorder, attention deficit disorder, benzodiazepine use/withdrawal, litigation, and malingering (Iverson, 2005). It has been argued that the average effect of MTBI on neuropsychological test performance is probably not distinguishable from that of matched controls by one month postinjury (Schretlen and Shapiro, 2003), and undetectable by 3 months postinjury (Binder et al., 1997). In their meta-analysis, Binder et al. (1997) found the overall effect of MTBI to be smaller than the measurement error of neurocognitive test three months after injury. It has been stated that the effects of preinjury characteristics, such as level of education, are as big as or bigger than the effects of MTBI on cognition (Dikmen et al., 2001). Importantly, litigation after MTBI has been shown to be associated with stable or worsening cognitive functioning over time (Belanger et al., 2005). Also, confounding variables other than brain injury, such as pain, insomnia, stress, and depression, may cause or perpetuate cognitive deficits after MTBI (Rees, 2003).

Comprehensive overview of the development of common data elements (CDE) for research on TBI and psychological health was published in Archives of Physical and Medical Rehabilitation (Wilde et al., 2010). The Interagency Traumatic Brain Injury Outcomes Workgroup concluded that "Objective measures of neuropsychological functions, such as attention, memory, and executive function, are very sensitive to effects of TBI and often affect everyday activities and social role participation" and made a recommendation for a selection of neuropsychological impairment outcome measures to be used in association on TBI (Wilde et al., 2010). This recommendation includes a variety of neuropsychological tests for adults and pediatric patients across the severity spectrum of TBI.

Specific recommendations for adult MTBI patients include the following well-established core tests: Rey Auditory Verbal Learning Test (Lezak, 2004), Trail Making Test (Army, 1944), and Wechsler Adult Intelligence Scale Processing Speed Index (Wechsler, 2005). Additional supplemental measures such as Automated Neuropsychological Assessment Metrics (Automated Neuropsychological Assessment, 2007), Brief Visuospatial Memory Test – Revised (Psychological Assessment Resources, Lutz, Florida), Color-Word Interference Test (Delis et al., 2001), Controlled Oral Word Association Test (Strauss et al., 2006), Grooved Pegboard Test (Lezak, 2004), NIH Toolbox Cognition Battery (Wilde et al., 2010 and http://www.nihtoolbox.org), Symbol Digit Modalities Test (Strauss et al., 2006), Wechsler Adult Intelligence Scale Digit Span subtest and Letter-Number Sequencing subtest (Wechsler, 2005), and Word Reading Subtest of the Wide Range Achievement Test (Wilkinson and Robertson, 2006) were recommended for consideration in MTBI research focusing on more specific topics (Wilde et al., 2010). In athletic settings, computer-based neuropsychological testing is widely used by sports teams, universities, and high schools. One of the most popular computerized test batteries in sports is ImPACT (Johnson et al., 2011).

2.3.1.2 Fatigue After Mild Traumatic Brain Injury

Fatigue is considered one of the most persistent and disabling symptoms in patients with TBI (Powell et al., 1996; Borgaro et al., 2005; Ziino and Ponsford, 2005; Stulemeijer et al., 2006; Bushnik et al., 2008). Fatigue following TBI is a complex and multidimensional problem (Cantor et al., 2008) that includes many components: physical, mental, motivational, situational, and activity-related (Bay and Xie, 2009). It has been suggested that fatigue is not related to injury severity because it does not seem to be more common in severe than in mild TBI (Belmont et al., 2006; Stulemeijer et al., 2006). Even after a mild TBI, fatigue can be a distressing and disruptive symptom in some patients and significantly impair quality of life.

Fatigue is a common complaint in healthy adults and it is also commonly experinced by patients with a variety of health problems. Previous studies have reported a strong association between fatigue and depression, and also overlap of the content of questionnaires assessing these constructs (Walker et al., 1991; Chwastiak et al., 2005). According to Ziino and Ponsford (2005), depression is common following TBI and may contribute to post-injury fatigue. In their study, Walker et al. (1991) reported significantly elevated levels of depression in the TBI group with fatigue compared with those without fatigue. It appears that fatigue and depression are inter-related and they share a complex set of etiologies. This strong association between fatigue and depressive symptomatology raises the question as to whether post-injury fatigue constitutes an independent symptom, or whether it is largely a manifestation of depression.

There are only few well validated measures that are designed to measure fatigue, and even fewer that are specifically intended for the TBI population. According to a review by Belmont and colleagues (2006), five questionnaires have been used to assess TBI-related fatigue: the Fatigue Severity Scale (FSS), Visual Analogue Scale for Fatigue (VAS-F), Fatigue Impact Scale (FIS), Barrow Neurological Institute (BNI) Fatigue Scale, and the Cause of Fatigue (COF) Questionnaire. In addition, Stulemeijer et al. (2006) have used the Checklist Individual Strength (CIS) in their study for fatigue severity and fatigue related dimensions in MTBI patients. Only the BNI Fatigue Scale and the COF Questionnaire are specifically designed for patients who have sustained TBIs.

The study of fatigue following MTBI is important because (a) it is a very common symptom in the initial days and weeks post injury (van der Naalt et al., 1999a; Borgaro et al., 2005; Norrie et al., 2010); (b) it is a common symptom at 3 months post injury (Mickeviciene et al., 2004; Lundin et al., 2006; Lannsjö et al, 2009); (c) when present at 3–6 months post injury it can remain a problem long term (Norrie et al., 2010); (d) it is related to subjectively-experienced cognitive problems (Stulemeijer et al., 2007); (e) it can interfere with social and occupational functioning (Stulemeijer et al., 2006; Johansson et al., 2009); and (f) its underlying causes can be complex, interwoven, and wholly or partially treatable (e.g., insomnia, anxiety, depression, chronic pain, life stress, and physical deconditioning).

The primary goal in assessing post-injury fatigue is to identify those at risk of persistent or protracted symptoms. Mechanisms of post-injury fatigue are not fully understood and it has been difficult to find an objective way of measuring it (Johansson et al., 2009). Previously, fatigue scales have been administered to heterogeneous samples which reduce the generalizability of the results (Borgaro et al., 2004). In sum, without adequate instruments for the assessment of post-injury fatigue, it is difficult

for professionals to sufficiently address the problem of TBI-related fatigue in its initial stages.

2.3.1.3 Return to Work After Mild Traumatic Brain Injury

Return to work (RTW) is one important outcome measure and marker of functional recovery following MTBI. It has been emphasized as a key component for evaluating outcome in the World Health Organization's International Classification of Functioning, Disability, and Health (World Health Organization, 2011). Unsuccessful return to work can have profound negative economic and psychosocial consequences for the individual. Although studies consistently find that individuals with MTBI return to work more rapidly than those with severe brain injuries, the literature has been quite inconsistent in terms of the length of time to RTW that is typical for individuals with MTBI. The one week RTW rates vary widely in the literature, ranging from 41% (Powell et al., 1996) to 84% (Stranjalis et al., 2004). The percentages of individuals returning to work by one month following injury has also varied widely across studies, ranging from 25% to 100% (Wrightson and Gronwall, 1981; Dikmen et al., 1994; Haboubi et al., 2001; Stranjalis et al., 2004; Vuadens et al., 2006).

Very few studies have analyzed neuroimaging results in association to RTW. There is some evidence, however, that MTBI patients with trauma related neuroradiological abnormalities take considerably longer to return to work (Iverson et al., 2012). Acute injury characteristics (PTA, LOC, GCS) were not correlated with duration off work in one study (Nolin and Heroux, 2006). Literature suggests that post-concussion symptom complaints may cause delay in RTW (Haboubi et al., 2001). The number of subjective complaints postinjury is related to RTW (Van der Naalt et al. 1999a; Nolin & Heroux, 2006).

2.3.2 Risk Factors of Poor Outcome Following Mild Traumatic Brain Injury

The risk factors for poor outcome after MTBI are diverse, complex, and not well understood (Andersson et al., 2011). A range of biological, psychological, and social factors, other than those directly reflecting the severity of injury, appear to be associated with outcome following MTBI. There are pre-existing risk factors such as age, gender, premorbid psychiatric symptoms, history of previous head injury, and lower level of education, that may predispose an individual to worse outcomes following MTBI (Ponsford et al., 2000). Also, there are peri-injury and post-injury risk factors such as

mechanism of injury (motor vehicle accident), lack of support system, context of injury (stress, combat-related, traumatic), and substance abuse that may be maintaining factors for worse outcome (Ponsford et al., 2000; Wood, 2004; Iverson et al., 2007).

Women have significantly higher odds of poor outcome after MTBI, both in terms of more symptoms and a longer duration of impairment (Farace and Alves, 2000; Bazarian et al., 2010; Ponsford et al., 2012). Age over 40 years has also been identified as a predictor of prolonged symptoms (Binder, 1997; Carroll et al., 2004a). It has been repeatedly demonstrated that patients with premorbid psychiatric or other health problems and other life stressors are more likely to have sustained post-concussion symptoms (Binder, 1997; Carroll et al., 2004a; Ghaffar et al., 2006; Kashluba et al., 2008; Meares et al., 2008; Ponsford et al., 2012) Premorbid vulnerable personality traits such as compulsive, histrionic, narcissistic, and dependent have been considered risk factors by some researchers (Evered et al., 2003; Wood, 2004). Personality characteristics influence the development and maintenance of the post-concussive disorder and these characteristics represent a large psychological component to the disorder (Iverson et al., 2007).

Some studies have reported that MTBI patients with trauma-related intracranial abnormalities are more likely to have worse outcome compared to those with uncomplicated MTBIs (patients with no intracranial abnormalities) (Williams et al., 1990; Wilson et al., 1996; van der Naalt et al., 1999b; Temkin et al., 2003; Iverson, 2006; Lange et al., 2009). Other studies, however, have not reported this association (Hofman et al., 2001; McCauley et al., 2001; Hughes et al., 2004).

Access to compensation is considered the strongest predictor of MTBI outcome (Carroll et al., 2004a). There is compelling evidence that increased reporting of post-concussion symptoms is associated with litigation or compensation-seeking (Binder and Rohling, 1996; Kashluba et al., 2008).

It has been suggested that there could be a genetic predisposition to poorer outcome following TBI, and one such candidate gene is the apolipoprotein E (APOE) gene (Han et al., 2007). However, considerable variability exists in studies concerning APOE and cognitive outcome following MTBI. In some studies, patients with specific APOE subtypes, namely APOE-epsilon4 (ε4), have increased risks of post-concussive symptoms (Smith et al., 2006). In contrast, some studies do not support the notion of relatively poorer neuropsychological functioning associated with the APOE-ε4 genotype shortly following mild or moderate brain injury (Han et al., 2007). Similarly, Ponsford et al. (2007) found no evidence of poorer cognitive performance, functional outcome, or slower improvement in moderate-severe TBI or control participants possessing APOE-ε4. In one pediatric study, it was reported that the APOE-ε4 allele was not consistently related to outcome from mild TBI (Moran et al., 2009).

3 AIMS OF THE STUDY

The purpose of this study was to examine biopsychosocial outcome from adult MTBI. The specific aims of the individual studies are listed below.

1) To examine the psychometric properties (reliability and validity) and clinical usefulness of the Barrow Neurological Institute Fatigue Scale in patients with MTBI and healthy controls (Study I).

2) To examine return to work rates and risk factors of slow return to work following MTBI (Study II).

3) To explore diffusion tensor imaging as a diagnostic modality to detect subtle, but clinically meaningful, changes following uncomplicated MTBI (Study III).

4) To examine the association between white matter integrity and subjective post-concussion symptom reporting following uncomplicated MTBI (Study III).

5) To examine multiple biopsychosocial factors relating to post-concussion symptom reporting at one month and one year following MTBI (Study IV).

4 METHODS

4.1 Subjects

A large scale prospective study of outcome from mild TBI was undertaken at Tampere University Hospital. A total of 2,479 consecutive patients from the Emergency Department of Tampere University Hospital were screened by a neurologist for inclusion between October 2006 and May 2009. All patients who had undergone head CT in the emergency department for evaluation of possible brain injury were screened. Of the patients screened, an inception cohort of one-hundred and forty-five (145) patients were recruited for the study. One-hundred and twenty-nine (129) patients met the criteria of MTBI and the other inclusion criteria; 16 patients had moderate TBIs based on GCS and/or PTA and were excluded from the study.

The sample of 129 patients (age: M=37.7, SD=13.5; education: M=12.6, SD=2.7, female 56.6 %) fulfilled criteria for an MTBI according to the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (Mild Traumatic Brain Injury Committee, 1993) and the World Health Organization (WHO) Collaborating Center Task Force on Mild Traumatic Brain Injury (page 115) (Carroll et al., 2004b). Inclusion criteria for the study were (a) biomechanical force applied to the head; (b) loss of consciousness, if present, for less than 30 minutes; (c) Glasgow Coma Scale score between 13 and 15 after 30 minutes following injury; and (d) post-traumatic amnesia, if present, of less than 24 hours. Exclusion criteria for this study were as follows: home municipality other than Pirkanmaa, not Finnish speaking, age under 16 or over 65, previous symptomatic brain injury, history of psychiatric disorder, history of major substance abuse or other medical condition resulting in cognitive changes. In addition, patients with major incidental (not trauma related) neuroradiological findings (such as tumor, cysts demyelinating disease, enlargement of cortical sulci, ventricular enlargement, ischemic lesions, and multiple subcortical signal changes) were excluded from the Study III. Minor incidental findings, such as isolated white matter hyperintensities, were not considered an exclusion criterion. In the inclusion group, the mechanisms of injury were as follows: 31.8% motor vehicle accident (MVA), 3.9%

pedestrian-MVA, 8.5% sports, 37.2% falls (low), 7.8% falls (high), 7.0% assaults, 3.9% other. None of the patients were involved in litigation.

Three separate healthy control groups were recruited from the community for the study: (a) two neuroimaging control groups (group 1 for 3T MRI and group 2 for 1.5T MRI), and (b) one neuropsychological control group. The neuroimaging control group 1 initially consisted of 30 age- and gender-matched participants with no history of brain injury, neurological disease, or psychiatric disorders who completed a neuroimaging protocol using 3 Tesla MRI (age: M=37.7, SD=11.3, female 70.0%). In Study III and Study IV, six participants were excluded due to major incidental findings (e.g., ischemic lesions, numerous white matter hyperintensities, or enlarged lateral ventricles). Twenty-four neuroimaging control subjects were included in the final sample (age: M=36.6 years, SD=10.1, female 66.7%). The neuroimaging control group 2 consisted of 10 age- and gender-matched participants with no history of brain injury, neurological disease, or psychiatric disorders who completed a neuroimaging protocol using 1.5 Tesla MRI (age: M=39.8, SD=12.9, female 50.0%).

The neuropsychological control group consisted of 36 age- and gender-matched participants with no previous history of brain injury, neurological disease, or psychiatric disorders (age: M=36.9 years, SD=13.6, female 64%, education: M=15.1 years, SD=2.5) who completed a battery of neurobehavioral and neurocognitive measures. The study population and the data collection procedure are presented schematically in Figure 2.

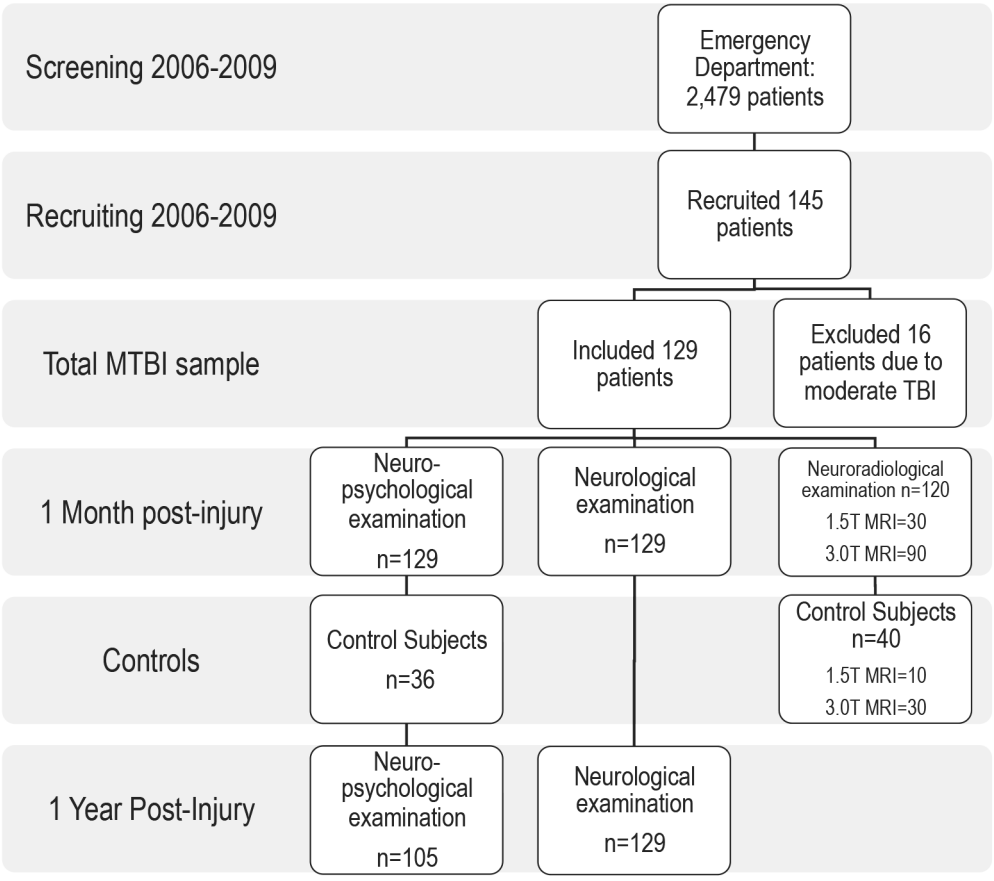


Figure 2. Data collection procedure

4.2 Withdrawal During Study

Twenty-three patients (17.8%, 23/129) dropped out from the study during the one-year follow-up. Those who did not come to the follow-up were compared to those who came to the follow-up (non-dropouts, n=106). Dropouts did not differ from non-dropouts on age (p=.22), education (p=.21), AUDIT at one month (p=.39), BDI-II at one month (p=.54), RALVT total score at one month (p=.11), RPCSQ total score at one month (p=.63), gender (p=.36), RTA (p=.38), previous psychiatric symptoms (p=.66.), previous diseases (p=.62), previous brain injuries (p=.40), abnormal CT findings (p=.21), abnormal MRI findings (p=.74), or duration of sick leave (p=.30). There was a significant difference in PTA and LOC: the dropout group had a significantly shorter duration of PTA (mean 30.8 minutes, SD 81.5) than the non-dropout group

(mean 232.2 minutes, SD 378.7) (t[119.10] = -4.36, p<.01). Also, the dropout group had a significantly shorter duration of LOC (mean .16 minutes, SD .47) than the non-dropout group (mean .96 minutes, SD 2.37) (t[107.96] = -2.94, p<.01).

The demographic and clinical characteristics of MTBI sample are presented in Table 10.

4.3 Ethical Issues

All participants provided written informed consent according to the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Tampere University Hospital.

Table 10. Sample demographic and clinical characteristics

		Total Sample N (100%) N = 129	Study I n (97.7%) n = 126	Study II n (84.5%) n = 109	Study III n (37.2%) n = 48	Study IV n (97.7%) n =126
Age in years [M (SD)]		37.7 (13.5)	37.8 (13.5)	37.4 (13.2)	36.4 (12.4)	37.8 (13.5)
Education in years [M (SD)]		12.6 (2.7)	12.6 (2.7)	12.8 (2.8)	12.7 (2.5)	12.6 (2.7)
Ethnicity [f (%)]	Caucasian	129 (100)	126 (100)	109 (100)	48 (100)	126 (100)
Gender [f (%)]	Female	73 (56.6)	71 (56.3)	57 (52.3)	29 (60.4)	71 (56.3)
Days tested+ post injury [M (SD)]		24.0 (5.4)	24.12 (5.4)	24.3 (5.4)	25.5 (3.3)	24.12 (5.4)
Days MRI conducted post injury [M (SD)]		28.6 (19.9)	29.1 (19.9)	29.3 821.1)	27.0 (8.9)	29.1 (19.9)
GCS [f (%)]	15	122 (94.6)	121 (96.0)	104 (95.4)	44 (91.7)	121 (96.0)
	14	6 (4.7)	5 (4.0)	5 (4.6)	4 (8.3)	5 (4.0)
	13	1 (0.8)	-	-	-	-
Loss of consciousness [f (%)]	None	78 (70.9)	78 (71.6)	70 (73.7)	28 (70.0)	78 (71.6)
	≤ 1min	14 (12.7)	13 (12.0)	10 (10.5)	6 (15.0)	13 (12.0)
	> 1min ≤ 5 min	15 (13.6)	15 (13.8)	14 (14.7)	5 (12.5)	15 (13.8)
	> 5min ≤ 10 min	2 (1.8)	2 (1.8)	1 (1.1)	1 (2.5)	2 (1.8)
	> 10 min	1 (0.9)	1 (0.9)	1 (1.1)	-	1 (0.9)
Posttraumatic amnesia [f (%)]	None	59 (46.8)	59 (48.0)	54 (50.9)	25 (53.2)	59 (48.0)
	≤ 1 hour	20 (15.9)	20 (16.3)	13 (12.3)	5 (10.6)	20 (16.3)
	> 1 hour ≤ 24 hours	47 (37.3)	44 (35.7)	39 (36.8)	17 (36.2)	44 (35.7)
Retrograde amnesia [f (%)]	None	102 (80.3)	101 (81.5)	87 (81.3)	35 (74.5)	101 (81.5)
	≤ 1 hour	20 (15.7)	20 (16.1)	17 (15.9)	11 (23.4)	20 (16.1)
	> 1 hour ≤ 24 hours	5 (3.9)	3 (2.4)	3 (2.8)	1 (2.1)	3 (2.4)
CT: Day-of-injury [f (%)]	Abnormal*	10 (7.8)	10 (7.9)	10 (9.2)	-	10 (7.9)
	Not Available	7 (5.4)	7 (5.6)	6 (5.5)	-	7 (5.6)

		Total Sample N (100%) N = 129	Study I n (97.7%) n = 126	Study II n (84.5%) n = 109	Study III n (37.2%) n = 48	Study IV n (97.7%) n =126
MRI Tesla [f (%)]	1.5	39 (30.2)	37 (29.4)	32 (29.4)	-	37 (29.4)
	3.0	90 (69.8)	89 (70.6)	77 (70.6)	48 (100)	89 (70.6)
MRI: 3 weeks post injury [f (%)]	Abnormal*	16 (12.4)	15 (11.9)	14 (12.8)	-	15 (11.9)
	Not Available	7 (5.4)	7 (5.6)	7 (6.4)	-	7 (5.6)
Multiple trauma [f (%)]	Present	36 (27.9)	35 (27.8)	33 (30.3)	11 (22.9)	35 (27.8)
Pre-Injury psychiatric Sx [f (%)]	Present	9 (7.0)	9 (7.1)	7 (6.4)	-	9 (7.1)
Mechanism of injury [f (%)]	MVA	41 (31.8)	41 (32.5)	37 (33.9)	10 (20.8)	41 (32.5)
	Pedestrian-MVA	5 (3.9)	5 (4.0)	5 (4.6)	2 (4.2)	5 (4.0)
	Sports	11 (8.5)	11 (8.7)	11 (10.1)	6 (12.5)	11 (8.7)
	Fall low	48 (37.2)	46 (36.5)	36 (33.0)	19 (39.6)	46 (36.5)
	Fall high	10 (7.8)	9 (7.1)	8 (7.3)	3 (6.3)	9 (7.1)
	Assault	9 (7.0)	9 (7.1)	7 (6.4)	5 (10.4)	9 (7.1)
	Other	5 (3.9)	5 (4.0)	5 (4.6)	3 (6.3)	5 (4.0)
Working Status [f (%)]	Working full time	88 (68.2)	85 (67.5)	83 (76.1)	38 (79.2)	85 (67.5)
	Working part time	3 (2.3)	3 (2.4)	3 (2.8)	-	3 (2.4)
	Student	20 (15.5)	20 (15.9)	20 (18.3)	5 (10.4)	20 (15.9)
	Unemployed	12 (9.3)	12 (9.5)	-	4 (8.3)	12 (9.5)
	Retired/					
partly retired	5 (3.9)	5 (4.0)	3 (2.8)	1 (2.1)	5 (4.0)	
	Sick leave	1 (0.8)	1 (0.8)	-	-	1 (0.8)

Abbreviations: CT = computed tomography; ED = Emergency Department; GCS = Glasgow Coma Scale; M = mean; min = minutes; MRI=magnetic resonance imaging; MVA = motor vehicle accident; SD = standard deviation

Note: + = Neuropsychological assessment, * = Trauma related intracranial abnormalities, Total Sample: LOC, n = 110, PTA, n = 126, RTA, n =127; Study I: LOC, n = 109, PTA, n = 123, RTA, n = 124; Study II: LOC, n = 95, PTA, n = 106, RTA, n = 107; Study III: LOC, n = 40, PTA, n = 47, RTA, n = 47

4.4 Measures

4.4.1 Neuropsychological Assessment

An extensive neuropsychological examination was conducted for each patient approximately one month and 12 months following MTBI. However, some test results were not used in the published studies. Neuropsychological tests were chosen based on their reported clinical usefulness in MTBI research. The NINDS Common Data Elements for TBI were not available when the study protocol was created (year 2005). Measures that were used in the published studies are described in detail below.

4.4.1.1 Neurocognitive Measures

The Rey Auditory Verbal Learning Test (RAVLT) (Lezak et al., 2004) and Four Word Short Term Memory Test (FWSTMT) (Morrow et al., 2002) were used to assess verbal memory. The RAVLT is a widely used test for learning and memory. In this study, immediate recall (total number of words recalled in trials 1–5), recall after interference word list, and delayed recall and recognition after 30 minutes were used. The FWSTMT is a test of working memory based on the Brown-Peterson paradigm (Lezak et al., 2004). In this study total scores for each three distractor intervals (5", 15", 30") were used which is the sum of 5 trials (min = 0, max = 20). Visual memory was assessed with the Rey-Osterrieth Complex Figure Test (ROCFT) immediate recall version (Rey, 1941). Verbal intelligence was assessed with Wechsler Adult Intelligence Scale – Third Edition (WAIS III) information subtest. Executive functions were assessed with a Stroop Test Golden version (color-word interference trial, number of items completed) (Lezak et al., 2004), Trail Making Test Part A and Part B (TMT, time in seconds) (Army Individual Test Battery, 1944), tests of phonemic (P\A\S) and semantic (animals) verbal fluency (total number of words in 1 minute) (Strauss et al., 2006), and ROCFT copy version (sum of correct responses) (Strauss et al., 2006).

4.4.1.2 Self-report Questionnaires

Self-reported fatigue was examined using the Barrow Neurological Institute Fatigue Scale (BNI-FS), an 11-item self-report questionnaire designed to assess fatigue during the early stages of recovery after brain injury (Borgaro et al., 2004). Subjects were asked

to use a 7-point scale to rate the extent to which each of the 10 primary items has been a problem for them since the injury. Response options were as follows: 0–1=rarely a problem; 2–3=occasional problem, but not frequent; 4–5=frequent problem; 6–7=a problem most of the time. The final item (item 11) asks subjects to provide an overall rating of their level of fatigue on a scale from 0 (no problem) to 10 (severe problem). In this study the total BNI-FS score is used, which is the sum of all 10 scores (min=0, max=70). The BNI-FS has high one-day test-retest reliability (r=.96) (Borgaro et al., 2004).

Post-concussion symptoms were assessed with the Rivermead Post Concussion Questionnaire (RPSQ) (King et al., 1995). The RPSQ is a 16-item self-report questionnaire that measures the severity of common post-concussion symptoms on a 5-point Likert scale. The patients rated the presence of the symptoms over the past 24 hours on a scale from 0 to 4 (0 = not experienced at all after the injury, 1 = experienced but no more of a problem compared with before the injury, 2 = a mild problem, 3 = a moderate problem, and 4 = a severe problem). A total score was calculated by adding all items with a score greater than 1 (not present anymore or no worse than prior to the injury). High test-retest reliability has been reported for 7–10 day (r=.90) and 6-month (r= .87) intervals (King et al., 1995).

Depressive symptoms were assessed using the Beck Depression Inventory-Second Edition (BDI-II) (Beck et al., 1996), a 21-item self-report questionnaire. Subjects are asked to rate each item on a four-point scale ranging from zero to three. In this study, we used the total score which is the sum of all 21 items, giving a range from zero to 63. It should be noted that many symptoms on this questionnaire overlap with post-concussion symptom measured by the RPSQ. The BDI-II has high internal consistency (coefficient alphas > .90 in different samples) and correlates with self-report measures with conceptually related constructs such as hopelessness (r = .68), as well as interviewer-rated depression symptoms (r = .71 with the Hamilton Rating Scale for Depression) (Beck et al., 1996).

The EuroQol Five Dimension (EQ-5D) Visual Analogue Scale (VAS) was used to evaluate general health-related quality of life. EQ-5D™ is a standardized instrument for use as a measure of health outcome and the EQ-5D™ is a trade mark of the EuroQol Group (EuroQol, 1990). The EQ-5D VAS is a visual scale that asks the respondent to consider and rate his/her health ”today” on a vertical scale calibrated from 0 (worst imaginable health state) to 100 (best imaginable health state).

The Alcohol Use Identification Test (AUDIT) was used to detect alcohol problems (Babor et al., 2001). The AUDIT is a widely used brief screening test to identify persons who have risky drinking, harmful drinking, or alcohol dependence. The AUDIT is a self-report measure that consists of 10 questions. Each of the questions has a set of

responses to choose from, and each response has a score ranging from 0 to 4 (questions 1–8). Questions 9 and 10 are scored 0, 2, or 4 only. All the response scores are added to create a total score. A total score of > 8 on the AUDIT is considered indicative of harmful or hazardous drinking. The AUDIT has a high test-retest reliability (r = .86; Sinclair et al., 1992). Neuropsychological measures are presented in Table 11.

Table 11. Neuropsychological test battery

Function	Neuropsychological test	Variable
Screening tests	WAIS-III: Information -subtest (Wechsler, 2005)	Age scaled scores
	SADD (Raistrick et al., 1983)	Total score
	AUDIT (Babor et al., 2001)	Total score
	CANTAB MOT (CANTAB®, 2004)	Reaction time in milliseconds
	GOAT (Leven et al., 1979)	Total score
Memory	RAVLT (Lezak, 2004):	
	Immediate recall	Sum of trials 1 to 5
	Delayed recall	Sum of words recalled after delay
	Recognition	Sum of hits
	Intrusions	Sum of intrusions
	Postinterference recall	Sum of words recalled after interference trial
	ROCFT (Rey, 1941):	
	Immediate recall	Sum of correct units recalled immediate after copying
	Delayed recall	Sum of correct units recalled after delay
	FWSMT (Morrow & Ryan, 2002)	Sum of words recalled after varying distractor intervals
	CANTAB PAL (CANTAB®, 2004)	Total number of errors
Attention and executive functions	TMT version A (Army, 1944)	Time in seconds
	TMT version B (Army, 1944)	Time in seconds
	ROCFT (Rey, 1944):	
	Copy	Sum of correct units and time in seconds
	COWAT (P,A,S) (Spreen & Strauss, 1991)	
	Total number of words in 1 minute	
	COWAT (animals) (Spreen & Strauss, 1991)	Total number of words in 1 minute
	Stroop Color Word Test – Golden version (Lezak, 2004):	
	Color-word	Total number of correct responses and errors in 45 seconds
	Word	Sum of words said in 45 seconds
	Color	Sum of colors said in 45 seconds

Function	Neuropsychological test	Variable
	Expected	(Sum of colors x sum of words) / (sum of colors + sum of words)
	Interference	Total correct responses – expected result
	CANTAB 5 CRTI (CANTAB®, 2004)	Reaction time in milliseconds
	CANTAB RVP A' (CANTAB®, 2004)	A prime; measures how good the subject is at detecting target sequences using p(hit) and p(false alarms)
Psychosocial functioning	Glascow Outcome Scale (GOS) (Jennett & Bond, 1975)	Total score (min 1–max 8)
	Differential Outcome Scale (DOS) (Van der Naalt et al., 1999a)	Total score (min 4–max 20)
	EuroQol 5D (EQ-5D) (EuroQol Group, 1990)	Total score & VAS score
	Beck Depression Inventory II (BDI-II) (Beck et al., 1996)	Individual items scores & total score
	RPCSQ (King et al., 1995)	Individual items scores & total score
	RHIFQ (Crawford et al., 1996)	Individual items scores & total score
	Fatigue Impact Scale (FIS) (Fisk et al., 1994):	
	Cognitive subscale	Total score
	Physical subscale	Total score
	Psychosocial subscale	Total score
	Total	Sum of subscale scores
	BNI Fatique Scale (Borgaro et al., 2004)	Individual items scores (from 0 to 7) and overall fatigue score on scale 0 to 7
	Length of sick leave after injury	Number of days

Abbreviations: A comprehensive battery was used in the larger study, but only a subset of measures was used in the individual published studies. WAIS III = Wechsler Adult Intelligence Scale – Third Edition; SADD = Short-form Alcohol Dependence Data Questionnaire; AUDIT = Alcohol Use Disorders Identification Test; CANTAB MOT = Cambridge Neuropsychological Test Automated Battery Motor Screening; GOAT = The Galveston Orientation and Amnesia Test; RAVLT = Rey Auditory Verbal Learning Test; ROCFT = Rey Osterrieth Complex Figure Test; FWSMT = The Four Word Short –Term Memory Test; CANTAB PAL = Cambridge Neuropsychological Test Automated Battery Paired Associates Learning; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Test; CANTAB 5 CRTI = Cambridge Neuropsychological Test Automated Battery Five-Choice Reaction Time; CANTAB RVP = Cambridge Neuropsychological Test Automated Battery Rapid Visual Information Processing; RPCSQ = The Rivermead Post Concussion Symptoms Questionnaire; RHIFQ = The Rivermead head injury follow-up questionnaire.

4.4.2 Magnetic Resonance Image Acquisition

Magnetic resonance imaging was performed on a 1.5 Tesla (T) MRI machine (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) and a 3T Siemens Trio (Siemens AG Medical Solutions, Erlangen, Germany) machine. MRI sequences were evaluated by a certified neuroradiologist. From the inception cohort,

45 patients underwent 1.5 T MRI and 100 patients underwent 3 T MRI. The MRI protocol included sagittal T1-weighted 3D IR prepared gradient echo, axial T2 turbo spin echo, conventional axial and high resolution sagittal fluid-attenuated inversion recovery (FLAIR), axial T2*, and axial susceptibility weighted imaging (SWI) series. White matter hyperintensities (WMHI) were recorded from FLAIR sequences. The parameters for FLAIR sequences were TI 2216 ms, TR 7000 ms, TE 87 ms, FOV 199 × 220 ms, matrix 232 × 256, slice/gap 4.0/1.2 mm. The DTI sequence was single-shot diffusion-weighted echo planar imaging. The parameters for DTI were TR 5144 ms, TE 92 ms, FOV 230 mm, matrix 128 × 128, 3 averages, slice/gap 3.0/0.9 mm, b-factor 0 and 1000 s/mm^2, and 20 diffusion gradient orientations. A 12-channel head matrix coil was used.

Region-of-interest (ROI) based DTI measurements were performed in eight different anatomical locations of each hemisphere and in three locations within the corpus callosum. Quantitative DTI parameters, including apparent diffusion coefficient (ADC) and fractional anisotropy (FA), were calculated symmetrically for multiple ROIs in the pyramidal tract (i.e., basal pons, cerebral peduncle, posterior limb of the internal capsule, corona radiata, and centrum semiovale) and frontobasal area (i.e., uncinate fasciculus, forceps minor, and anterior corona radiata). In the corpus callosum, the ROIs included three regions: the genu, body, and splenium. ROIs were selected on the basis of prior studies that have demonstrated exclusive abnormalities on DTI parameter in these areas (Arfanakis et al., 2002; Inglese et al., 2005; Bazarian et al., 2007; Kraus et al., 2007; Wilde et al., 2008; Chu et al., 2010).

All diffusion parameter analyses and white matter fiber tracking were performed by one observer (physicist; UH) on a workstation using commercially available software (Neuro 3D; Siemens Medical Solution, Malvern, USA). Mean values for FA and ADC for each region were calculated from the mean values of the right and left hemispheres. Circular ROIs were manually placed on color-coded axial fractional anisotropy (FA) maps and automatically transferred on the non-diffusion-weighted b0 and ADC maps. The ROIs of the corpus callosum were drawn onto the median-line sagittal images because the structure was most clearly visible on that slice. The size of the ROI was modified to the axial structure of each fiber tract. The size of the ROI circle varied slightly due to the size differences at the target areas. The circular ROIs were centered in the region taking care to avoid border areas, such as overlapping with cerebrospinal fluid spaces and neighboring tracts. The data quality was excellent in most cases, except in certain regions that had artifacts caused by air cavities and fluid flow.

A reliability study of this method was undertaken using the control sample (n=30) (Hakulinen et al., 2011; Hakulinen et al., 2012). Each ROI was sampled twice by the same rater to evaluate intrarater reliability. Intraclass correlation coefficients (ICCs)

were calculated for all FA and ADC using a two-way random-model analysis with absolute agreement. The ICC values were considered as excellent agreement if greater than 0.8, as substantial agreement if they were from 0.60 to 0.79, and as fair/poor agreement if below 0.6. All ROIs that did not met criteria for substantial agreement for intrarater reliability (>0.65) were excluded from analysis namely, Cerebral Peduncle-ADC (0.19), Centrum Semiovale-FA (0.48), Centrum Semiovale-ADC (0.63), Forceps Minor-ADC (0.64), Anterior Corona Radiata-ADC (0.27), Corpus Callosum Body-FA (0.23), and Corpus Callosum-Body-ADC (0.26). The number of ROIs used in the analysis (Study III, Study IV) was 16 for FA and 10 for ADC because some of the regions were excluded based on results from the reliability study.

4.5 Statistical Methods

Prior to the analyses, all variables were examined for departures from normality and heterogeneity of variance (Levene's test). Group differences were assessed using chi-square analyses for categorical variables (e.g., gender). Fishers Exact test statistics were interpreted when cell sizes were less than five. Independent t-tests or Mann Whitney U tests were used for all continuous variables (e.g., age, education, neuroradiological results, neurocognitive tests, self-report measures). Nonparametric analyses (Mann Whitney U tests, Wilcoxon Signed Ranks test) were conducted for those variables that were not normally distributed. Bonferroni correction was used for multiple comparisons in Study II and Study IV. In Study III, alpha was adjusted for sets of analyses dealing with specific hypotheses. It was not corrected for some of the exploratory multiple comparisons due to the small sample sizes (resulting in reduced power) and the exploratory nature of the analyses. However, the implications of adjusting versus not adjusting alpha are discussed for some specific findings. Effect sizes (Cohen's d) were reported as a measure of clinical significance and to guard against Type II statistical errors. Correlations between variables were calculated by using Spearman's rank correlation coefficient. For some analyses raw scores were converted to z-scores to get them all on a common metric. Z-score conversions (age, sex, and education corrected) were done by meta-norms of Mitrushina and co-workers (2005). In Study I, the internal consistency reliability for the BNI-FS was determined by using Cronbach's alpha. To explore the factor structure, principal components analysis with varimax rotation was conducted. Convergent and discriminant validity were evaluated by assessing the level of association between scores on the BNI-FS and the other questionnaires. In Study II, step-wise regression analysis was used to determine risk factors of the number of days taken to RTW. Also, logistic regression analyses was used to determine whether

identified risk factors could predict binary groups defined by the number of days taken to RTW (i.e., RTW cutoffs = 7, 14, 21, and 30 days). In Study IV, logistic regression analysis was used to determine the extent to which ICD-10 PCS could be predicted at one month and one year following injury. Statistical analyses were conducted by using SPSS for Windows versions 16.0 (Studies I and I) and 20.0 (Study III and IV).

5 RESULTS

5.1 Neuroradiological Factors

Study III was designed to address significant gaps in the literature relating diffusion tensor imaging (DTI) and functional outcome following MTBI. Specifically, the aim was to examine the association between white matter integrity and functional outcome in comprehensive way (subjective post-concussion symptom reporting, mental health, return to work, cognitive outcome) following uncomplicated MTBI. Only patients with uncomplicated MTBIs who underwent 3T MRI were included in this study.

5.1.1 Exploratory Diffusion Tensor Imaging Analyses

Exploratory analyses revealed no significant differences between the uncomplicated MTBI and neuroimaging control group on 24 of 26 DTI measures. Correcting for multiple comparisons, there would be no statistically significant differences between groups in any ROI. There were significant differences for ADC in the genu of the corpus callosum (p=.022, d=.58, medium effect size) and FA in splenium of the corpus callosum (p=.027, d=.56, medium effect size). For both ROIs, there was increased ADC (genu) and increased FA (splenium) in the MTBI group compared to controls. Increased FA in the splenium is the opposite of what is expected based on the literature.

Previous reports have suggested that high FA in subacute mTBI appears to be related to the post injury interval (Bazarian et al., 2007; Wilde et al., 2008; Henry et al., 2011). Therefore, a scatter plot was created to visualize the association between Total number of low FA scores and time post injury (Figure 3). The scatterplot reveals no correlation between time post injury and number of low scores.

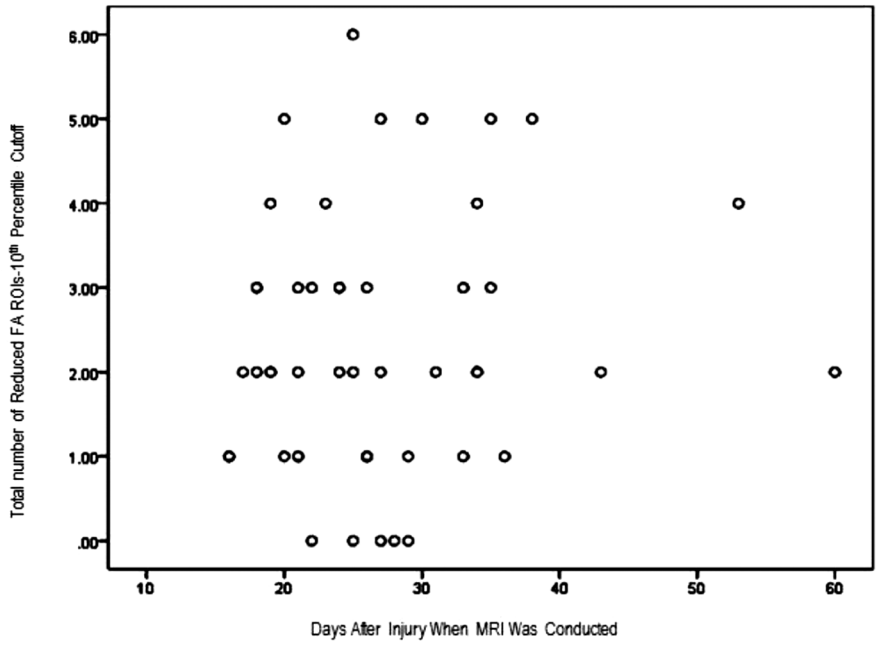


Figure 3. Total number of low FA scores and time post injury.

Also, we ran exploratory regression analyses to examine whether time post injury predicts FA scores. Regression analysis was run with total number of low FAs as a dependent factor and time post injury as an independent factor. Time post injury did not predict total number of low FAs (R= .141, R^2=.020, p=.339).

5.1.2 Multivariate Region of Interest Analysis

To explore whether uncomplicated MTBI patients will have reduced white matter integrity in a greater number of regions of interest compared to healthy controls, multivariate ROI analysis was used. For these analyses, the 16 ROIs for FA and 10 ROIs for ADC were considered simultaneously. To examine the prevalence of low or high scores, when all ROIs were considered simultaneously, a cut-off score for each ROI was set at 1.28 SDs below or above the mean of control values. The 1.28 SDs below the mean for each FA score for each ROI was selected as a cutoff score for abnormally low FA scores (i.e., 10th percentile) and 1.28 SDs above the mean for each ADC score for each ROI was selected as a cutoff score for abnormally high ADC scores (i.e., 90th percentile). The 10th and 90th percentiles were selected because the control sample

was relatively small and this would create more variability, and mediate the effects of possible outliers, in the control sample.

Overall, there were a greater number of low FA scores in the MTBI group compared to the control group, i.e. patients with uncomplicated MTBIs had reduced white matter integrity in a greater number of regions of interest compared to healthy controls. Chi-square analyses revealed that there was a significantly greater number of low FA scores when using 2 or more low scores as the criterion (p=.003, 66.7% MTBI, 29.2% controls). Similarly, there were also a greater number of high ADC scores in the MTBI group compared to the control group. Chi-square analyses revealed that there was a significantly greater number of high ADC scores when using 2 or more high scores (p=.011, 47.9% MTBI, 16.7% controls) and 3 or more high scores (p=.007, 33.3% MTBI, 4.2% controls) as the criterion.

5.1.3 Diffusion Tensor Imaging and Clinical Outcome

To examine the relation between DTI abnormalities and clinical outcome, the MTBI sample was divided into two groups based on the presence or absence of multiple areas of abnormally low FA values or abnormally high ADC values: (a) broadly normal white matter (WM) group (n=23, 47.9%), and (b) multifocal abnormal WM group (n=25, 52.1%). The multifocal abnormal WM group was defined as follows: 4 or more areas of abnormally low FA values OR 3 or more areas of abnormally high ADC values. The broadly normal WM group was defined as follows: <4 areas of abnormally low FA values AND <3 areas of abnormally high ADC values. Based on this criterion, 52.1% of the MTBI group and only 12.5% of the control group showed evidence of multifocal white matter findings (χ^2=10.55, p=.002; OR=13.1, 95% CI=3.5–50.0).

For the demographic and injury-related variables, there were no significant differences between groups for age, education, gender, RTA, or LOC (all p > .05). However, the broadly normal WM group had a significantly longer duration of PTA compared to the multifocal abnormal WM group (p=.034, d=.75, large effect size). The two groups were compared on the neurocognitive measures and number of days to return to work. There were no significant differences between groups for the majority of measures, with the exception of the 15" and 30" retention interval trials on the FWSTMT. For these two measures, the multifocal abnormal WM group had higher scores (performed better) compared to the broadly normal WM group (15" retention trial, p=.035; d=.64; 30" retention trial, p=.026, d=.68). The multifocal abnormal white matter group did not take longer to return to work than the broadly normal white matter group (p=.939).

5.1.4 Diffusion Tensor Imaging and Post-concussion Symptoms

To examine the relation between self-reported post-concussion symptoms and neuropsychological and DTI measures, the MTBI sample (Study III) was divided into two groups based on International Classification of Diseases (ICD-10; World Health Organization, 1992) Category C symptom criteria for Postconcussional Syndrome (PCS): (a) PCS-Present (n=11), and (b) PCS-Absent (n=37). PCS was classified using symptoms endorsed as moderate or higher on the RPSQ.

There were no significant differences between groups on all demographic (gender, age, education) and injury related variables (LOC, PTA, RTA), and for the majority of neurocognitive measures. There were significant differences and very large effect sizes between groups on both measures of fatigue (FIS total score, $p<.01$; $d=1.60$; BNI-FS total score, $p <.01$; $d=1.49$), depression (BDI-II total score, $p <.01$; $d=1.55$), and general health (EQ-5D™ VAS score, $p = .028$, $d = .79$). For the DTI measures, there were no significant differences between the two groups for all ROIs for FA and ADC (all $p>.05$, see Table 12). In addition, when all ROIs were considered simultaneously, the prevalence of low FA scores or high ADC scores did not differ between groups (Table 13).

Table 12. Exploratory comparisons of apparent diffusion coefficient and fractional anisotropy of post-concussion absent (PCS -) and post-concussion present (PCS +) groups.

	PCS – (n=37)		PCS + (n=11)			Cohen's Effect Size (d)
	M	SD	M	SD	*p*	
ADC (10^{-3} mm^2/sec)						
Basilar Pons right	.685	.068	.716	.069	.197	0.45
Basilar Pons left	.717	.105	.730	.078	.690	0.13
Internal Capsule right	.688	.036	.695	.030	.524	0.20
Internal Capsule left	.677	.042	.689	.023	.225	0.14
Corona Radiata posterior right	.667	.044	.652	.024	.285	0.38
Corona Radiata posterior left	.646	.081	.658	.029	.655	0.17
Uncinate Fasciculus right	.776	.043	.776	.049	.982	0.00
Uncinate Fasciculus left	.780	.043	.753	.060	.092	0.58
Corpus Callosum: Genu	.792	.083	.810	.091	.532	0.21
Corpus Callosum: Splenium	.710	.068	.716	.043	.774	0.10
FA						
Basilar Pons right	.636	.075	.594	.087	.125	0.54
Basilar Pons left	.626	.083	.611	.078	.589	0.18
Cerebral peduncle right	.857	.052	.857	.057	.998	0.00
Cerebral peduncle left	.857	.060	.846	.046	.608	0.19
Internal Capsule right	.725	.045	.727	.045	.892	0.04
Internal Capsule left	.724	.046	.712	.027	.425	0.29
Corona Radiata posterior right	.440	.065	.457	.098	.517	0.23
Corona Radiata posterior left	.517	.073	.513	.092	.902	0.05
Anterior Corona Radiata right	.556	.070	.549	.082	.771	0.10
Anterior Corona Radiata left	.546	.082	.548	.065	.923	0.03
Uncinate Fasciculus right	.545	.066	.509	.080	.140	0.52
Uncinate Fasciculus left	.541	.066	.506	.089	.156	0.49
Forceps Minor right	.543	.090	.566	.073	.430	0.27
Forceps Minor left	.569	.091	.561	.102	.802	0.09
Corpus Callosum: Genu	.834	.058	.800	.058	.090	0.57
Corpus Callosum: Splenium	.884	.039	.856	.055	.148	0.66

Note: ADC = apparent diffusion coefficient. FA = fractional anisotropy; * $p < 0.05$

Table 13. Cumulative frequency distribution of 16 low FA and 10 high ADC scores considered simultaneously by PCS group.

	FA						ADC				
	PCS - (n = 37)		PCS + (n = 11)				PCS - (n = 37)		PCS + (n = 11)		
Low Scores	f	cp	f	cp	p	High Scores	f	cp	f	cp	p
6	0	-	1	9.1	.229	6	0	-	0	-	-
5	5	13.5	0	-	1.00	5	1	2.7	0	-	1.00
4	3	21.6	1	18.2	1.00	4	4	13.5	1	-	1.00
3	5	35.1	4	45.6	.248	3	9	37.8	1	4.2	.293
2	10	62.1	3	81.9	.293	2	4	48.6	3	16.7	.852
1	9	86.4	2	100.0	.576	1	9	72.9	4	66.7	.705
0	5	100.0	0	-		0	10	100	2	100	

Note: f = Frequency; cp = Cumulative Percentage; p based on χ^2-test

In study IV, the relation between self-reported post-concussion symptoms and DTI measures was further examined in a larger sample of patients with MTBIs (including those with complicated MTBIs) and prospectively (at one month and one year post injury). Multifocal abnormal WM was found in 12.5% of the control group (3/24) and 50.7% of the MTBI group (36/71). Patients in the MTBI group were significantly more likely to show evidence of multifocal diminished white matter than participants in the control group [$\chi^2(1,95)=10.82$, p=.001; RR=4.06, 95% CI (1.44–16.01)]. However, the presence of multifocal diminished white matter was not significantly associated with the presence or absence of ICD-10 PCS. In sum, there were no significant differences in DTI measures between those who met ICD-10 criteria for PCS and those who did not meet criteria for PCS.

5.2 Psychological and Neuropsychological Factors

5.2.1 Fatigue

5.2.1.1 Symptoms of Fatigue Among Mild Traumatic Brain Injury Patients Compered to Controls

In study I, the MTBI group (n=126) had significantly greater total scores on the BNI-FS (M = 15.7, SD = 15.4) than the control group (n=36) (M = 10.3, SD = 7.4; p < .005, Cohen's d = .40) using a t-test with Levene's correction for heterogeneity of variance at one month post-injury. The total scores did not differ when compared with a Mann Whitney U Test. Individual items that differed significantly between groups, were #3

(staying awake during the day), #7 (staying out of my bed during the day), and #10 (lasting the day without taking a nap). In the MTBI group (Study IV), fatigue was the most frequent moderate to severe symptom (in RPSQ) both at one month (23.0%) and twelve months following injury (11.7%). None of the control group reported moderate to severe fatigue although few control subjects reported mild fatigue (8.3%).

In further analyses (Study I), MTBI patients were categorized into two levels of fatigue on the basis of the BNI-FS scores: mild-moderate fatigue (total score ≤ 29) or heavy fatigue (total score ≥ 30). Nearly 17% of the MTBI sample reported heavy fatigue at one month after injury. Healthy control subjects reported mild to moderate fatigue but none of the controls reported heavy fatigue based on this criteria. There were 105 patients in the mild-moderate fatigue group and 21 in the heavy fatigue group. The two groups did not differ in gender, age, education, Glasgow Coma Scale scores, duration of loss of consciousness, duration of post-traumatic amnesia, or the presence of other bodily injuries. However, the heavy fatigue group endorsed greater symptoms of depression (d=1.4), greater symptoms of the post-concussion syndrome (d = 1.6), and worse quality of life (d=1.4).

Unpublished additional analyses revealed that at 12 months post-injury, there was no significant difference between the MTBI group (n=103) and controls (n=36) in fatigue reporting as measured by BNI-FS total score (t(137)=-.396, p=.621, M=9.5, SD=12.2 MTBI group; M=10.3, SD=7.4 control group). However, there were 8 individuals in MTBI group (7.8%) who reported heavy fatigue at 12 months post-injury. Notably, five out of those eight individuals (62.5%) reported heavy fatigue also in the acute phase ($\chi^2(1,103)=11.189$, p=.005).

In additional (unpublished) analyses, fatigue was examined in MTBI patients and healthy controls using another self-report fatigue scale, namely the Fatigue Impact Scale (FIS). At one month after injury, patients with MTBI had almost two times as many fatigue-related symptoms as controls in the FIS. As shown in Table 14, the most pronounced differences at one month post-injury were found in the physical subscale, where the MTBI group had significantly higher scores compared to controls. The result was statistically significant with a Mann Whitney U Test (p=.003) and t-test (p<.001). The MTBI patient group also had a significantly higher mean cognitive subscale score (p=.004), mean psychosocial score (p=.002), and mean total score than controls (p<.001) at one month post-injury with t-test. However, median scores did not differ when compared with a Mann Whitney U Test. There were no statistically significant differences in FIS mean scores between the MTBI group and controls at one year post-injury based on a t-test. In contrast, the two groups differed in psychosocial subscale score and total score when compared with a Mann Whitney U Test. On these subscales, the control group had higher median scores than the MTBI group at one

year post-injury, indicating that control subjects reported more symptoms than MTBI patients one year following injury.

In sum, MTBI patients reported significantly more fatigue than controls at one month post-injury. At 12 months post-injury, there was no significant difference between the MTBI group and controls in fatigue reporting.

Table 14. Fatigue Impact Scale descriptive statistics, group comparisons, and effect sizes.

	MTBI patients								Controls				MTBI		MTBI	
	1 month (n = 124)				12 months (n=103)				N=36				1 month vs. controls		1 year vs. controls	
FIS subscale	M	SD	Md	IQR	M	SD	Md	IQR	M	SD	Md	IQR	p	d		d
Cognitive	7.3	7.8	5.0	1-12	4.3	6.8	1.0	0-6	4.5	4.1	4.0	1-7	.189 (.004)	.41	.066 (.867)	.03
Psycho-social	10.3	12.7	4.0	1-17	6.8	12.3	1.0	0-8	5.9	5.0	5.5	1.25-8.75	.607 (.002)	.40	.017 (.584)	.08
Physical	7.0	7.9	4.0	1-10.75	4.1	7.1	1.0	0-5	2.9	4.7	1.5	0-3.75	.003 (<.001)	.57	.563 (.249)	.19
Total	24.6	26.7	13.0	4-40	15.1	25.2	4.0	0-19	13.3	11.3	11.0	5-17.75	.152 (<.001)	.49	.048 (.562)	.08

Note: d = Cohen's d, M=mean, Md = median, SD=standard deviation, IQR=interquartile range. P values are for Mann Whitney U tests first and independent t-tests in parentheses. The p-values for the t-tests were corrected following Levene's test for heterogeneity of variance.

5.2.1.2 Psychometric Properties of the Barrow Neurological Institute Fatigue Scale

Study I aimed at evaluating the psychometric properties and clinical usefulness of the BNI Fatigue Scale (BNI-FS) in MTBI patients and healthy controls. The internal consistency reliability of the BNI-FS was very high as reflected by Cronbach's alpha (r_{11}=.96 for the MTBI group and r_{11}1=.87 for the control group) and the factor analysis. The 10 items were submitted to an exploratory principal components factor analysis with varimax rotation in the MTBI group. The Kaiser-Meyer-Olkin measure of sampling adequacy was .93. Bartlett's test of sphericity was rejected (p<.0001). The eigenvalues (Kaiser criterion) and scree plot unequivocally indicated that a one-factor solution, accounting for 73.3% of the total variance, appropriately summarized the data.

The BNI-FS was highly correlated with the Fatigue Impact Scale (rs=.84, p < 0.01). It was also correlated with measures of depression, post-concussion symptoms, and quality of life – but to a lesser extent. The statistically significant correlations between the BNI-FS and other measures were rs=.68 for the BDI-II, rs=.68 for the RPSQ, and rs=-.39 for the EQ-5D. Also, BNI-FS correlated positively with number of days post-injury before returning to work (rs=.27, p<.001). The measures of depression and post-concussion symptoms have item content that overlaps with the BNI-FS. Therefore, bivariate correlations between the BNI-FS and the other two measures (BDI-II and RPSQ), after the sleep and fatigue items were removed from the other scales, were conducted. The correlations were rs=.59 (p<.001) for BDI-II and rs=.66 (p<.001) for RPSQ.

5.2.1.3 Post-injury Fatigue in Association to Diffusion Tensor Imaging

In unpublished DTI analyses, all MTBI patients who underwent 3T MRI (n=89) were categorized into two levels of fatigue on the basis of the BNI-FS scores: mild-moderate fatigue (total score ≤ 29, n=76) or heavy fatigue (total score ≥ 30, n=13). For the DTI measures, there were no significant differences between the two groups for all ROIs for FA and ADC (all p>.05, see Table 15). Multifocal abnormal WM was found in 31.4% of the mild-moderate fatigue group and 23.1% of the heavy fatigue group. Patients in the heavy fatigue group were not significantly more likely to show evidence of multifocal diminished white matter than participants in the mild-moderate group [χ^2(1,83)=.363, p=.745; RR=.734, 95% CI (.26–2.10)].

Table 15. Exploratory comparisons of apparent diffusion coefficient and fractional anisotropy of Mild-Moderate Fatigue and Severe Fatigue groups.

	Mild-Moderate Fatigue (n=76)		Severe Fatigue (n=13)			
	M	SD	M	SD	p	d
ADC (10^{-3} mm^2/sec)						
Basilar Pons right	0.694	0.072	0.733	0.129	.122	.48
Basilar Pons left	0.722	0.091	0.737	0.066	.562	.18
Internal Capsule right	0.694	0.036	0.691	0.035	.817	.07
Internal Capsule left	0.677	0.040	0.690	0.033	.260	.34
Corona Radiata posterior right	0.667	0.044	0.648	0.046	.155	.43
Corona Radiata posterior left	0.650	0.080	0.656	0.062	.814	.07
Uncinate Fasciculus right	0.798	0.101	0.775	0.047	.423	.25
Uncinate Fasciculus left	0.781	0.049	0.781	0.061	.981	.01
Corpus Callosum: Genu	0.797	0.082	0.815	0.069	.462	.22
Corpus Callosum: Splenium	0.712	0.068	0.744	0.068	.121	.47
FA						
Basilar Pons right	0.628	0.080	0.619	0.068	.695	.12
Basilar Pons left	0.619	0.075	0.642	0.077	.328	.30
Cerebral peduncle right	0.858	0.052	0.852	0.062	.686	.12
Cerebral peduncle left	0.848	0.058	0.863	0.049	.405	.25
Internal Capsule right	0.722	0.042	0.724	0.048	.896	.04
Internal Capsule left	0.721	0.046	0.721	0.037	.957	.02
Corona Radiata posterior right	0.448	0.071	0.444	0.090	.850	.06
Corona Radiata posterior left	0.507	0.080	0.508	0.087	.979	.01
Anterior Corona Radiata right	0.544	0.078	0.547	0.077	.897	.04
Anterior Corona Radiata left	0.540	0.084	0.530	0.066	.697	.12
Uncinate Fasciculus right	0.533	0.088	0.535	0.080	.934	.03
Uncinate Fasciculus left	0.533	0.070	0.517	0.068	.456	.23
Forceps Minor right	0.537	0.091	0.569	0.100	.258	.34
Forceps Minor left	0.551	0.091	0.563	0.120	.670	.13
Corpus Callosum: Genu	0.818	0.058	0.794	0.088	.208	.39
Corpus Callosum: Splenium	0.870	0.046	0.863	0.036	.620	.15

Note: DTI results were obtained from 70 MTBI patiens in the Mild-Moderate Fatigue -group, Cohen's effect size (d): small (.20), medium (.50), large (.80). p=t- test. Abbreviations: ADC = apparent diffusion coefficient; FA = fractional anisotropy.

5.2.2 Cognitive Outcome

Based on unpublished results, the MTBI groups' test results were consistent with a) the general population (z-scores calculated based on international meta-norms by Mitrushina et al., 2005) and to b) the control group (see Figure 4). When looking at the MTBI groups' (n=126) mean test scores, all results were within average range (all scores between 25th and 75th percentile).

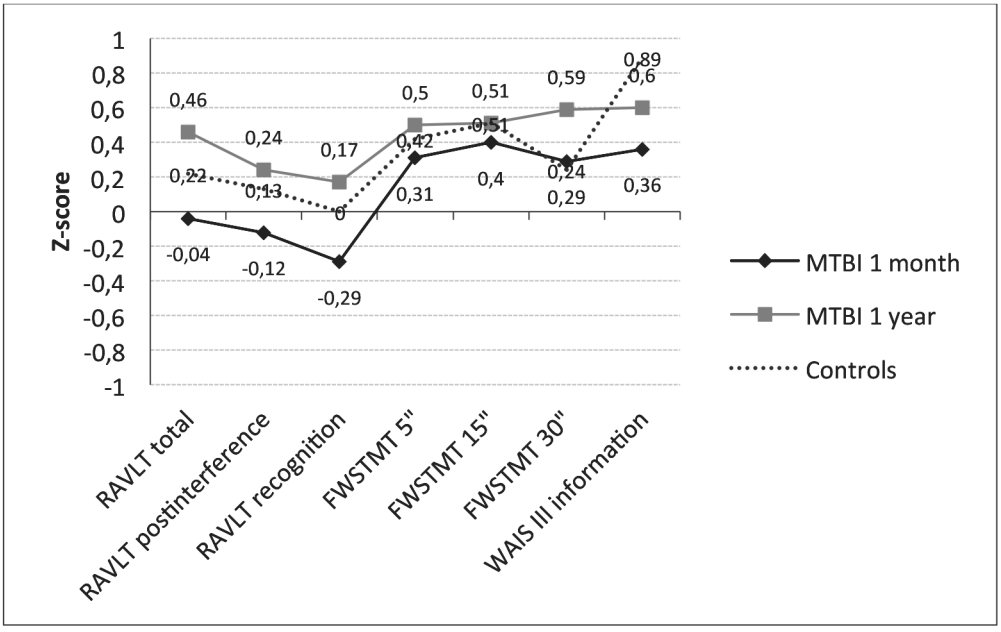


Figure 4. MTBI groups and control groups mean z-scores on selected neuropsychological tests

There was no difference between the MTBI groups' test performance compared to controls at one month and one year following injury. However, using group statistics can obscure a small subgroup of individuals who have abnormally low test z-scores (below -1.5SD). Frequencies of such low scores are presented in Table 16. In this study, the control group did not complete all neuropsychological tests. Therefore, it was not possible to compare all test results between the MTBI group and the control group.

Table 16. Means (+SD) and frequency distribution of low z-scores (≤ -1.5) on neuropsychological tests for MTBI patients at the acute phase and at the one-year follow-up

	MTBI 1 Month (n=126)		MTBI 1 Year (n=103)		MTBI 1 month Vs MTBI 1 year		Controls (n=36)		MTBI 1 month vs Controls		MTBI 1 year vs Controls	
Neurocognitive Tests	M (SD)	f (%)	M (SD)	f (%)	p	d	M (SD)	f (%)	p	d	p	d
RAVLT total recall	-.04 (1.00)	9 (7.1)	.46 (.97)	2 (1.9)	<.001	.51	.22 (.97)	2 (5.6)	.179	.26	.191	.25
RAVLT post-interference recall	-.12 (.94)	13 (10.3)	.24 (.82)	2 (1.9)	<.001	.41	.13 (.93)	2 (5.6)	.164	.27	.491	.13
RAVLT recognition	-.29 (1.31)	21 (16.7)	.17 (.82)	7 (6.8)	<.001	.42	.00 (1.08)	2 (5.6)	.224	.23	.308	.19
FWSMT 5"	.31 (.97)	5 (4.1)	.50 (1.16)	5 (5.1)	.040	.18	.42 (.99)	1 (2.8)	.556	.11	.714	.07
FWSMT 15"	.40 (.97)	5 (4.1)	.51 (1.06)	4 (4.0)	.065	.11	.51 (.75)	0 (0)	.508	.12	.994	.00
FWSMT 30"	.29 (.99)	3 (2.5)	.59 (1.07)	3 (3.0)	<.001	.29	.24 (.81)	0 (0)	.754	.05	.072	.35
WAIS III Information	.36 (1.44)	3 (2.4)	.60 (1.06)	2 (3.6)	.956	.18	.89 (.88)	0 (0)	.039	.40	.179	.29
ROCFT copy	.47 (.57)	2 (1.6)	.38 (.73)	3 (2.9)	.250	.14	NA	-	-	-	-	-
ROCFT memory	-.03 (.92)	9 (7.3)	.24 (.86)	2 (1.9)	<.001	.30	NA	-	-	-	-	-
TMT A (in seconds)	-.19 (1.06)	15 (12.1)	-.02 (1.28)	6 (5.8)	.006	.15	NA	-	-	-	-	-
TMT B (in seconds)	-.11 (1.10)	11 (8.9)	-.16 (1.46)	10 (9.7)	.923	.04	NA	-	-	-	-	-

	MTBI 1 Month (n=126)		MTBI 1 Year (n=103)		MTBI 1 month Vs MTBI 1 year		Controls (n=36)		MTBI 1 month vs Controls		MTBI 1 year vs Controls	
Neurocognitive Tests	M (SD)	f (%)	M (SD)	f (%)	p	d	M (SD)	f (%)	p	d	p	d
STROOP Color-Word	-.38 (1.11)	18 (14.3)	.06 (1.21)	12 (11.7)	<.001	.38	NA	-	-	-	-	-
Verbal Fluency Total	-.26 (1.08)	12 (9.5)	-.03 (1.14)	7 (6.8)	.033	.21	NA	-	-	-	-	-
Animal Naming Total	.33 (1.27)	6 (4.8)	.42 (1.25)	5 (4.9)	.111	.07	NA	-	-	-	-	-
CANTAB 5 CRTI	.17 (1.12)	5 (4.2)	.19 (1.07)	6 (5.9)	.120	.02	NA	-	-	-	-	-
CANTAB RVP A'	-.44 (.98)	15 (12.5)	-.16 (1.16)	13 (12.7)	<.001	.26	NA	-	-	-	-	-
CANTAB RVP B'	-.11 (.86)	8 (7.1)	-.40 (2.69)	8 (8.0)	.537	.17	NA	-	-	-	-	-
CANTAB PAL Total Adjusted Errors	.01 (1.09)	8 (6.8)	.16 (.93)	5 (5.0)	.151	.15	NA	-	-	-	-	-
CANTAB PAL Total Adjusted Errors (6 shapes)	.07 (.91)	5 (4.2)	.06 (.88)	8 (8.1)	.372	.01	NA	-	-	-	-	-

Abbreviations: CANTAB PAL=Cambridge Neuropsychological Test Automated Battery Paired Associates Learning; CANTAB 5 RTI=Cambridge Neuropsychological Test Automated Battery Five-Choice Reaction Time; CANTAB RVP=Cambridge Neuropsychological Test Automated Battery Rapid Visual Information Processing; FWSMT=The Four Word Short –Term Memory Test; min=minutes; MTBI=mild traumatic brain injury; NA=not assessed, RAVLT=Rey Auditory Verbal Learning Test, ROCFT=Rey Osterrieth Complex Figure Test; TMT=Trail Making Test; SD=standard deviation; WAIS=Wechsler Adult Intelligence Scale. Note: Cohen's effect size (d): small (.20), medium (.50), large (.80). p=t- test; FWSTM n=122 at one month and n=99 at one year, WAIS III information n=55 at one year, CANTAB 5 CRTI n=120 at one month and n=102 at one year, CANTAB RVP A' n=120 at one month and n=102 at one year, CANTAB RVP B n=113 at one month and n=100 at one year, CANTAB PAL Total Adjusted Errors n=118 at one month and n=101 at one year, CANTAB PAL Total Adjusted Errors 6 shapes n=118 at one month and n=99 at one year, ROCFT Copy n=122 at one month, ROCFT Memory n=123 at one month, TMT A n=124 at one month, TMT B n=123 at one month.

There was an increase in the MTBI group's test performance during the follow-up. A significant difference between the results at one month and at one year was observed on four tests of memory (mean z-scores; RAVLT total score, RAVLT postinterference score, RAVLT recognition score, and ROCFT memory score) and two tests of attention and executive function (mean z-scores, Stroop Color-Word and CANTAB RVP A'). This result is, however, referring to statistical significance (based on the means of z-scores for MTBI and control groups). Whether the change is clinically meaningful is not revealed from the t-test results: based on Cohen's effect sizes (d') the only clinically meaningful change was observed on RAVLT memory tests (Cohen's d .41 to .51, medium effect size); all other effect sizes can be considerd small (.38) to very small (.01). The extent to which the improvement from one month to one year on some tests represents real improvement in cognition, practice effects, or both cannot be determined because the control group was only tested once. Based on our results (unpublished), the computerized neuropsychological tests were not more sensitive in detecting cognitive decline following MTBI.

Spearman correlations were used to examine the relations between demographic and injury-related variables and the neurocognitive and self-report measures (Study III). In the MTBI group, there were no significant correlations between age, education, LOC, PTA, or RTA and the self-report measures or the majority of the neurocognitive measures. There were a few significant positive correlations between education and RAVLT total ($r=.45$, $p<0.01$), education and FWSTMT 30" ($r=.37$, $p<0.05$), duration of LOC and FWSTMT 30" ($r=.34$, $p<0.05$), and duration of PTA and FWSTMT 15" ($r=.31$, $p<0.05$). In the neuropsychological control group, there were no significant correlations between education and the self-report or neurocognitive measures. For age, significant negative correlations were found for all neurocognitive measures [range: $r=-.36$ to $r=-.55$; except FWSTMT 5" ($r=-.29$)], but not for any of the self-report measures. See Table 17 for detailed results.

Table 17. Intercorrelation matrix in the MTBI sample and healthy controls.

	Uncomplicated MTBI (n = 48)					Healthy Controls (n = 36)	
Neurocognitive Tests	Age	Edn	LOC	PTA	RTA	Age	Edn
Beck Depression Inventory-II	.06	.13	.02	.08	.05	-.09	-.15
Fatigue Impact Scale	.02	.21	.03	.11	-.01	-.06	-.25
BNI-Fatigue Scale	.04	.09	.04	.06	.03	-.12	-.14
Rivermead PCS Questionnaire	.22	.10	-.08	.01	-.00	-.08	-.29
RAVLT total	-.24	.45**	.07	.26	.11	-.55**	.04
RAVLT postinterference	-.13	.19	.06	-.00	-.25	-.44**	.13
RAVLT delayed	-.21	.26	-.01	.04	-.10	-.36*	.02
RAVLT recognition	-.24	.09	-.10	-.09	-.20	-.50**	-.09
FWSTMT 5”	.13	.25	.06	.13	.10	-.29	.26
FWSTMT 15”	-.27	.25	.10	.31*	.26	-.48**	.20
FWSTMT 30”	-.02	.37*	.34*	.26	.19	-.53**	.12

Note: * $p < 0.05$, ** $p < 0.01$.
BNI = Barrow Neurological Institute. Edn = education. FWSMT = Four Word Short Term Memory Test. LOC = loss of consciousness. PTA = post-traumatic amnesia. RTA = retrograde amnesia. RAVLT = Rey Auditory Verbal Learning Test. PCS = Post-Concussion Symptoms.

There were no significant differences between the uncomplicated MTBIs and neuropsychological control group on any measure of working memory, learning, or memory. Effect sizes ranged from very small (d=.01) to small (d=.37) (see Table 18, Study III).

Table 18. Comparison of memory measures by group.

	Uncomplicated MTBI (n=48)		Healthy Controls (n=36)			
Neurocognitive Tests	M	SD	M	SD	p	d
RAVLT total recall	55.4	8.0	55.6	9.0	.920	.02
RAVLT post-interference recall	11.1	2.7	11.8	2.9	.310	.22
RAVLT delayed recall	10.7	2.9	11.8	3.1	.118	.35
RAVLT recognition	13.4	2.0	13.7	1.9	.481	.15
FWSMT 5”	15.5	2.7	16.1	3.0	.340	.21
FWSMT 15”	12.3	3.7	13.6	3.2	.103	.37
FWSMT 30”	11.1	3.7	11.1	3.4	.977	.01

Note: Cohen’s effect size (d): small (.20), medium (.50), large (.80). p = t-test; FWSMT = Four Word Short Term Memory Test; MTBI = mild traumatic brain injury; RAVLT = Rey Auditory Verbal Learning Test

In Study II, the MTBI sample was divided into two groups using a cutoff score of 30 days to return to work (RTW): (a) RTW-Rapid (n = 82, 75.2%), and (b) RTW-Delayed (n = 27, 24.8%). Patients who took longer to return to work did not perform more poorly on neurocognitive measures. The groups did not differ on any neuropsychological test measures (all p >.05; see Table 19).

Table 19. Descriptive statistics (raw scores) and effect sizes: Neurocognitive tests.

	RTW ≤30 days n = 82		RTW >30 days n = 27			
Neurocognitive Tests	M	SD	M	SD	p	d
RAVLT Total Score	53.9	9.2	51.4	9.0	.221	.27
RAVLT Delayed Recall	10.2	3.4	10.2	3.7	.998	.00
Verbal Fluency Total	39.9	11.6	39.4	13.0	.849	.04
Animal Naming Total	24.3	5.2	23.1	5.8	.316	.23
Trails A (in seconds)	30.4	9.8	29.0	10.5	.532	.14
Trails B (in seconds)	72.2	30.4	63.1	20.6	.162	.33
Stroop Color-Word	40.3	8.1	40.6	7.0	.885	.03

Note: N=109; Cohen's effect size (d): small (.20), medium (.50), large (.80). p = t-test, BDI-II = Beck Depression Inventory-Second Edition; BNI-FS = Barrow Neurological Institute Fatigue Scale; EQ-5D VAS = EuroQol Five Dimension Visual Analogue Scale; RPSQ = Rivermead Post Concussion Symptoms Questionnaire; RAVLT = Rey Auditory Verbal Learning Test

There were no significant differences between PCS-Present and PCS-Absent groups for the majority of neurocognitive measures (Study III). The one exception to this was the 15" retention interval trial in FWSTMT in which the PCS-Absent group had higher (better) scores compared to the PCS-Present group (p=.015; d=0.87). In addition, the multifocal abnormal WM group was compared on the neurocognitive measures to the broadly normal white matter (WM) group (Study III). There were no significant differences between groups for the majority of measures, with the exception of the 15" and 30" retention interval trials on the FWSTMT. For these two measures, the multifocal abnormal WM group had higher (better) scores compared to the broadly normal WM group (15" retention trial, p=.035; d=.64; 30" retention trial, p=.026, d=.68).

5.2.3 Persistent Post-concussion Symptoms

Study IV aimed to examine the prevalence of, and multiple biopsychosocial factors related to, persistent post-concussion symptom reporting at one month and one year

following MTBI. Also, the study compared two different diagnostic criteria, namely postconcussional syndrome (PCS) per the International Classification of Diseases-10th edition (World Health Organization, 1992) and postconcussional disorder (PCD) per the Diagnostic and Statistical Manual of Mental Disorders-IV.

Compared to the neuropsychological control group, the MTBI group reported a greater number of post-concussion symptoms (Study III, $p<.01$, $d=.76$, medium effect size). The MTBI group total score on RPCSQ was significantly higher compared to controls at both one month [$t(129)=5.32$, $p<.001$, $d=.71$] and one year [$t(119)=2.48$, $p=.015$, $d=.36$] following injury. Rivermead Post Concussion Symptoms questionnaire (RPCSQ) for MTBI patients at one month post injury was 10.4 (SD=10.7, Range=0–44). The average score on the RPCSQ at one year post injury was 6.8 (SD=9.6, Range=0–41). The average score on the RPCSQ for the control group was 3.7 (SD=4.9, Range=0–17). The four most common symptoms in the MTBI group at one month were fatigue, tiring more easily, sleep disturbance, feeling frustrated or impatient, and headaches. All these symptoms were reported by more than 10% of patients using the criteria "moderate or greater" symptom reporting.

In MTBI group, fatigue was most frequent symptom using "moderate or greater" symptom reporting at both one month and one year following injury (Study IV). No one in the control group reported moderate or greater fatigue although a few control subjects reported mild fatigue (8.3%). Also, poor concentration was uniquely reported by MTBI group compared to controls (0%) both one month (9.7%) and one year (7.8%) post-injury (Study IV). In the MTBI group, post-concussion-like symptoms (RPCSQ total score) at both one month and one year following injury had a significant correlation with depressive symptoms (BDI-II total score/ 10 items most reflective of depression) ($r=.51$, $p<.01$ at four weeks; $r=.59$, $p<.01$ at 12 months).

5.2.3.1 Prevalence of Postconcussional Disorder /Postconcussional syndrome

The rate at which the PPCS is diagnosed was significantly lower using the DSM-IV criteria versus the ICD-10 criteria. Also, the rate of diagnosis using both systems was significantly lower if symptoms were conceptualized as "moderate or greater" on the rating scale versus simply being present (i.e., "mild or greater").

5.2.3.2 ICD-10 Postconcussional Syndrome

Using the mild or greater ICD-10 criteria for PCS, 59% of the MTBI cases met criteria at one month post injury and 38% met criteria at one year post injury. In the control group, 31% met the criteria. Using the moderate or greater ICD-10 criteria for the PCS, 20% of the MTBI cases met criteria at one month post injury and 12% met criteria at one year. In the control group, 0% met the criteria. At one month post injury, a significantly greater proportion of MTBI patients met PCS criteria than control participants using symptom endorsement as "mild or greater" [$\chi^2(1,160) = 8.97$, p=.003] and "moderate or greater" [$\chi^2(1,158) = 8.35$, p=.007]. At one year post-injury, a significantly greater proportion of MTBI patients met PCS criteria compared to controls when using "moderate or greater" criterion [$\chi^2(1,139) = 4.59$, p=.036].

5.2.3.3 DSM-IV Postconcussional Disorder

Using the mild or greater DSM-IV criteria for PCD, only 1.6% of the MTBI cases met criteria at one month post injury, and 1.0% met criteria at one year. In the control group, 0% met the criteria. Using the moderate or greater DSM-IV criteria for the syndrome, 0% of the MTBI cases met criteria one month post injury, and 1.0% met criteria at one year. None of the controls met the criteria. There were too few cases of PCD to run statistical analysis. All patients who met DSM-IV PCD criteria also fulfilled ICD-10 PCS criteria.

5.2.3.4 Correlates of Persistent Post-concussion Symptoms

Post-injury depression was strongly associated with a diagnosis of the PCS. There was a significant positive Pearson correlation between the BDI-II subscale scores (i.e., the 10 items most reflective of depression) and the RPSQ total scores in the MTBI group at one month post injury (r=.51; p<.001) and at one year post injury (r=.59; p<.001). Of the 73 patients who met criteria for PCS at one month post injury based on "mild or greater" symptom reporting, 9.6% also met criteria for concurrent depression [$\chi^2(1,126)=5.18$, p=.02]. Of the 24 patients who met criteria for PCS at one month post injury based on "moderate or greater" symptom reporting, 16.7% met criteria for concurrent depression [$\chi^2(1,126)=8.82$, p< 0.01]. Of the 39 patients who met criteria for PCS at one year post injury based on "mild or greater" symptom reporting, 7.7% met criteria for concurrent depression [$\chi^2(1,103)=1.05$, p=.30]. Of the 12 patients who met criteria for PCS at one

year post injury based on "moderate or greater" symptom reporting, 25% met criteria for concurrent depression [$\chi^2(1,103)=11.78$, $p< 0.01$].

Those with a pre-injury history of mental health problems were more likely to have PCS at one month. Of the 73 patients who met ICD-10 criteria for PCS at one month post injury based on "mild or greater" symptom reporting, 10.9% (n=8) had previous mental health problems [$\chi^2(1,126)=3.61$, $p=.080$]. Of those 8 patients, who had a history of mental health problems, 88.9% met the ICD-10 criteria for PCS based on "mild or greater" symptom reporting. Using symptom endorsement as "moderate or greater" in those with a pre-injury mental health problem (n=8), 62.5% [$\chi^2(1,122)=9.94$, $p=.007$] met the PCS criteria at one month. At one year, there was not a significant association between PCS group membership and previous mental health problems.

5.2.3.5 Post-concussion Symptom Reporting Trajectory

The natural history of post-concussion symptom reporting from one month to one year post-injury was examined in each individual MTBI subject (n=101). (Study IV, see unpublished Figure 5).

Of the 58 patients who met criteria for ICD-10 PCS at one month based on "mild or greater" symptom reporting, 53.4% (31 patients) met and 46.6% (27 patients) did not meet the PCS criteria at one year. Of those 43 patients who did not meet the ICD-10 PCS criteria ("mild or greater" symptom reporting") at one month, 16.3% (7 patients) met and 83.7% (36 patients) did not meet the PCS criteria at one year. Those initially met criteria for PCS based on "moderate or greater" symptom reporting, 79% improved and 10% remained symptomatic (met the PCS criteria at one-year follow-up).

At one year, there were seven cases of delayed-onset PCS with "mild or greater" symptom reporting (18%; 7/38) and eight cases with "moderate or greater" symptom reporting (67%, 8/12). Of those 12 patients who met the PCS criteria at one year based on "moderate or greater" symptom reporting, 66.7% (8 patients) did not meet the criteria based on "moderate or greater" symptom reporting at one month. However, there were only two cases (1.9%, 2/103) that can be considered "pure" delayed-onset PCSs based on "moderate or greater" symptom reporting: these patients did not meet the PCS criteria for even "mild or greater" symptom criteria at four weeks. Thus, a significant minority of patients got worse during the follow-up. From those patients, who did not met the criteria for PCS based on mild or greater symptom reporting at one month post injury, over 16% reported more symptoms at the follow-up and were diagnosed as having PCS at one year following injury. Based on moderate or greater symptom reporting, almost 10% of the PCS absent group at one month post-injury

met the diagnosis of PCS at 12 month follow-up. In sum, of those who initially met the criteria ICD-10 criteria (mild or greater symptom reporting) for PCS (n=58), 46.6% improved and 53.4% remained symptomatic. Of those who did not meet the ICD-10 PCS criteria at one month (n=43), 16.3% worsened and met the criteria at one year.

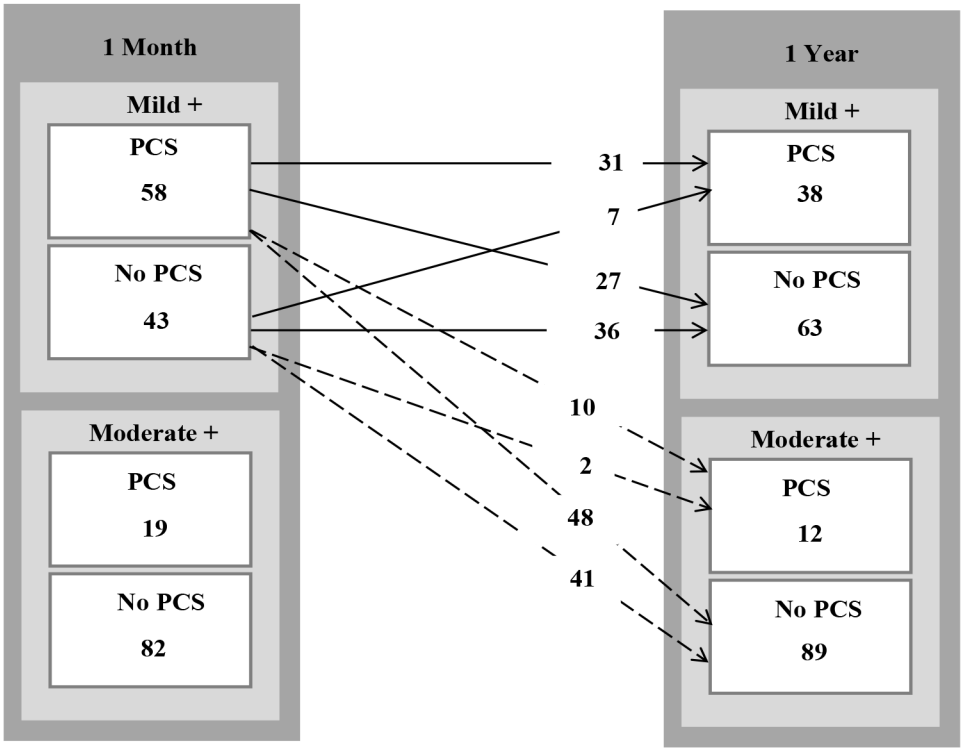


Figure 5. Natural history of mild or greater post-concussion symptom reporting (ICD-10 PCS) in each individual MTBI subject presented in frequencies

5.3 Social Factors

5.3.1 Return to Work

In Study II, the main purpose was to examine factors relating to return to work (RTW) following MTBI. The influence of 17 factors (demographic, background history, injury severity, and clinical outcome variables) was investigated in relation to RTW rates following MTBI. The vast majority of this cohort (n=109) returned to work within two months (91.7%). The cumulative RTW rates were as follows: 1 week=46.8%, 2

weeks=59.6%, 3 weeks=67.0%, 4 weeks=70.6%, 2 months=91.7%, and 1 year=97.2%. Of the total sample, 11.9% (n=13) had no time off work after injury. For the logistic regression analyses, four variables were significant predictors of RTW at 7, 14, 21, and 30 days post injury: age, multiple bodily injuries, day-of-injury intracranial abnormality, and fatigue ratings (all $p<.001$). The largest amount of variance accounted for by these variables in the prediction of RTW was between individuals who returned to work in less than 30 days and individuals who returned to work in 30 days or more ($p<.001$, $R2=.55$).

Based on the results of the logistic regression analyses, the sample was divided into two groups using a cutoff score of 30 days to RTW: (a) RTW-Rapid (n=82, 75.2%), and (b) RTW-Delayed (n=27, 24.8%). Demographic and injury related variables by group are presented in Table 20. The groups did not differ on any of the variables (age, education, sex, alcohol use, or pre-injury medical or mental health problems RTA, PTA, LOC, GCS, all $p>.05$), with the exception of multiple trauma ($p<.001$). A larger proportion of individuals in the RTW-Delayed group had experienced multiple bodily injuries compared to the RTW-Rapid group. There was a trend for a larger proportion of individuals in the RTW-Delayed group to have one or more trauma-related abnormalities on head CT ($p<.014$) and MRI ($p<.019$) compared to the RTW-Rapid group, though these differences were not statistically significant after adjusting for multiple comparisons.

Table 20. Demographic and injury severity characteristics of RTW groups

		RTW ≤30 days n = 82		RTW >30 days n = 27			
		M	SD	M	SD	p	d
Age (in years)		36.5	13.3	40.1	12.6	.218	.28
Education (in years)		12.5	2.8	13.5	2.6	.101	.37
WAIS-III Information (SS)		10.9	2.8	10.7	3.3	.761	.07
AUDIT		6.2	5.5	6.7	5.6	.673	.09
GCS		15.0	0.2	15.0	0.2	.803	.05
Days tested post injury		24.5	5.6	23.8	4.6	.570	.13
Duration of LOC (min)		0.7	2.3	0.8	1.3	.835	.05
Duration of PTA (min)		195.8	344.4	260.6	448.5	.442	.18
Duration of RA (min)		7.8	31.4	12.0	46.6	.597	.12
		f	%	f	%	χ^2	
Ethnicity	Caucasian	82	100.0	27	100.0	--	--
Gender	Female	47	57.3	10	37.0	.067	--
CT: Day-of-injury	Abnormal	4	4.9	6	22.2	.014	--
	Not Available	4	4.9	2	7.4	--	--
MRI: 3 weeks post injury	Abnormal	7	8.5	7	25.9	.019	--
	Not Available	4	4.9	3	11.1	--	--
Previous TBI	Present	30	36.6	7	25.9	.310	--
Multiple trauma	Present	17	20.7	16	59.3	<.001	--
Pre-Injury psychiatric Sx	Present	6	7.3	1	3.7	.679	--
Pre-Injury medical condition	Present	8	9.8	4	14.8	.487	--
Mechanism of Injury	MVA	24	29.3	13	48.1	--	--
	Ped-MVA	3	3.7	2	7.4	--	--
	Sports	10	12.2	1	3.7	--	--
	Fall low	31	37.8	5	18.5	--	--
	Fall high	4	4.9	4	14.8	--	--
	Assault	6	7.3	1	3.7	--	--
	Other	4	4.9	1	3.7	--	--

Note: N=109; Cohen's effect size (d): small (.20), medium (.50), large (.80); AUDIT=Alcohol Use Disorders Identification Test; CT=computed tomography; ED=Emergency Department; MRI=magnetic resonance imaging; GCS=Glasgow Coma Scale; min=minutes; LOC=loss of consciousness; MTBI=mild traumatic brain injury; MVA=motor vehicle accident; PTA=posttraumatic amnesia; RA=retrograde amnesia; SS=standard score; WAIS=Wechsler Adult Intelligence Scale

For exploratory purposes, subjects with multiple bodily injuries were excluded in order to control for the known influence of bodily injury on outcome from MTBI. When the 33 patients with multiple bodily injuries were excluded, the groups differed in terms of intracranial abnormalities: a larger proportion of individuals in the RTW-Delayed group had one or more trauma-related abnormalities on day-of-injury CT (p<.001) scans.

Participants who returned to work less than 30 days (n=82, 75.2%) versus greater than 30 days (n=27, 24.8%) did not differ on any neuropsychological test measures (all p >.05) (see Table 21). Those who returned to work later on average reported significantly greater fatigue on the BNI-FS (p<.001, Cohen's d=.98) and worse general health on EQ-5D VAS (p<.001, d=.83).

Table 21. Descriptive statistics (raw scores) and effect sizes: Self-report measures and Neurocognitive tests

	RTW ≤30 days n = 82		RTW >30 days n = 27			
	M	SD	M	SD	p	d
Self-Report Measures						
BNI-FS Total Score	12.3	12.9	26.1	17.8	<.001	.98
BDI-II Total Score	6.2	6.9	8.8	7.4	.098	.37
RPSQ Total Score	9.7	10.7	13.3	9.8	.084	.35
EQ-5D VAS Score	76.4	14.1	63.8	18.6	<.001	.83
Neurocognitive Tests						
RAVLT Total Score	53.9	9.2	51.4	9.0	.221	.27
RAVLT Delayed Recall	10.2	3.4	10.2	3.7	.998	.00
Verbal Fluency Total	39.9	11.6	39.4	13.0	.849	.04
Animal Naming Total	24.3	5.2	23.1	5.8	.316	.23
Trails A (in seconds)	30.4	9.8	29.0	10.5	.532	.14
Trails B (in seconds)	72.2	30.4	63.1	20.6	.162	.33
Stroop Color-Word	40.3	8.1	40.6	7.0	.885	.03

Note: N=109; Cohen's effect size (d): small (.20), medium (.50), large (.80). p=t- test, ** p < 0.01. BDI-II=Beck Depression Inventory-Second Edition; BNI-FS=Barrow Neurological Institute Fatigue Scale; EQ-5D VAS=EuroQol Five Dimension Visual Analogue Scale; RPSQ=Rivermead Post Concussion Symptoms Questionnaire; RAVLT=Rey Auditory Verbal Learning Test.

However, after excluding patients with multiple injuries (n=33), the groups did not differ in terms of fatigue (BNI total score, p=.092) or general health ratings (EQ-5D VAS, p=.324). There were no significant differences between the two groups for self-reported depression (BDI-II) or post-concussion symptoms (RPSQ). There were,

however, small-medium effect sizes for the BDI-II total score (d=.37) and RPSQ total score (d=.35) between groups. These effects sizes suggest that the RTW-Delayed group reported slightly more depression symptoms and post-concussion symptoms compared to the RTW-Rapid group.

6 DISCUSSION

Despite decades of extensive research, it is still unclear why some individuals recover faster than others after a mild TBI. MTBIs occur on a broad spectrum of severity, ranging from someone with no loss of consciousness and a minute or two of PTA to someone with many hours of PTA and a contusion on day-of-injury CT (Ruff, 2005). There has been great debate about the relative contributions of psychological factors and physiological factors in symptom genesis for well over 100 years (McAllister & Stein, 2010). Recent data has suggested that both psychological and physiological factors may be involved from the very beginning (Silverberg & Iverson, 2011). It has become clear that there is no simple, reasonably explanatory model for good or poor outcome following MTBI. As Iverson (2012, p. 53) states: "The only reasonable approach to understanding poor outcome from MTBI is a biopsychosocial perspective. This perspective, by necessity, embraces a multifactorial, interwoven, biopsychosocial conceptualization of poor outcome from this injury." Therefore, in this study, we applied the biopsychosocial approach in the context of MTBI. We aimed to explore the same subject (outcome from MTBI) from different angles by combining a variety of neuroloradiological, psychological, neuropsychological, and psychosocial measures. This chapter explores the significance of the results.

6.1 Neuroradiological Factors

There has been tremendous interest in the past few years in determining whether microstructural changes in white matter integrity, as measured by DTI, occur in patients across the spectrum of MTBI severity – and whether these changes are associated with worse functional outcome. A summary of this literature is provided in Study III. In part, the present thesis was designed to address significant gaps in the literature relating DTI and functional outcome following MTBI. It is the first study to examine the relation between DTI findings and multiple outcome measures (i.e., post-concussion symptoms, cognition, mental health, and return to work) in a large sample of patients with MTBIs.

DTI is not yet routinely used clinically. In part, this is because DTI data require a relatively large amount of careful postprocessing once acquired and normative data from the same scanner is not always available for comparison. Also, the gold standard for determination of DTI metrics has not been yet determined (Shaw & Ham, 2011). Clinicians require diagnostic information about individuals. However, most research studies report group results and therefore data from research is not readily applicable for individual cases. At present, group-level DTI findings are not useful at the single-patient level (Wortzel et al., 2011).

The results of DTI studies in MTBI have been mixed and yielded large discrepancies in the DTI values in relation to outcome measures. Different approaches to analyzing the results, such as voxel-based, tract-based, whole-brain, and ROI, have been used. Therefore, it is not surprising that DTI studies of MTBI have shown some inconsistency. Lack of consistency may be due to time frame of scanning, the heterogeneous nature of MTBI, and/or technological issues involved in DTI quantification (Zhang et al., 2010). The current study used a ROI approach that involves the investigation of a relatively small amount of white matter, within a-priori defined regions.

Exploratory analyses on all ROI revealed no significant differences between the MTBI and neuroimaging control group on 24 of 26 DTI measures. Differences were observed in two ROIs in corpus callosum: compared to controls, the MTBIs had increased ADC in the genu and increased FA in the splenium. However, correcting for multiple comparisons, there would be no statistically significant differences between groups in any ROI. Although somewhat inconsistent with several previous studies, this is not a particularly surprising finding if one considers that MTBIs are heterogeneous in regards to mechanisms of injury, biomechanics, and severity. This heterogeneity reduces the likelihood of finding abnormalities, at the group level, in specific brain regions.

The corpus callosum (CC) forms the largest and highest density commissural white matter bundle in the brain, connects the left and right hemispheres (Zhang et al., 2010), and is especially vulnerable to TBI because of its unique location (Maller et al., 2010). DTI studies suggest, that CC is the most frequently damaged in TBI (Wilde et al., 2008; Zhang et al., 2010; Aoki et al., 2012). Based on the recent meta-analysis, studies of MTBI patients demonstrate significantly reduced FA and significantly increased MD in the CC compared with controls (Aoki et al., 2012). As such, increased FA is the splenium in the current study is the opposite of what is expected based on the literature.

As a general rule, it is widely accepted that FA values decrease and ADC values increase after moderate-to-severe TBI, and in the post-acute stage of recovery following MTBI (Niogi et al., 2010). Some studies, however, have reported increased FA values and decreased diffusivity in the acute phase after the injury (Bazarian et al., 2007; Wilde et al., 2008; Mayer et al., 2010; Henry et al., 2011). It has been suggested that these

initial findings (increased FA, decreased diffusivity) might be due to inflammatory changes during the acute recovery phase (i.e., cytotoxic edema/ axonal swelling) rather than classic shear-strain lesions (Bazarian et al., 2007; Chu et al., 2010). This issue is far from resolved, however, because recent studies have suggested that FA values might be increased and MD values decreased in chronic stage after MTBI (Lo et al., 2009; Henry et al., 2011; Lipton et al., 2012); these findings are inconsistent with cytotoxic edema theory (Lipton et al., 2012). The implications of high FA values are not understood. It has been suggested that elevated FA values post-injury might reflect compensatory neuroplastic responses to injury, rather than a direct manifestation of injury pathology (Lipton et al., 2012; Toth et al., 2013). In all, abnormalities detected by DTI appear to be dynamically related to the time post injury (Toth et al., 2013) and the pattern, extent, and magnitude of these abnormalities might show considerable individual differences (Lipton et al., 2012).

In lognitudinal studies, acute DTI differences have been reported in association with MTBI with evidence of normalization over 3–5 months post trauma (Mayer et al., 2010). In the present study, we used a relatively wide window for DTI (interval of 16–60 days). It is possible that this influenced the results. Also, the present study used a cross-sectional design, which is a limitation in relation to identifying possible transient MRI findings. Therefore, we ran exploratory regression analysis to examine whether time post injury predicts FA scores. In the present study, time post injury did not predict total number of low FA scores ($R= .141$, $R^2=.020$, $p=.339$).

The present study shows that those with MTBIs were significantly more likely to have reduced white matter integrity in a greater number of regions of interest on DTI compared to control subjects. This is consistent with the literature on DTI in MTBI. Importantly, however, the white matter changes were not associated with functional outcome. MTBI patients with multifocal white matter changes did not perform more poorly on any neuropsychological test, did not take longer to return to work, and did not report more post-concussion symptoms compared to MTBI patients with broadly normal white matter.

6.2 Psychological and Neuropsychological Factors

6.2.1 Fatigue

Results of the current study indicate that symptoms of fatigue are frequent in patients with MTBI in the first month after injury. However, within one year the prevalence of fatigue returns to the level in the general population. Furthermore, it was found that

fatigue and depression are highly correlated with each other but not with injury-related or demographic variables. Post-TBI fatigue has been viewed as a multidimensional symptom that includes many components: physical, mental, motivational, situational, and activity-related (Bay & Xie, 2009). In the present study, with the BNI-FS, we have focused on self-reported mental fatigue – other important dimensions to examine with future studies would be cognitive fatigue and physical fatigue.

The primary goal in assessing post-injury fatigue is to identify those at risk of persistent or protracted symptoms. Without successful identification, fatigue or depression related problems may remain unrecognized because MTBI patients are generally not referred to follow-up visits. The present study revealed that fatigue is related to both time to return to work and the severity of post-concussion symptoms in the initial weeks following injury.

In this study, we examined the scores on two self-report fatigue scales, BNI Fatigue Scale and FIS, between the MTBI patients and the normal controls. The BNI-FS is a relatively new, brief, highly reliable measure of fatigue. Our results indicate taht the BNI-FS is a rapid and easy screening tool in clinical settings. Patients can complete the scale in less than five minutes. The psychometric properties of the BNI-FS support its clinical usefulness in assessing fatigue in patients who have sustained TBIs. In sum, the BNI-FS will be a valuable scale for future studies interested in symptoms of fatigue in mild traumatic brain injury patients.

6.2.2 Cognitive Sequelae

In the present study (Studies I–IV), patients with MTBIs did not perform more poorly than healthy controls on neuropsychological testing. This finding is consistent with some past studies illustrating that cognitive deficits resolve in most people within the first month following injury, as reported in meta-analyses (Schretlen & Shapiro, 2003; Belanger et al., 2005; Frencham et al., 2005; Rohling et al., 2011). It is inconsistent, however, with some studies that have reported differences between those with MTBIs and control subjects at one or three months following injury (Hugenholtz et al., 1988; Bohnen et al., 1993; Ponsford et al., 2000; Pertab et al., 2009).

It has been clearly demonstrated that neuropsychological deficits following a single uncomplicated MTBI are measurable, but transient (Rohling et al., 2011; Larrabee et al., 2013). Persistent cognitive symptoms are possible but not probable following MTBI (Binder et al., 1997). Neuropsychological tests can be useful in the detection of cognitive impairment and symptom severity following MTBI. However, the sensitivity of traditional neuropsychological testing to residual cognitive deficits following MTBI

has been questionned (Bigler et al., 2013). Although traditional neuropsychological techniques clearly differentiate TBI patients with moderate to severe injuries, it has been demonstrated that traditional neuropsychological measures poorly differentiate MTBI patients from controls (Bigler & Bazarian, 2010; Mayer et al., 2010). It has been suggested that self-reported cognitive and emotional symptoms offer no differential diagnostic value, and diagnosis based on symptomatology is likely to be inaccurate (Binder, 1997).

6.2.3 Persistent Post-concussion Symptoms

Consistent with previous studies (Boake et al., 2005; McCauley et al., 2008), the rate of PCS varied strongly depending on 1) the criteria used for diagnosis (the DSM-IV criteria versus the ICD-10 criteria) and 2) the symptom thresholds for diagnosis. The rate at which the PCS is diagnosed was considerably lower using the DSM-IV PCD criteria versus the ICD-10 PCS criteria. Further, the rate of diagnosis using both systems was significantly lower if symptoms were conceptualized as "moderate or greater" on the rating scale versus simply being present (i.e., "mild or greater"). In the current study, the prevalence of PCS diagnosis at one month based on mild or greater symptom reporting (59%) is similar to previous studies in the United States (64% at three months post-injury, Boake et al., 2005; 44.6% at six months post-injury, McCauley et al., 2008). However, considerably higher prevalence was found than in some European studies. Also, considerably lower prevalence was found for PCD diagnosis (1.6%; one month post-injury; mild or greater symptom reporting) than in previous studies (11%, Boake et al., 2005; 14.4% McCauley et al., 2008).

Previous European studies, where presence or absence of PCS has been diagnosed according to the ICD-10 criteria, have reported a wide variety of prevalence rates. In Greece (Spinos et al., 2010), the rate of PCS at 1 month, 3 months, and 6 months postinjury was estimated to be 10.3%, 6%, and 0.9%, respectively. In the United Kingdom (Hou et al., 2012), the rate of PCS at 3 months postinjury was estimated to be 22% and at 6 months postinjury was 21%. In France (Messe et al., 2012), the rate of PCS at 8–21 days following injury was 41.5%. The finding of Messe and collegues (Messe et al., 2012) is in line with the Scandinavian study by Ingebrigtsen and co-workers (Ingebrigtsen et al., 1998) in which a total of 40% of MTBI patients fulfilled the diagnostic criteria for post-concussion syndrome at 3 months after injury. In all these aforementioned studies, symptoms were conceptualized as simply being present (presence of three or more of the eight symptoms). In a Norwegian study (Sigurdardottir et al., 2009), 40% of persons with MTBI fulfilled the criteria for a PCS at 3 months

and 27.3% at one year after the trauma. However, in that study, post-concussion symptoms were considered present only when they were endorsed as moderate or greater (Sigurdardottir et al., 2009). In comparison, when using the definition of three or more symptoms as present, it has been shown that as many as 47% of the trauma controls will meet PCS diagnosis (Mickevičiene et al., 2004). Besides differences in research methodology, a possible explanation as to why the numbers are so different may be found in a variety of different insurance policies between the countries. For example in Lithuania (Mickevičiene et al., 2004), where there is little possibility of financial compensation for PCS, the prevalence of PCS has shown to be remarkably low.

The choice of which criteria set to use for clinical or research purposes is not easy. ICD-10 criteria has been recommended over the DSM-IV criteria based on the rationale that cognitive impairments are not likely to persist over three months following the MTBI and post-concussion symptoms occur frequently in the absence of detectable cognitive impairment (Mittenberg & Strauman, 2000). However, the usefulness of the ICD-10 PCS diagnostic criteria has been questioned and further refinement of the DSM-IV and ICD-10 criteria for PCS has been called for (Boake et al., 2005). It has been shown that there is a high base rate of PCS in control patients without brain injury when ICD-10 criteria are used (Iverson & Lange, 2003; Kashluba et al., 2006; Meares et al., 2008). Moreover, in one study ICD-10 PCS symptoms were unable to accurately classify the MTBI patients at three months post-injury (Kashluba et al., 2006). Therefore, ICD-10 criteria for PCS are not considered specific to mTBI, and these criteria are problematic because they may misleadingly suggest that the basis of PCS is a brain injury (Meares et al., 2008). According to Boake and coworkers, there is minimal justification for preferring either criterion set in the absence of evidence about their relative advantages (Boake et al., 2005).

Previously, it has been suggested that compromised microstructural white matter might be associated with increased post-concussion symptom reporting following MTBI (Garnett et al., 2000; Lipton et al., 2009). Therefore, it was hypothesized that patients with abnormalities on DTI would endorse more symptoms than patients with broadly normal DTI findings. This hypothesis was not supported. MTBI patients with multifocal white matter changes did not report more persistent post-concussion symptoms than those with broadly normal white matter. In addition, the diagnosis of PCS was unrelated to injury severity and demographic factors. Patients who sustained complicated MTBIs (i.e., those with trauma-related abnormalities on day of injury CT or subacute MRI) did not report greater post-concussion symptoms at approximately one month following injury. Also, patients with longer periods of post-traumatic amnesia were not more likely to develop PCS. To conclude, our results do not provide

support for the hypothesis that patients with greater injury severity will report more post-concussion symptoms than patients with milder injuries.

Our findings suggest that those with a pre-injury history of mental health problems and/or post-injury depression were more likely to meet criteria for PCS (ICD-10) at one month. One year following injury, pre-injury mental health problems and concurrent depression were no longer found to be associated with a diagnosis of PCS in this study. In the current study, the prevalence of pre-injury psychiatric symptoms was low because all patients with a known history of mental disorders were initially excluded. In the MTBI group, only a small percentage met criteria for depression at one month (5.6%, n=7) and one year post injury (4.9%, n=5). In the control group 0% met the depression criteria. Yet, some patients brought up some pre-injury symptoms of depression and anxiety in the detailed neuropsychological evaluation only after recruiting them into the study. Therefore, it appears as if most of the depressive symptoms reported in this study might have arisen only following MTBI. It is noteworthy, however, that concurrent depression following MTBI was more common in people with a previous mental health history. In sum, our results indicate that psychological factors are important for the initial development of the PCS.

6.2.4 Social Factors

Return to work is one important marker of functional recovery following MTBI. At one week post injury, 47% had returned to work. The proportion returning to work in the current study is comparable to studies of Powell and co-workers (2006) and Haboubi and co-workers (2001), but considerably lower than in other studies (Stranjalis et al., 2004; Wrightson et al., 1981).

At one month post injury, 71% of the sample had returned to work. The one month return-to-work rates vary widely in the literature. Two lines of evidence suggest that the diversity in these estimates is possibly attributable to cultural differences between the samples they are derived from. First, expecting that post-concussion symptoms will resolve quickly predicts shorter recovery times (Whittaker et al., 2007; Snell et al., 2011). This expectation is stronger in certain countries, where lower rates of persistent disability after MTBI are found (Ferrari et al., 2001; Spinos et al., 2010). Second, differing injury compensation systems between countries may be another factor, as access to compensation is the strongest predictor of MTBI outcome (Carroll et al., 2004a). Methodological differences between studies, such as inclusion or exclusion criteria, the setting in which the research is conducted, and how RTW is defined also likely influence, in substantial ways, the published return to work rates. A careful

examination of methodological and possible cultural differences in RTW rates across the MTBI literature would be a good topic for a future systematic review.

The one week and one month time periods are important to consider because they are commonly used in the literature, and the one month mark corresponds with the ICD-10 time period criteria for Post-concussion Syndrome. Having ongoing functional impairment at one month following injury (i.e., not returning to work) justifies fairly aggressive clinical intervention. In the current study, "slow return to work" was operationally defined as 30 or more days post injury. Exploratory analyses were run on four time categories (the one, two, three, and four weeks) for RTW (Study II).

Return to work during the first four weeks following MTBI was strongly predicted by a combination of age, multiple bodily injuries, intracranial abnormality on day-of-injury CT, and fatigue ratings. Classic injury severity variables (i.e., duration LOC, GCS score, and duration of PTA) were not associated with length of time to return to work. Similar findings were reported by Nolin and Heroux (2006). In the present study, neurocognitive functioning, measured at approximately 3–4 weeks post injury, was not related to time off work. Self-reported post-concussion symptoms and symptoms of depression, measured at 3–4 weeks post injury, were very modestly (not significantly) related to return to work status. In contrast, self-reported fatigue and perceived overall health status (EQ-5D VAS) were strongly related to the duration of time off work.

The presence of multiple bodily injuries was strongly associated with duration of time off work. Understandably, recovery time from physical injuries can influence time off work. It may be hypothesized that the patients who had multiple bodily injuries had longer sick leaves not because of MTBI itself but only because of additional injuries (e.g., orthopedic injuries). Notably, after excluding patients with multiple bodily injuries, the group with prolonged (> 30 days) RTW did not differ from the group with RTW within 30 days in terms of fatigue or in general health. This finding provides support for the idea that the self-reported problems with fatigue and general health were mostly associated with bodily injuries. Based on these findings, it can be argued that the only MTBI specific finding that was associated with greater duration of time off work in the current study was trauma-related intracranial findings.

It seems logical to assume that worse neuropsychological and functional outcome would result from greater injury (complicated versus uncomplicated MTBIs). However, the the research findings are mixed. To date, few studies have compared neurocognitive outcome and self-reported symptoms combined following uncomplicated and complicated MTBI. Most studies have compared neurocognitive outcome or self-reported symptoms in isolation (Iverson et al., 2012).

In a study by our research group, patients with complicated MTBIs took longer to return to work. They did not, however, perform more poorly on neurocognitive

measures, or report more symptoms, at 3–4 weeks post injury compared to those with uncomplicated MTBIs (Iverson et al., 2012). One possible reason why intracranial lesions were correlated with longer time off work may be that doctors are likely to grant longer sick leaves when there is objective evidence of brain injury; in that case the duration of the post-injury sick leave might reflect, in part, the behavior of doctors in the Finnish system. This idea is indirectly supported by our results from Study III. The multifocal abnormal white matter group did not take longer to return to work than the broadly normal white matter group (p=.939). Results obtained from DTI are not visible on conventional MRI and are not yet readily available for doctors in clinical settings.

Our results suggest that MTBI is associated with a favorable functional outcome in most people. The vast majority (91.7%) of this cohort returned to work within two months. However, some patients are slow to return to work and suffer from persistent symptoms. Predictors of return to work were sustaining a complicated mTBI, having multiple bodily injuries, increased age, and fatigue.

6.3 Strengths and Limitations

6.3.1 Strengths

The present study was large, carefully controlled, and prospective. In addition, strengths of the study include a reasonable sample size, inclusion of biopsychosocial outcome measures, the exclusion of confounders, and the use of outcome measures that are also suggested as Common Data Elements. To enhance the validity of our data, we tried to carefully exclude premorbid conditions (substance abuse, psychiatric disorders, previous brain injuries, developmental cognitive disorders, and other medical conditions resulting in cognitive changes) to rule out the possible influence of premorbid moderator variables and to avoid possible bias due to confounding factors. Furthermore, we ensured that none of the patients were involved in litigation, and had no financial incentives to exaggerate their symptoms. This is the first study to examine the relation between DTI findings and functional outcome in a comprehensive way (i.e., post-concussion symptoms, cognition, mental health, and return to work). However, despite the aforementioned strengths, this study has some methodological limitations and issues that should be considered.

6.3.2 Limitations

6.3.2.1 Control Group

First, the study included age and gender matched community controls as a comparison group instead of an orthopedically-injured trauma control group. In general, trauma control subjects are a better and more generalizable control group. Future studies should include trauma controls (i.e., orthopedic patients) instead of healthy controls to control for the effects of patienthood and possible premorbid differences between trauma patients and others (Binder, 1997).

Second, the imaging control group was a convenience sample that did not undergo psychological and neuropsychological testing. Using separate comparison groups for outcome measures and imaging is a weakness because it precludes looking at the interrelationships in subjects without TBI; this needs to be taken into account when interpreting the overall results.

Third, the neuropsychological control group was assessed only once. Therefore, we could not calculate reliable change estimates for neuropsychological measures. Also, the neuropsychological battery that was administered to controls was considerably shorter than the one that was administerd to MTBI patients. Lack of identical test batteries limited comprehensive comparisons between the groups.

6.3.2.2 Self-report and Cognitive Measures

First, self-reported pain was not specifically examined in the current study. Pain is reported frequently after MTBI, even more than after more severe brain injuries (Uomoto & Esselman, 1993; Sherman et al., 2006). It has been shown that post-concussive symptoms are often endorsed by patients with chronic pain (Iverson & McCracken, 1997; Smith-Seemiller et al., 2003; Stålnacke, 2012). Because of this overlap in symptoms, it is important for pain to be taken into account when assessing patients with MTBI in future studies. Post-TBI fatigue identified by self-report measures (such as the BNI-FS) is not necessarily due to MTBI and is not necessarily neurological, it might also relate to psychological distress and bodily injuries. Clearly, not assessing pain was a significant methodological limitation.

Second, we did not control for possible sleep disorders, which can be considered a weakness and should be taken into account in future studies. This is especially important when studying post-TBI fatigue. For example, it has been suggested that even a small level of sleepiness might worsen fatigue in severe TBI patients (Chaumet et al., 2008).

In MTBI, it has been shown that sleep disturbances (besides pain) are being reported more frequently after MTBI than in more severe injuries (Clinchot et al., 1998; Ouellet et al., 2004).

Third, performance validity and symptom validity testing were not included in the neuropsychological test battery because none of the patients were involved in litigation, and it was assumed that patients had no incentives to underperform on testing or exaggerate their symptoms. It is known, however, that inadequate effort or motivation in the testing process is possible in the absence of obvious external incentives. Therefore, it is important to include performance validity and symptom validity measures in MTBI research.

6.3.2.3 Diffusion Tensor Imaging

Although there was good reliability in the ROI analysis, the lack of tract-based spatial statistics (TBSS) or other advanced analytic approaches to DTI is also a limitation. To date, the ROI method is the most commonly used in the MTBI literature, the present results were fairly consistent with the majority of the literature, and this study examined numerous outcome variables (i.e., symptoms, cognition, return to work, and neuroimaging). Therefore, additional analyses of the DTI data were not undertaken. Also, at the time of this study, our lab did not have the technology or expertise to do TBSS properly. Both methods have their advantages and disadvantages, and some studies comparing methods illustrate that they can yield different results (Seo et al., 2013). The aim of the current study was not to evaluate concordance between measures of DTI derived using TBSS and ROI analyses. In future studies, however, it would be important to compare different results to enrich the data interpretation.

6.4 Clinical Implications

Critical issues in the acute clinical management of MTBIs include managing the symptoms, evaluating risk factors for long-term problems, and determining when patients have recovered so that they can safely return to work (or to school/play). The challenge remains how to ensure that an injury, no matter how mild, be properly assessed and treated appropriately in order to reduce the potential prolonged negative consequences.

In the current study, self-reported complaints were higher at one month following the injury in the MTBI group in all tested domains: physical, cognitive, emotional,

and fatigue. This is consistent with previous studies (Shumskaya et al., 2012). However, within a year the prevalence of self-reported symptoms returned to the level of general population in majority of cases. Although MTBI is usually associated with relatively rapid and spontaneous recovery, it has been widely acknowledged that a subgroup of patients may have persistent symptoms like fatigue. This was demonstrated in the current study. There was a subgroup of patients who showed an abnormal level of post-concussion symptoms one year post-injury. Clinically, it is noteworthy that there was a subgroup of patients who got worse in the follow-up (10%–16% depending on the diagnosis threshold).

The complex multifactorial nature of post-concussion symptoms, as well as individual variability, adds to the challenge of MTBI management. In view of the high frequency of MTBI, it is neither realistic nor necessary to provide comprehensive treatment to all people who are injured. Rather, targeting at-risk individuals may prove to be a more rational and cost-effective approach (Ghaffar et al., 2006; Ponsford et al., 2012). Identification of a subgroup of individuals who may benefit from intervention has important implications for the allocation of limited health care resources (Ghaffar et al., 2006).

It has been proposed that those individuals with a history of psychiatric disorder and those showing high levels of anxiety at 1 week following MTBI may be targeted for cognitive-behavioral interventions (Ponsford et al., 2012). Our results indicate that pre-injury mental health problems and concurrent depression were strongly associated with a diagnosis of PCS and should be considered important factors in the management of MTBI. Notably, post-concussion symptoms and depression were highly correlated with each other but not with injury-related or demographic variables. In all, our findings highlight the importance of an evaluation of emotional status and depression, even after the mildest form of TBI to ensure proper identification and treatment.

Clearly, no simple theory relating to the etiology of persistent symptom reporting following MTBI will have sole explanatory value. The manifestation of PPCS likely represents the cumulative effect of multiple variables, such as genetics, mental health history, current life stress, general medical problems, chronic pain, and co-occurring depression and/or substance abuse. A comprehensive, integrated model should provide a clearer picture of risk and resiliency in patients with MTBI, and thereby promote more efficient clinical management. Specifically, more research is needed to explore individual trauma tolerance and psychological resilience in relation to MTBI. There is some evidence that preinjury resilience and mood status are significantly related to outcome following MTBI (McCauley et al., 2012). Based on resent reseach, levels of preinjury depressed mood and low resilience are related to postinjury anxiety and post-concussion symptoms (McCauley et al., 2012). Also, the relationship between post-

traumatic stress (PTSD) and MTBI is still poorly understood. PTSD is closely related to other forms of emotional distress, such as depression and anxiety, that are known to have an adverse impact on outcome following MTBI (Stulemeijer et al., 2008).

In conclusion, it is likely that a complex syndrome such as PPCS results from different combinations of physiological, situational, psychological, and social factors in different patients. Treating individuals with MTBI as a homogenous group would be imprudent. It is important to accurately identify patients that may be at-risk to develop PPCS following MTBI so that adequate intervention can be applied in timely manner.

7 MAIN FINDINGS AND CONCLUSIONS

The main findings of the study are summarized below.

1. The vast majority of this cohort returned to work within two months (91.7%).
2. Return to work during the first 4 weeks following MTBI was strongly predicted by a combination of age, multiple bodily injuries, intracranial abnormality on day-of-injury CT, and fatigue ratings. Classic injury severity variables (i.e., duration of unconsciousness, GCS scores, and duration of PTA) were not associated with length of time to return to work.
3. MTBI patients reported more post-concussion symptoms than healthy controls at one month and one year following injury, but did not perform more poorly than healthy controls on neuropsychological testing.
4. The rate of persistent post-concussional symptoms varied depending on the symptom threshold for diagnosis. Pre-injury mental health problems and concurrent depression were strongly associated with post-concussion symptom reporting, whereas injury severity and DTI measures did not have any predictive value.
5. The MTBI group reported significantly more fatigue at one month following injury (greater total scores on the BNI-FS) than the control sample. However, within a year the prevalence of self-reported fatigue returns to the level of general population. At one-year post-injury, MTBI patients' self-reported fatigue ratings were on the same level as the healthy controls.
6. The BNI-FS is a rapid and easy screening tool in clinical settings. Patients can complete the scale in less than five minutes. The psychometric properties of the BNI-FS support its clinical usefulness in assessing fatigue in patients who have sustained TBIs.
7. Those with MTBIs were significantly more likely to show multifocal areas of diminished white matter on DTI compared to control subjects.
8. MTBI patients with multifocal white matter changes did not show evidence of worse symptoms, cognitive impairment, or slower return to work compared to MTBI patients with broadly normal white matter.

The main conclusions of the study are summarized below.

1. Most patients with MTBI appear to recover fully, from a functional perspective.
2. Results of the present study do not provide support for the hypothesis that patients with greater injury severity will report more post-concussion symptoms than patients with milder injuries.
3. White matter changes identified using DTI were not associated with functional outcome.
4. Results of the current study indicate that psychological factors are important for the initial development of the PCS.
5. The Barrow Neurological Institute Fatigue Scale is brief, highly reliable measure of fatigue. BNI-FS will be a valuable scale for future studies interested in symptoms of fatigue in MTBI patients.

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ORIGINAL ARTICLE

Reliability, validity and clinical usefulness of the BNI fatigue scale in mild traumatic brain injury

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Abstract

Objectives: The purpose of this study was to examine the reliability, validity and clinical usefulness of the Barrow Neurological Institute Fatigue Scale (BNI-FS) in patients with mild traumatic brain injuries (MTBI).

Methods and procedure: Participants were 125 patients enrolled from the Emergency Department (ED) of Tampere University Hospital, Finland who had sustained an MTBI. The average number of days from injury to the interview and questionnaires was 24.1 (SD = 5.4, Range = 8–38). The patients were compared to a healthy control sample. Patients completed the Barrow Neurological Institute Fatigue Scale, Fatigue Impact Scale (FIS), Beck Depression Inventory-Second Edition (BDI-II), Rivermead Post-concussion Symptom Questionnaire (RPSQ) and the health assessment measure EuroQol five Dimension (EQ-5D) Visual Analogue Scale (VAS).

Results: The MTBI group had significantly greater total scores on the BNI-FS than the control group ($p < 0.005$, Cohen's $d = 0.40$). The internal consistency reliability for the BNI-FS, as measured by Cronbach's alpha, was 0.96 for the MTBI group and 0.87 for the control group. The 10 items were submitted to an exploratory principal components factor analysis with varimax rotation in the MTBI group. A one-factor solution, accounting for 73.3% of the total variance, appropriately summarized the data. The correlation between the BNI-FS and other measures was $rs = 0.68$ ($p < 0.001$) for the BDI-II, $rs = 0.68$ ($p < 0.001$) for the RPSQ, $rs = -0.39$ ($p < 0.001$) for the EQ-5D VAS and $rs = 0.84$ ($p < 0.001$) for the FIS. Fatigue ratings correlated positively with number of days post-injury before returning to work ($rs = 0.27$, $p < 0.006$).

Conclusion: The BNI-FS is a relatively new, brief and highly reliable measure of fatigue.

Keywords: *Fatigue, measurement, mild traumatic brain injury*

Introduction

Fatigue following traumatic brain injury (TBI) is a complex and multidimensional problem [1]. Fatigue is considered one of the most persistent and disabling symptoms in patients with TBI [2–6]. It has been suggested that fatigue is not related to injury severity because it does not seem to be more common in severe than in mild traumatic brain injury (MTBI) [2, 7]. The study of fatigue following MTBI is important because (i) it is a very common symptom in the initial days and weeks post injury [8–10]; (ii) it is a common symptom at 3 months post-injury [11–13]; (iii) when present at 3–6 months post-injury it can remain a problem long-term [8]; (iv) it is related

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to subjectively-experienced cognitive problems [14]; (v) it can interfere with social and occupational functioning [2, 15]; and (vi) its underlying causes can be complex, interwoven and wholly or partially treatable (e.g. insomnia, anxiety, depression, chronic pain, life stress and physical deconditioning).

There are only few validated instruments for measuring fatigue following TBI [2, 16]. According to a review by Belmont et al. [7], five questionnaires have been used to assess TBI-related fatigue: the Fatigue Severity Scale (FSS), Visual Analogue Scale for Fatigue (VAS-F), Fatigue Impact Scale (FIS), Barrow Neurological Institute (BNI) Fatigue Scale and the Cause of Fatigue (COF) Questionnaire. Only the BNI Fatigue Scale and the COF Questionnaire are specifically designed for patients who have sustained TBIs.

The BNI Fatigue Scale is a measure of self-reported fatigue introduced by Borgaro et al. [4] in 2004. It was developed to assess self-reported fatigue associated with acquired brain injury during the early stages of recovery. Good psychometric properties for this scale were reported in a sample of heterogeneous neurological patients [4]. Specifically, in a sample of 84 patients with diagnoses of cerebrovascular accident, traumatic brain injury, brain tumour, spinal cord injury, encephalopathy and hydrocephalus, the internal consistency reliability of the scale was 0.94. Factor analysis revealed a one factor structure; all 10 of the items loaded on a single factor.

The purpose of this study was to examine the reliability, validity and clinical usefulness of the Barrow Neurological Institute Fatigue Scale in patients with mild TBI. Specifically, this study examined the internal consistency reliability; factor structure; and convergent, discriminant and construct validity of the scale in a large sample of patients assessed a few weeks post-injury.

Method

Participants

From 2006–2009, an inception cohort of 145 patients admitted to the Tampere University Hospital Emergency Department (ED) with head trauma and evidence of brain injury were enrolled. Of this cohort, 126 fulfilled criteria for an MTBI according to the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine [17] and the World Health Organization (WHO) Collaborating Center Task Force on Mild Traumatic Brain Injury ([18], p. 115). Inclusion criteria were (i) biomechanical force applied to the head, (ii) loss of consciousness, if present, for less than 30 minutes, (iii) Glasgow Coma Scale score between 13–15 after 30 minutes following injury and (iv) post-traumatic amnesia, if present, of less than 24 hours. This sample included patients ($n = 17$; 13.5%) who had an intracranial abnormality on day-of-injury CT or follow-up MRI (i.e. a complicated MTBI).

The average age of the sample was 37.8 years (SD = 13.5; Range = 16–64), their average education was 12.6 years (SD = 2.7; range = 8–22) and 43.7% of the sample was male. At the time of injury, the employment status of the sample was as follows: 65.1% working full time, 2.4% working part time, 15.9% students, 4.0% retired/partly retired, 9.5% unemployed, 0.8% on sick leave and 2.4% missing data. The percentages of patients with previous MTBIs were as follows: none = 65.1%, one = 32.5%, two = 2.4%. The psychiatric history of this sample was as follows: 90.5% none, 7.1% yes, 2.4% unknown. The mechanisms of injury were as follows: 32.5% motor vehicle accident (MVA), 4.0% pedestrian-MVA, 8.7% sports, 36.5% fall (low), 7.1% fall (high), 7.1% assault and 4.0% other. Their average Glasgow Coma Scale (GCS) score was 14.96 (SD = 0.20, Range = 14–15, 96% = 15). Their average duration of loss of consciousness was 0.8 minutes (SD = 2.2, range = 0–15). Duration of post-traumatic amnesia was as follows: 48% no PTA, 22% PTA $\leq$ 2 hours, 30% PTA > 2 hours. The average duration of sick leave after the injury was 42.1 days (SD = 112.1, IQR = 3.0–30.5, range = 0–729). None of the patients were involved in litigation. All patients provided written informed consent according to the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Tampere University Hospital.

The control subjects consisted of 36 age- and sex-matched individuals (63.9% female) with no history of head injury. This was a convenience sample recruited from the community. The mean age of the controls was 36.9 years (range = 17–61) and their average education was 15.1 (range = 8–19) years.

Procedure

All the MTBI patients in this study were recruited from the ED of Tampere University Hospital. CT brain scans were performed in all patients within 24 hours of admission. Self-reported fatigue assessments were conducted as part of a more comprehensive neuropsychological evaluation. The average number of days from injury to the interview and questionnaires was 24.1 (SD = 5.4, range = 8–38).

Measures

Barrow Neurological Institute Fatigue Scale. The BNI Fatigue Scale is an 11-item self-report

questionnaire designed to assess fatigue during the early stages of recovery after TBI [4]. Subjects are asked to rate the extent to which each of the 10 primary items has been a problem for them since the injury on a 7-point scale. Response options are as follows: 0–1 = rarely a problem; 2–3 = occasional problem, but not frequent; 4–5 = frequent problem; 6–7 = a problem most of the time. The final item (item 11) asks subjects to provide an overall rating of their level of fatigue on a scale from 0 (no problem) to 10 (severe problem). In this study the total BNI-FS score is used which is the sum of all 10 scores (min = 0, max = 70).

Fatigue Impact Scale. Self-reported fatigue was also examined using FIS, which has been used in studies involving a variety of medical conditions [19] including TBI [20]. FIS is a structured 40-item self-report questionnaire that focuses on the ways in which fatigue affects everyday life [21]. It has three separate sub-scales (10 physical items, 10 cognitive items and 20 psychosocial items). Subjects are asked to rate how much of a problem fatigue has been for them during the past month, including the day of testing. The response options are as follows: 0 = no problem, 1 = small problem, 2 = moderate problem, 3 = big problem and 4 = extreme problem. In this study, the total FIS score is used. The total score is the sum of all 40 items (min = 0, max = 160).

Beck Depression Inventory. Possible depressive symptoms were assessed using the Beck Depression Inventory-Second Edition (BDI-II) [22] 21-item self-report questionnaire. Subjects are asked to rate each item on a 4-point scale ranging from 0–3. This study used the total score, which is the sum of all 21 items, giving a range from 0–63. Previous studies have shown that the BDI-II is sensitive in identifying symptoms of depression following TBI [23–25].

Rivermead Post-Concussion Symptom Questionnaire. Post-concussional symptoms were assessed with the Rivermead Post-Concussion Questionnaire (RPSQ) [26]. The RPSQ is a 16-item self-report questionnaire that measures the severity of common post-concussion symptoms on a 5-point Likert scale. On the RPSQ, the patients rated the presence of the symptoms over the past 24 hours on a scale from 0–4 (0 = not experienced at all after the injury, 1 = experienced but no more of a problem compared with before the injury, 2 = a mild problem, 3 = a moderate problem and 4 = a severe problem). A total score was calculated by adding all items with a score greater than 1 (not present anymore).

EuroQol Five Dimension Visual Analogue Scale. EuroQol 5D™ (EQ-5D) is a standardized instrument for use as a measure of health outcome and the EQ-5D™ is a trademark of the EuroQol Group [27]. In this study, the EQ-5D Visual Analogue Scale (VAS) was used to evaluate general health-related quality-of-life. The EQ-5D VAS is a visual scale that asks the respondent to consider and rate his or her health 'today' on a vertical scale calibrated from 0 (worst imaginable health state) to 100 (best imaginable health state).

Data analyses

Differences between groups were assessed by chi-square for categorical variables. Variables were analysed for departures from normality and heterogeneity of variance (Levene's test). Because some of the variables were not normally distributed, both parametric and non-parametric analyses were conducted. In most cases, both independent *t*-tests and non-parametric Mann Whitney U-tests are reported. The internal consistency reliability for the BNI-FS was determined by using Cronbach's alpha. To explore the factor structure, principal components analysis with varimax rotation was conducted. Convergent and discriminant validity were evaluated by assessing the level of association between scores on the BNI-FS and the other questionnaires. Correlations between BNI-FS and other measures (FIS, RPSQ, EQ-5D and BDI-II) were calculated by using Spearman's rank correlation coefficient. Statistical analyses were conducted using SPSS for Windows version 16.0.

Results

The MTBI and control groups did not differ on age ($t(160) = 0.336$, $p = 0.737$) or gender ($\chi^2 = 0.654$, $p = 0.419$). The MTBI group differed from the control group on education ($t(160) = -4.890$, $p = 0.001$). The mean years of education for MTBI patients and control subjects were 12.6 (SD = 2.7) and 15.1 (SD = 2.5), respectively.

The MTBI group had significantly greater total scores on the BNI-FS ($M = 15.7$, SD = 15.4) than the control group ($M = 10.3$, SD = 7.4; $p < 0.005$, Cohen's $d = 0.40$) using a *t*-test with Levene's correction for heterogeneity of variance. The total scores did not differ when compared with a Mann Whitney U-test. Individual items that differed significantly between groups, with medium effect sizes, were #3 (staying awake during the day), #7 (staying out of my bed during the day) and #10 (lasting the day without taking a nap). There were trends toward significant differences for items #2 (participating in activities because of fatigue), #4 (completing a task

Table I. Barrow Neurological Institute Fatigue Scale descriptive statistics, component loadings, group comparisons and effect sizes.

	MTBI sample					Control sample					
Item	*M*	Median	SD	IQR	Component loadings	*M*	Median	SD	IQR	*p*- value	Cohen's d
1	2.0	2.0	1.8	1–3	0.85	1.7	2.0	1.2	1–2	0.90 (0.263)	0.18
2	1.8	1.0	2.0	0–3	0.89	1.0	1.0	1.1	0–2	0.07 (0.002)	0.44
3	1.3	1.0	1.6	0–2	0.87	0.6	0.0	0.8	0–1	0.02 (0.001)	0.49
4	1.3	1.0	1.7	0–2	0.88	0.8	1.0	0.9	0–1	0.21 (0.006)	0.33
5	1.5	1.0	1.8	0–2	0.89	0.9	1.0	1.0	0–2	0.15 (0.008)	0.37
6	1.4	1.0	1.7	0–2	0.77	1.3	1.0	1.1	1–2	0.37 (0.789)	0.06
7	1.4	1.0	1.9	0–2	0.83	0.4	0.0	0.9	0–1	0.01 (0.000)	0.60
8	1.6	1.0	1.8	0–3	0.90	1.3	1.0	1.3	0–2	0.65 (0.266)	0.18
9	1.8	1.0	1.8	0–3	0.85	1.6	1.0	1.3	1–3	0.80 (0.539)	0.12
10	1.6	1.0	2.0	0–2	0.83	0.7	0.0	1.2	0–1	0.01 (0.002)	0.49
Total	15.7	11.0	15.4	3.8–21.3	na	10.3	11.0	7.4	4.3–13.0	0.27 (0.005)	0.40

There were 126 patients with MTBIs and 36 control subjects. *M*, mean; SD, standard deviation; IQR, interquartile range. Exploratory factor analysis was not conducted with the control sample due to the small sample size. *p*-values are for Mann Whitney U-tests first and independent *t*-tests in parentheses. The *p*-values for the *t*-tests were corrected following Levene's test for heterogeneity of variance.

without becoming tired) and #5 (staying alert during activities) (see Table I).

The internal consistency reliability for the BNI-FS, as measured by Cronbach's alpha, was $r_{11} = 0.96$ for the MTBI group and $r_{11} = 0.87$ for the control group. The 10 items were submitted to an exploratory principal components factor analysis with varimax rotation in the MTBI group. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.93. Bartlett's test of sphericity was rejected ($p < .0001$). The eigenvalues (Kaiser criterion) and scree plot unequivocally indicated that a one-factor solution, accounting for 73.3% of the total variance, appropriately summarized the data. The correlations between each item and the component were uniformly high (i.e. the component loadings). The factor loadings are reported in Table I. The scree plot is presented in Figure 1.

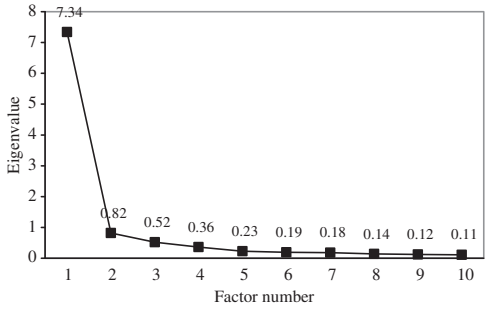

Figure 1. Scree plot of eigenvalues from principal components factor analysis of the BNI-FS scale.

An inter-correlation matrix illustrating the bivariate relations among the questionnaires within the MTBI group is presented in Table II. The statistically significant correlations between the BNI-FS and other measures were $rs = 0.68$ for the BDI-II, $rs = 0.68$ for the RPSQ, $rs = -0.39$ for the EQ-5D and $rs = 0.84$ for the FIS. BNI-FS correlated positively with number of days post-injury before returning to work ($rs = 0.27$, $p < 0.001$). The measures of depression and post-concussion symptoms have item content that overlaps with the BNI-FS. Therefore, bivariate correlations between the BNI-FS and the other two measures (BDI-II and RPSQ), after the sleep and fatigue items were removed from the other scales, were conducted. The correlations were $rs = 0.59$ ($p < 0.001$) for BDI-II and $rs = 0.66$ ($p < 0.001$) for RPSQ.

On the basis of the BNI-FS scores, MTBI patients were categorized into two levels of fatigue: mild–moderate fatigue (total score $\leq$29) or heavy fatigue (total score $\geq$30). Nearly 17% of the MTBI sample reported heavy fatigue. Healthy control subjects reported mild-to-moderate fatigue, but none of the controls reported heavy fatigue based on this criteria. There were 105 patients in the mild–moderate fatigue group and 21 in the heavy fatigue group. The two groups did not differ in gender, age, education, Glasgow Coma Scale scores, duration of loss of consciousness, duration of post-traumatic amnesia or the presence of other bodily injuries.

By design, there was an enormous difference between groups on the BNI-FS ($M = 9.9$, SD = 7.8 and $M = 44.6$, SD = 10.4; Cohen's $d = 4.2$; mild–moderate vs heavy fatigue groups). There were also large statistically significant differences between the two groups on the FIS total score ($M = 16.3$, SD = 18.0 and $M = 65.1$, SD = 25.5; Cohen's d = 2.5; mild-moderate vs heavy fatigue groups), BDI-II ($M = 5.4$, SD = 5.9 and $M = 14.3$, SD = 8.3;

Table II. Inter-correlation matrix in the MTBI sample.

	BNI-FS	BDI-II	EQ-5D	RPSQ	FIS
Barrow Neurological Institute Fatigue Scale (BNI-FS)	1.00				
Beck Depression Inventory-Second Edition (BDI-II)	0.68**	1.00			
EuroQol five Dimension Visual Analogue (EQ-5D)	−0.39**	−0.52**	1.00		
Rivermead Post Concussion Symptom Questionnaire (RPSQ)	0.68**	0.77**	−0.47**	1.00	
Fatigue Impact Scale (FIS)	0.84**	0.77**	−0.45**	0.81**	1.00
Mean	15.7	6.9	73.4	10.4	24.6
Median	11.0	4.5	76.0	6.0	13.0
Standard Deviation	15.4	7.2	16.3	10.7	26.7
Range	0–61	0–32	0–100	0–44	0–115

There were 126 patients with MTBIs. **$p < 0.01$.

Cohen's $d = 1.4$; mild-moderate vs heavy fatigue groups), RPSQ ($M = 8.0$, SD = 9.0 and $M = 22.6$, SD = 10.3; Cohen's $d = 1.6$; mild-moderate vs heavy fatigue groups) and the EQ-5D VAS score ($M = 76.9$, SD = 13.2 and $M = 56.7$, SD = 19.9; Cohen's $d = 1.4$; mild-moderate vs heavy fatigue groups).

On average, the patients with MTBIs were on sick leave for 42.1 days (SD = 112.1, IQR = 3.0–30.5, range 0–729). MTBI patients were divided into two groups based on time taken to return to work: short-to-moderate length (length of sick leave 0–30 days; $n = 92$) or long (length of sick leave over 30 days, $n = 30$). The two groups did not differ in gender, age, education, Glasgow Coma Scale scores, duration of loss of consciousness or duration of post-traumatic amnesia. However, being slow to return to work was associated with having other bodily injuries ($p < 0.001$). There were large statistically significant differences between the two groups on the BNI-FS total score ($M = 13.2$, SD = 13.7 and $M = 24.2$, SD = 18.05; Cohen's $d = 0.75$; short–moderate vs long RTW groups), FIS total score ($M = 21.7$, SD = 25.8 and $M = 36.0$, SD = 27.7; Cohen's $d = 0.55$; short–moderate vs long RTW groups) and the EQ-5D VAS score ($M = 75.8$, SD = 14.7 and $M = 64.1$, SD = 17.7; Cohen's $d = 0.76$; short–moderate vs long RTW groups). There were no statistically significant differences between the two groups on the BDI-II or RPSQ.

Patients with complicated MTBIs (i.e. those with trauma-related abnormalities on CT or MRI) were compared to patients with uncomplicated MTBIs ($n = 17$ for the complicated group and 109 for the uncomplicated group). The two groups did not differ in gender, age, education, Glasgow Coma Scale scores, duration of loss of consciousness, duration of post-traumatic amnesia or the presence of other bodily injuries. The uncomplicated MTBI group reported significantly more depressive symptoms than the complicated group ($t(43) = 2.7$, $p = 0.01$) using a t-test with Levene's correction for heterogeneity of variance (BDI-II total score $M = 7.3$, SD = 7.5 and $M = 4.2$, SD = 3.6; Cohen's $d = 0.44$; uncomplicated vs complicated group). The BDI-II total scores did not differ when compared with a Mann Whitney U-test. The groups did not differ on fatigue measures (BNI-FS, FIS), post-concussion symptoms (RPSQ) or general health (EQ-5D VAS) (all $p > 0.05$). There was only one subject who had trauma-related neuroradiological findings and reported heavy fatigue.

Discussion

This study examined the psychometric properties and clinical usefulness of the BNI Fatigue Scale (BNI-FS) in MTBI patients and healthy controls. The MTBI group had greater total scores on the BNI-FS than the control sample. The individual items that differed the most between the MTBI sample and the controls were #3 (How difficult it is for me to stay awake during the day), #7 (How difficult it is for me to stay out of my bed during the day) and #10 (How difficult it is for me to last the day without taking a nap). The internal consistency reliability of the BNI-FS in this study was very high, as reflected by Cronbach's alpha ($\alpha = 0.95$) and the factor analysis and similar to that reported in the original study ($\alpha = 0.94$) [4]. Exploratory principal components factor analysis with varimax rotation unequivocally indicated that a one-factor solution appropriately summarized the data. This further supports the strong internal consistency of this 10-item scale. The original study also reported a one-factor solution for this scale.

The BNI-FS was highly correlated with the Fatigue Impact Scale (see Table II). It was also correlated with measures of depression, post-concussion symptoms and quality-of-life, but to a lesser extent. This pattern of correlations supports the convergent and divergent validity of the scale. The strong positive correlation between

self-reported fatigue and the BDI-II is similar to previous studies reporting an association between fatigue and depression and also overlap of the content of questionnaires assessing these constructs [28, 29]. This strong association between fatigue and depressive symptomatology raises the question as to whether post-injury fatigue constitutes an independent symptom or whether it is largely a manifestation of depression. According to Ziino and Ponsford [3], depression is common following TBI and may contribute to post-injury fatigue. In their study, Walker et al. [29] reported significantly elevated levels of depression in the TBI group with fatigue compared with those without fatigue. These results support the notion that self-reported fatigue after MTBI is associated with depressive symptomatology. However, the results do not establish the nature or direction of a causal connection.

The present MTBI sample had lower total scores on the BNI-FS than the heterogeneous neurological sample from the original study (BNI FS total score $M = 15.7$, SD = 15.4 vs $M = 24.6$, SD = 16.6; current study, original study) [4]. However, there was a sub-group in the MTBI sample that reported very high levels of fatigue (i.e. ~17% had BNI-FS total scores ≥ 30). No control subject had a score this high. When the MTBI patients with high levels of fatigue were compared to MTBI patients with mild–moderate fatigue, important differences emerged. The heavy fatigue group endorsed greater symptoms of depression ($d = 1.4$), greater symptoms of the post-concussion syndrome ($d = 1.6$) and worse quality-of-life ($d = 1.4$).

This study has several important limitations. First, it did not study test–re-test reliability. Therefore, reliable change estimates could not be calculated for clinical use. Second, BNI-FS items emphasize daytime sleepiness (for example item: 'How difficult is it for me to attend to something without becoming sleepy?'), which is a construct that might be distinct from fatigue, although the two may certainly co-exist. This study did not control for possible sleep disorders, which can be considered a weakness and could be taken into account in future studies. For example, it has been suggested that even a small level of sleepiness might worsen fatigue in severe TBI patients [30]. Third, no collateral information from an informant was obtained, so it is not possible to evaluate the external validity of the BNI-FS scores. Fourth, the fatigue being identified by the BNI-FS is not necessarily due to MTBI and is not necessarily neurological, it might also relate to psychological distress and bodily injuries. In this respect, not assessing pain was a significant methodological limitation.

Fifth, the measures of depression and post-concussion symptoms have item content that overlaps with the BNI-FS. This is unavoidable because those conditions include fatigue as a cardinal symptom. The overlapping content would contribute, in part, to the positive correlations among these scales. The correlations between the BNI-FS and the other two measures (BDI-II and RPSQ) were run after the sleep and fatigue items were removed from the other scales. The correlations attenuated but remained significant, indicating an association independent of the item overlap. Finally, post-TBI fatigue has been viewed as a multidimensional symptom that includes many components: physical, mental, motivational, situational and activity-related [31]. The present study, with the BNI-FS, has focused on self-reported mental fatigue—other important dimensions to examine with future studies would be cognitive fatigue and physical fatigue.

In conclusion, the BNI-FS is a relatively new, brief, highly reliable measure of fatigue. The BNI-FS will be a valuable scale for future studies interested in symptoms of fatigue in MTBI patients. The BNI-FS is a rapid and easy screening tool in clinical settings. Patients can complete the scale in less than 5 minutes. The psychometric properties of the BNI-FS support its clinical usefulness in assessing fatigue in patients who have sustained TBIs.

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Return to Work Following Mild Traumatic Brain Injury

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Objective: To examine factors relating to return to work (RTW) following mild traumatic brain injury (mTBI). **Participants:** One hundred and nine patients (Age: M = 37.4 years, SD = 13.2; 52.3% women) who sustained an mTBI. **Design:** Inception cohort design with questionnaires and neuropsychological testing completed approximately 3 to 4 weeks postinjury. **Setting:** Emergency Department of Tampere University Hospital, Finland. **Main Outcome Measures:** Self-report (postconcussion symptoms, depression, fatigue, and general health) and neurocognitive measures (attention and memory). **Results:** The cumulative RTW rates were as follows: 1 week = 46.8%, 2 weeks = 59.6%, 3 weeks = 67.0%, 4 weeks = 70.6%, 2 months = 91.7%, and 1 year = 97.2%. Four variables were significant predictors of the number of days to RTW: age, multiple bodily injuries, intracranial abnormality at the day of injury, and fatigue ratings (all $P < .001$). The largest amount of variance accounted for by these variables in the prediction of RTW was at 30 days following injury ($P < .001$, $R^2 = 0.504$). Participants who returned to work fewer than 30 days after injury ($n = 82$, 75.2%) versus more than 30 days ($n = 27$, 24.8%) did not differ on demographic or neuropsychological variables. **Conclusions:** The vast majority of this cohort returned to work within 2 months. Predictors of slower RTW included age, multiple bodily injuries, intracranial abnormality at the day of injury, and fatigue. **Key words:** *mild traumatic brain injury*, *outcome*, *return to work*

MOST individuals recover rapidly and return to their everyday activities soon after sustaining a mild traumatic brain injury (mTBI).[1,2] However, some suffer persistent symptoms for a prolonged period after mTBI, which interferes with their return to work (RTW).[3] The risk factors for poor outcome and specifically for delayed RTW after mTBI are diverse, complex, and not well-understood.[4]

Traditional brain injury severity variables (eg, duration of loss of consciousness [LOC], Glasgow Coma Score [GCS])[2] or postinjury cognitive impairment have shown limited usefulness in predicting outcome after mTBI.[5,6] Some studies,[7–12] but not all,[13–15] have reported that mTBI patients with trauma-related intracranial abnormalities are more likely to have worse outcome than those with uncomplicated mTBIs (patients with no intracranial abnormalities). Other factors such as duration of posttraumatic amnesia,[2] personality characteristics, pre- and postinjury physical functioning, psychological status, protracted litigation, employment status, substance abuse problems, and presence of extracranial injuries are considered potential correlates of outcome.[16] Nolin and Heroux[17] emphasized the importance of focusing on subjective complaints that arise following the injury. In their study, only the total number of symptoms reported at follow-up was related to vocational status. Patient characteristics, injury severity indicators, and cognitive functioning were not associated with vocational status after mTBI.[17]

Return to work is an important outcome measure of TBI. It has been emphasized as a key component for

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evaluating outcome in the World Health Organization's International Classification of Functioning, Disability and Health.[18] Unsuccessful RTW can have profound negative economic and psychosocial consequences for affected individuals and their families. When considering the full spectrum of TBI, rate of RTW is related to injury severity. Although studies consistently find that individuals with mTBI RTW more rapidly than those with severe brain injuries, the literature has been quite inconsistent in terms of the length of time to RTW that is typical for individuals with mTBI. One-week RTW rates following mTBI vary widely in the literature. In a study from Greece ($N = 100$), 84% of a very mildly injured sample (ie, GCS = 15 and PTA < 15 minutes) returned to work in the first week postinjury.[19] In a study from New Zealand ($N = 66$), 82% returned to work in the first week.[20] In contrast, researchers from the United Kingdom ($N = 39$) found that only 41% of patients returned to work within 5 days after minor head injury.[21] Moreover, in a sample of 391 patients seen in a rehabilitation clinic in the United Kingdom, 44% had returned to work within 2 weeks.[22] The percentages of individuals returning to work by 1 month following injury has also varied widely across studies, ranging from 25% to 100%.[19,20,22–25] It has been suggested that such differences in findings may be due in part to methodological differences in study design and differences among countries in cultural, socioeconomic, and/or political factors. However, this article will not explore such possibilities.

The purpose of this study was to examine factors relating to RTW following mTBI. In this study, we investigated the influence of 17 factors (demographic, background history, injury severity, and clinical outcome variables) on RTW rates following mTBI. Consistent with the literature,[2,22,26] we hypothesized that more serious mTBIs (ie, greater likelihood of an abnormality on neuroimaging and greater duration of posttraumatic amnesia [PTA]) and greater postconcussion symptom reporting would be associated with slower RTW. Better understanding of variables related to outcome after mTBI will aid clinicians in identifying those individuals who are at risk of developing a prolonged postconcussive syndrome and whose RTW is likely to suffer from extended delay. Interventions can then be developed with relevant factors in mind.

METHOD

Participants

From 2006 to 2009, an inception cohort of 145 consecutive patients admitted to the Tampere University Hospital Emergency Department (ED) with head trauma and evidence of brain injury were enrolled. Inclusion criteria were (i) biomechanical force applied to the head resulting in loss or alteration of consciousness, confusion, and/or PTA, (ii) LOC, if present, for less than 30 minutes, (iii) Glasgow Coma Scale (GCS) score of 13 to 15 after 30 minutes following injury, (iv) posttraumatic amnesia, if present, of less than 24 hours, and (v) being employed or a student at the time of injury. Of this cohort, 33 patients were excluded because their injuries were too severe to meet the inclusion criteria. Of the remaining 112 patients, 3 were excluded because of unknown duration of sick leave. A total of 109 patients had known duration of sick leave and they fulfilled the criteria for an mTBI according to the mTBI Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine[27] and the World Health Organization Collaborating Center Task Force on mTBI.[28] The average age of the sample was 37.4 years (SD = 13.2), 52.3% were women, and their average education was 12.8 years (SD = 2.8; interquartile range = 11–15). All were working or students at the time of injury (working full-time 76.1%, working part-time 5.6%, student 18.3%). This sample included some patients ($n = 16$; 14.7%) who had an intracranial abnormality on day-of-injury CT or follow-up MRI (ie, a complicated mTBI). Return to work, defined as the duration of sick leave, is represented by the number of days between injury and return to preinjury duties (return to work or school). No patient was involved in litigation. All patients provided written informed consent according to the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Tampere University Hospital.

Procedure

All participants with mTBI were recruited from the Tampere University Hospital ED. Patients underwent computed tomographic (CT) scanning, an evaluation by an ED traumatologist, and other examinations as needed. It (CT scanning) was performed within 24 hours of admission. Magnetic resonance imaging (MRI) was conducted at approximately 3 weeks postinjury. All patients completed self-report measures and neurocognitive testing at approximately 3 to 4 weeks postinjury (M = 24.3, SD = 5.4, Range = 8-38 days). Duration of time off work for illness or following injury, referred to as sick leave, is carefully documented in the Finnish healthcare system. It is normal and expected for this information to be documented precisely. For this study, the dates for the end of sick leave were extracted from the medical records and then verified with the patient during a later clinical interview.

Measures

Neuroimaging

Magnetic resonance imaging at 3 weeks postinjury was performed either on a 1.5 Tesla (Magnetom Avanto A TIM system Siemens Medical Solutions, Erlangen, Germany) ($n = 32$, 29.4%) or a 3T Siemens Trio (Siemens AG Medical Solutions, Erlangen, Germany) ($n = 77$, 70.6%) machine. The MRI protocol included sagittal T1-weighted 3-dimensional inversion recovery prepared gradient echo, axial T2 turbo spin echo, conventional axial and high resolution sagittal FLAIR (fluid-attenuated inversion recovery), axial T2*, and axial SWI (susceptibility weighted imaging) series. Only trauma-related findings in CT and MRI were counted as abnormal; minor incidental findings, such as isolated white matter hyperintensities, were not considered as abnormal.

Self-report questionnaires

Self-reported fatigue was examined using the Barrow Neurological Institute Fatigue Scale (BNI-FS), an 11-item self-reported questionnaire designed to assess fatigue during the early stages of recovery after brain injury.[29] Participants were asked to use a 7-point scale to rate the extent to which each of the 10 primary items has been a problem for them since the injury. Response options were as follows: 0-1 = rarely a problem; 2-3 = occasional problem, but not frequent; 4-5 = frequent problem; 6-7 = a problem most of the time. The final item (item 11) asks for an overall rating of their level of fatigue on a scale from 0 (no problem) to 10 (severe problem). In this study, the total BNI-FS score is used, which is the sum of all 10 scores (min = 0, max = 70). The BNI-FS has high 1-day test-retest reliability ($r = 0.96$).[29]

Postconcussion symptoms were assessed with the Rivermead Post Concussion Questionnaire (RPSQ).[30] The RPSQ is a 16-item self-reported questionnaire that measures presence and perceived severity of common postconcussion symptoms over the past 24 hours using a 5-point Likert scale (0, *not experienced at all after the injury*; 1, *experienced but no more of a problem compared with before the injury*; 2, *a mild problem*; 3, *a moderate problem*; and 4, *a severe problem*). A total score was calculated by adding all items with a score greater than 1. High test-retest reliability has been reported for 7- to 10-day ($r = 0.90$) and 6-month ($r = 0.87$) intervals.[30]

Symptoms of depression were assessed using the Beck Depression Inventory–Second Edition (BDI-II),[31] a 21-item self-report questionnaire with each item rated on a scale from zero to 3. We used the total score, the sum of all 21 items, giving a range from zero to 63. It should be noted that many symptoms on this questionnaire overlap with postconcussion symptom measured by the RPSQ. Statistically there is some collinearity between these measures (ie, the Pearson correlation between them was $r = 0.61$) and clinically it is often not possible to differentiate depression from persistent postconcussion symptoms. The BDI-II has high internal consistency (coefficient $\alpha > .90$ in different samples) and correlates with self-report measures with conceptually related constructs such as hopelessness ($r = 0.68$), as well as interviewer-rated depression symptoms ($r = 0.71$, with the Hamilton Rating Scale for Depression).[32]

The EuroQol Five Dimension (EQ-5D) Visual Analog Scale (VAS) was used to evaluate general health-related quality of life. EQ-5D is a standardized measure of health outcome, and the EQ-5D is a trademark of the EuroQol Group.[33] The EQ-5D VAS is a visual scale that respondents use to rate their health "today" on a vertical scale calibrated from 0 (worst imaginable health state) to 100 (best imaginable health state).

The Alcohol Use Disorders Identification Test (AUDIT) was used to detect alcohol problems.[34] The AUDIT is a widely used brief screening test to identify persons with risky drinking, harmful drinking, or alcohol dependence. The AUDIT is a 10-item self-report measure, each of which has a set of responses to choose from, and each response has a score ranging from 0 to 4 (questions 1–8). Questions 9 and 10 are scored 0, 2, or 4 only. Item scores are added to create a total score, with more than 8 considered indicative of harmful or hazardous drinking. The AUDIT has a high test-retest reliability ($r = 0.86$)[35] and is highly correlated with the MAST ($r = 0.88$)[36] and CAGE ($r = 0.78$).[37]

Neurocognitive tests

General verbal intelligence was assessed with the Wechsler Adult Intelligence Scale–Third Edition information subtest.[38] Learning and memory was assessed with a list-learning task, the Rey Auditory Verbal Learning Test. Total score (total number of words recalled in trials 1 through 5) and delayed recall (number of words recalled after 30 minutes delay) were used in the analysis.[39] Attention and executive functioning were assessed with the Stroop Color Word Test (color-word interference score, Golden version),[39] Trail Making Test A and B (time needed to finish the task),[40] and 2 verbal fluency tasks: animal naming (total number of words in 1 minute) and single letter–based word generation (total number of words produced across the 3 trials).[41] In general, raw scores for the neurocognitive tests were analyzed. For some analyses, raw scores were converted to z scores[42] to create a common metric, and then a mean z score was calculated to reflect a global measure of cognitive functioning. A small number of people did not complete some of the tests: AUDIT = 1, EQ-5D = 2, and Trail Making Test = 2.

RESULTS

The vast majority of this cohort returned to work within 2 months. Their cumulative postinjury RTW rates were as follows: 1 week = 46.8%, 2 weeks = 59.6%, 3 weeks = 67.0%, 4 weeks = 70.6%, 2 months = 91.7%, and 1 year = 97.2% (see the Figure). Of the total sample, 11.9% ($N = 13$) had no time off work after injury (see the Figure).

Standard regression analyses

Two standard regression analyses were undertaken to determine if the number of days required to RTW could be predicted by 17 variables classified into 2 categories: (i) 11 demographic and injury severity factors and (ii) 6 clinical outcome factors. The demographic and injury severity factors were as follows: (*a*) age (in years), (*b*) education (in years), (*c*) gender, (*d*) previous TBI (present/absent), (*e*) preinjury psychiatric history (present/absent), (*f*) preinjury medical condition (present/absent), (*g*) duration of LOC (in minutes), (*h*) duration of PTA (in minutes), (*i*) multiple bodily injuries (present/absent), (*j*) intracranial abnormality on day-of-injury CT (present/absent), and (*k*) mechanism of injury (MVA/non-MVA). The clinical outcome factors were as follows: (*a*) depression (BDI-II total score), (*b*) fatigue ratings (BNI-FS total score), (*c*) global health rating (EQ-VAS total score), (*d*) postconcussion symptoms (RPSQ total score), (*e*) problematic alcohol use (AUDIT total score), and (*f*) cognitive functioning (mean normative *z* score of 6 individual cognitive measures). First, the 11 demographic and injury severity factors were entered into the regression analysis together. The majority of variables were not significant predictors of the number of days to RTW and were excluded from the final model. Three variables, however, were significant predictors, including age ($P = .008$), multiple bodily injuries ($P < .001$), and intracranial abnormality on day-of-injury CT ($P = .003$) and were retained in the final model ($P < .001$). Together, these 3 variables accounted for 29.7% of the variance in the prediction of the number of days to RTW.

Second, the 6 clinical outcome factors were entered into the regression analysis. The majority of variables were not significant predictors of the number of days to RTW and were excluded from the final model. Only fatigue rating was a significant predictor and was retained in the final model ($P < .001$), accounting for 15.1% of the variance in the prediction of the number of days to RTW.

Logistic regression analyses

To determine whether these variables can predict binary groups defined by the number of days taken to RTW, a series of logistic regression analyses were undertaken. The sample was divided into binary groups based on whether or not they returned to work within 7 days (51 RTW, 58 not-RTW), 14 days (65 RTW, 44 not-RTW), 21 days (73 RTW, 36 not-RTW), and 30 days (82 RTW, 27 not-RTW). The 1-week and 1-month time periods are important to consider because they are commonly used in the literature, and the 1-month mark corresponds with the ICD-10 (*International*

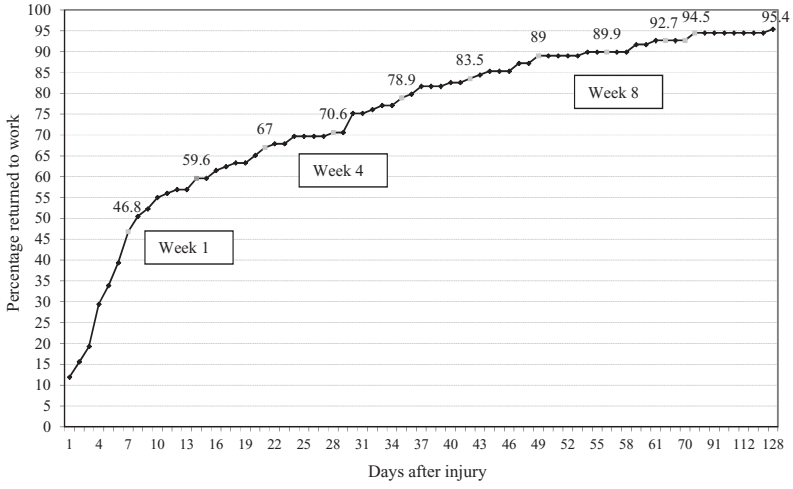

Figure. Return to work rates. Cumulative percentage distribution of return to work rates. The numbers above the line represent the cumulative percentages that returned to work each week (ie, weeks 1-11; week 11 = 94.5%).

Classification of Diseases, Tenth Revision) time period criteria for postconcussional syndrome. Having ongoing functional impairment at 1 month following injury (ie, not returning to work) justifies fairly aggressive clinical intervention. The 2- and 3-week time periods were included for exploratory purposes. A series of 4 binary logistic regression analyses were undertaken to determine whether age, multiple bodily injuries, intracranial abnormality on day-of-injury CT (see Table 1), and fatigue ratings (see Table 2) could predict RTW at each one of these time periods.

For the logistic regression analyses, age, multiple bodily injuries, intracranial abnormality on day-of-injury CT, and fatigue ratings were significant predictors of RTW at 7, 14, 21, and 30 days postinjury (all $P < .001$). The largest amount of variance accounted for by these variables in the prediction of RTW was between individuals who returned to work in fewer than 30 days and individuals who returned to work after that time. The highest successful classification rate for RTW versus non-RTW was observed at 30 days postinjury; that is, when participants were divided into those who returned to work within 30 days versus those who returned in 30 days or more. At 21 days and at 30 days, the rate of false positives (ie, 100 minus "RTW" % Correct) is quite low (9.6% and 8.5%, respectively), but the rate of false negatives (ie, 100 minus "Did Not RTW" % Correct) is rather high (41.7%, 40.7%). This shows that age, multiple bodily injuries, intracranial abnormality, and fatigue ratings are highly accurate at these points in time for predicting successful RTW but not for predicting failure to RTW. As such, these variables were useful in identifying individuals who had successful RTW but not those at risk for slow RTW.

Exploratory group comparisons

The sample was divided into 2 groups using a cutoff score of 30 days to RTW: (*a*) RTW-rapid ($n = 82$, 75.2%), and (*b*) RTW-delayed ($n = 27$, 24.8%). As previously noted, the 1-month time period corresponds with the *ICD-10* duration criteria for postconcussional syndrome. A larger proportion of individuals in the RTW-delayed group (59.3%) had experienced multiple bodily injuries compared with the RTW-rapid group (20.7%; $P < .001$). There was a trend for a larger proportion of individuals in the RTW-delayed group to have 1 or more trauma-related abnormalities on head CT (22.2% vs 4.9%; $P < .014$) and MRI (25.9% vs 8.5%; $P < .019$) compared with the RTW-rapid group, though these differences were not statistically significant after adjusting for multiple comparisons and because of small sample sizes.

The groups did not differ on any neuropsychological test measure (all $P > .05$). Those who returned to work later on average reported significantly greater fatigue on the BNI-FS ($P < .001$, Cohen d = 0.98) and worse general health on EQ-5D VAS ($P < .001$, Cohen d = 0.83). However, after excluding patients with multiple injuries ($n = 33$, 30.3%), the groups did not differ in terms of fatigue (BNI total score, $P = .092$) or general health ratings (EQ-5D VAS, $P = .324$). There were no significant differences between the 2 groups for self-reported depression (BDI-II) or postconcussion symptoms (RPSQ).

DISCUSSION

Return to work is one important marker of functional recovery following mTBI. Using a prospective inception

TABLE 1 *Logistic regression classification results and summary for age, multiple bodily injuries, and intracranial abnormality on day-of-injury CT*

	P	Cox and snell R^2	Nagelkerke R^2	Actual group status	Predicted group status		% Correct
					RTW	Not RTW	
RTW <7 d	<.001	0.252	0.337	RTW	41	10	80.4
				Did not RTW	22	36	62.1
				Overall	. . .	. . .	70.6
RTW <14 d	<.001	0.248	0.335	RTW	56	9	86.2
				Did not RTW	15	29	65.9
				Overall	. . .	. . .	78.0
RTW <21 d	<.001	0.211	0.293	RTW	63	10	86.3
				Did not RTW	16	20	55.6
				Overall	. . .	. . .	76.1
RTW <30 d	<.001	0.243	0.361	RTW	74	8	90.2
				Did not RTW	15	12	44.4
				Overall	. . .	. . .	78.9

TABLE 2 *Logistic regression classification results and summary for fatigue ratings*

	P	Cox and snell R^2	Nagelkerke R^2	Actual group status	Predicted group status: RTW	Predicted group status: Not RTW	% Correct
RTW <7 d	<.001	0.134	0.178	RTW	34	17	66.7
				Did not RTW	24	34	58.6
				Overall	. . .	. . .	62.4
RTW <14 d	.003	0.076	0.103	RTW	57	8	87.7
				Did not RTW	29	15	34.1
				Overall	. . .	. . .	66.1
RTW <21 d	.001	0.101	0.140	RTW	68	5	93.2
				Did not RTW	25	11	30.6
				Overall	. . .	. . .	72.5
RTW <30 d	<.001	0.133	0.197	RTW	77	5	93.9
				Did not RTW	20	7	25.9
				Overall	. . .	. . .	77.1

cohort design, we examined RTW rates and risk factors of slow RTW in a Finnish sample identified in the ED of a level 1 trauma center. At 1-week postinjury, 47% had returned to work, a proportion comparable to those in studies by Powell et al[21] and Haboubi et al[22] but considerably lower than in other studies.[19,20]

At 1-month postinjury, 71% of the sample had returned to work. The 1-month RTW rates vary widely in the literature. In a US sample recruited from a trauma center ($N = 213$), only 25% had returned to work at this time point.[23] In a Dutch sample recruited from a trauma center ($N = 43$), 39% had returned to work at 1 month. In contrast, in the aforementioned Greek[19] and New Zealand[20] studies, the 1-month RTW rates following mTBI were 99%. The role of cultural factors was not examined in this study. Past researchers, however, have reported that people who have expectations that their symptoms will resolve quickly actually have shorter recovery times,[43,44] and these expectations are stronger in certain countries, where lower rates of persistent disability after mTBI have been reported.[45,46] There are also differing injury compensation systems between countries. Personal injury litigation is uncommon in Finland, and there is a social safety net for sick and injured adults in that they receive government compensation for time off work due to illness or injury. A careful examination of methodological differences and possible cultural differences in RTW rates across the mTBI literature would be a good topic for a future systematic review.

Numerous variables were examined to determine whether they were associated with slow RTW. We found that RTW during the first 4 weeks following mTBI in a Finnish sample was strongly predicted by a combination of age, multiple bodily injuries, intracranial abnormality on day-of-injury CT, and fatigue ratings. Classic injury severity variables (ie, duration of unconsciousness, GCS scores, and duration of PTA) were not associated with length of time to RTW. Similar findings were reported by Nolin and Heroux.[17] In this study, neurocognitive functioning, measured at approximately 3 to 4 weeks postinjury, was not related to time off work. Self-reported postconcussion symptoms and symptoms of depression, measured at 3 to 4 weeks postinjury, were very modestly (not significantly) related to RTW status. In contrast, self-reported fatigue and perceived overall health status (EQ-5D VAS) were strongly related to the duration of time off work. For example, there were statistically large effect size differences associated with these variables when comparing those who returned to work in the first month versus those who did not. In this study, persons with complicated mTBIs (ie, those with trauma-related intracranial abnormalities on neuroimaging) took longer to RTW. This is consistent with some previous studies that have reported that those with complicated mTBIs are at increased risk for slow or incomplete recovery.[7] Another possible reason why intracranial lesions were predictors of longer RTW may be that physicians are likely to grant longer sick leaves when there is objective evidence of brain injury. This issue was not examined in the study, however.

The presence of multiple bodily injuries was strongly associated with duration of time off work. Obviously, recovery time from physical injuries can influence time off work. What is less obvious, however, is the role of mental health factors associated with polytrauma—and their relation to duration of time off work. Multiple studies have reported fairly high rates of traumatic stress and depression following polytrauma,[47–50] mental health problems that certainly could contribute to slower RTW rates. In this study, however, those with bodily injuries did not report more postconcussion symptoms or symptoms of

depression. Therefore, in this study, there was not a clear interaction among bodily injuries, mental health problems, and duration of time off work.

There are some limitations to this study that warrant attention. First, bodily injuries were not described in detail and their functional consequences were not assessed with standardized measures. It can be hypothesized that the participants who had multiple bodily injuries had longer sick leaves not because of mTBI itself but only because of additional injuries (eg, orthopedic injuries). In these combined cases, it is impossible to differentiate the sole effect of mTBI. After excluding patients with multiple bodily injuries, the group with prolonged (>30 days) RTW did not differ from the group with RTW within 30 days in terms of fatigue or in general health. This finding provides support for the idea that the self-reported problems with fatigue and general health were associated with bodily injuries. On the basis of these findings, it can be argued that the only mTBI-specific finding that was associated with greater duration of time off work in this study was trauma-related intracranial findings. Second, our information regarding RTW was limited. The evaluation of successful/unsuccessful RTW can vary on the basis of a complex interaction of many factors when comparing preinjury to postinjury employment. These factors include but are not limited to (*a*) the number of hours worked, (*b*) return to same/different job, (*c*) level of duties and responsibilities, (*d*) level of physical and mental demands, and (*e*) work efficiency. Information regarding these factors was not available. As such, we were unable to differentiate between those individuals who returned to work in the same capacity versus those who returned in a reduced capacity. Future research in this area is encouraged to assess these factors and to report RTW rates on a continuum of success rather than in a dichotomous manner (eg, Good RTW-Full capacity, Good RTW-Reduced capacity, RTW-Significant difficulties, and did not RTW).

Previously, it was noted that most patients returned to work after injury despite having symptoms.[2] In the current study, the majority (70%) of the study population had returned to work by the time of the neuropsychological assessment. Thus, the results of self-reported symptoms obtained in the neuropsychological assessment can be considered to reflect the situation after returning to work, supporting the idea that it is common to RTW while still symptomatic.

The vast majority of this cohort returned to work within 2 months. Predictors of delayed RTW were sustaining a complicated mTBI, having multiple bodily injuries, increased age, and fatigue. Patients who took longer to RTW did not perform more poorly on neurocognitive measures or report more depressive symptoms.

Mild TBI is associated with a favorable functional outcome in most people, but some are slow to RTW and suffer from persistent symptoms. Identifying early risk factors for slow functional recovery has important implications for individual patients, employers, and the healthcare system. With the tremendous international investment in research relating to mTBI over the past 5 years, hopefully we will see results from multiple prospective studies that can be combined to inform clinical decision making and practice. Through systematic reviews and meta-analyses, future researchers might help translate this diverse literature into more specific models for predicting rapid, "normal," and slow functional recovery in individuals following mTBI.

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Biopsychosocial Outcome after Uncomplicated Mild Traumatic Brain Injury

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Abstract

The purpose of this study was to examine the biopsychosocial outcome from uncomplicated mild traumatic brain injury (MTBI) within the first 3 weeks post injury. Participants were 48 prospectively enrolled patients from the Emergency Department of Tampere University Hospital, Finland, who sustained an uncomplicated MTBI. At 3 weeks post injury, diffusion tensor imaging (DTI) of the whole brain was undertaken using a Siemens 3T scanner. Measures of fractional anisotropy (FA) were calculated for 16 regions of interest (ROIs) and measures of apparent diffusion coefficient (ADC) were calculated for 10 ROIs. Twenty-four healthy control participants also completed DTI of the whole brain for comparison. Participants were administered a brief battery of self-report (e.g., postconcussion symptoms, depression, and fatigue) and neurocognitive measures (e.g., verbal learning and memory). There were no significant differences between the uncomplicated MTBI and healthy control group on any measures of learning and memory. Compared to the control group, the uncomplicated MTBI group reported a greater number of postconcussion symptoms and fatigue, but not depression. When considering all DTI ROIs simultaneously, the MTBI group had a significantly larger number of low DTI measures (FA values) compared to the healthy controls. MTBI patients with multifocal white matter changes did not show evidence of worse symptoms, cognitive impairment, or slower return to work compared to MTBI patients with broadly normal white matter.

Key words: cognition; diffusion tensor imaging; mild traumatic brain injury; postconcussion syndrome

Introduction

Mild traumatic brain injury (MTBI) is associated with a favorable functional outcome in most people, but some are slow to return to work and suffer from persistent symptoms. It is now well established that a minority of people who sustain MTBIs report symptoms long after the original injury. This has been reported in cohorts of patients from the 1970s,[1] 1980s,[2] 1990s,[3] and this century.[4,5] It has been reported in children,[6] adults,[7,8] older adults,[9] and veterans.[10] This minority is present across cultures from North America,[7,8] Western Europe,[3] Scandinavia,[4] Eastern Europe,[11] Asia,[12] and Australia.[5] However, the symptoms that are attributed to MTBI are nonspecific, and frequently occur in patients with depression,[13,14] chronic pain,[15–17] and post-traumatic stress disorder.[18] These nonspecific symptoms are common in healthy adults.[19]

It is overly simplistic and inaccurate to assume that symptoms reported long after an MTBI are caused mostly or entirely by mild damage to the brain. In the first week following injury, patients with orthopedic injuries report postconcussion-like symptoms at a rate similar to those with MTBIs.[5,20] Acute psychological distress in the first 2 weeks following injury is associated with postconcussion-like symptom reporting at 1–3 months post injury.[5,21,22] Moreover, diverse psychosocial factors are associated with greater symptom reporting, such as expectations and misattribution,[23–26] retrospective recall biases,[24,25,27–29] and involvement in litigation.[30] Even the method by which data are collected (i.e., interview vs.

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questionnaire) can influence rates of symptom reporting.[31] Therefore, a binary polarized view of the cause of poor outcome, be it pathophysiogenesis or psychogenesis,[32] is simplistic and inconsistent with the body of diverse accumulated evidence over the past 30 years. A multi-factorial, interwoven, biopsychosocial model is necessary for conceptualizing both good and poor outcome following MTBI.[33,34]

Without question, psychosocial factors influence outcome from MTBI. It is also reasonable to assume that damage to the brain influences outcome. MTBI is associated with cognitive deficits in the initial days and sometimes weeks following injury, but due to natural recovery these deficits typically are not seen after 1–3 months in group studies.[35–41] Those who experience complicated MTBIs (i.e., have a visible abnormality on computed tomography or magnetic resonance imaging) have greater acute cognitive deficits[42–45] and they are at increased risk for slower return to work.[46] Interestingly, however, some researchers have reported that those with complicated MTBIs do not report more symptoms than those with uncomplicated MTBIs.[47–50] In fact, in some studies, those with complicated MTBIs are less likely to meet criteria for the postconcussion syndrome than those with uncomplicated MTBIs.[51]

Conventional neuroimaging [i.e., computed tomography (CT) and magnetic resonance imaging (MRI)] has obvious limitations for understanding possible neurobiological underpinnings of poor outcome from MTBI. In the past few years, there has been tremendous interest in using diffusion tensor imaging (DTI) to investigate changes in white matter following an MTBI.[52–54] DTI is sensitive to subtle microstructural changes in the brain that cannot be detected by conventional structural MRI (e.g., FLAIR, T1, T2). Studies that have examined microstructural white matter integrity using DTI following MTBI have found differences in multiple brain regions relative to controls. Regions of the brain most commonly affected include the corpus callosum, internal and external capsule, and centrum semiovale.[55–60] Some differences have also been reported in the frontal association pathways (anterior corona radiata, uncinate fasciculus, and superior longitudinal fasciculus, forceps minor) and commissural fibers of the corpus callosum.[53] Some studies, however, have not shown differences between MTBI patients and trauma controls using DTI at 4 weeks[61] and 6–8 weeks following injury.[62] In a recent meta-analysis of the MTBI literature, the corpus callosum was identified as the structure that is most likely to show DTI changes.[63]

Some of the inconsistencies in DTI research findings are likely due to current MRI technology constraints, timeframe of scanning, sample characteristics, and study inclusion criteria.[61] As a general rule, it is widely accepted that FA values decrease and ADC values increase after moderate-to-severe TBI, and in the post-acute stage of recovery following MTBI.[53] Some studies, however, have reported increased FA values and decreased diffusivity [i.e., ADC or mean diffusivity (MD) or radial diffusivity (RD)] within 72 hours,[56] 6 days,[60,64] and 21 days following MTBI.[65] It has been suggested that elevated or reduced FA values likely reflect different types of white matter abnormalities. Further, it has been suggested that increased FA and decreased diffusivity values are evident only in the very acute phase after the injury,[60] and these initial findings (increased FA, decreased diffusivity) might be due to inflammatory changes during the acute recovery phase (i.e., cytotoxic edema/axonal swelling) rather than classic shear-strain lesions.[56,57] This issue is far from resolved, however, because recent studies have suggested that FA values might be increased and MD values decreased in chronic stage after MTBI;[64,66,67] these findings are inconsistent with cytotoxic edema theory.[66] The implications of high FA values are not understood. It has been suggested that elevated FA values post-injury might reflect compensatory neuroplastic responses to injury, rather than a direct manifestation of injury pathology.[66,68] In all, abnormalities detected by DTI appear to be dynamically related to the time post injury[68] and the pattern, extent, and magnitude of these abnormalities might show considerable individual differences.[66]

It has been suggested that compromised microstructural white matter might be associated with impaired cognition and increased postconcussion symptom reporting following MTBI.[56,67,69–71] Many studies involving DTI, however, have not examined functional outcome. The association between DTI findings and functional outcome in 50 studies of patients with MTBIs is summarized in Table 1. Two systematic reviews published in 2012 served as the foundation for the information presented in Table 1.[52,72] Most of the past studies are based on small unrepresentative samples of patients, making generalizability of the findings difficult. However, 88% of the studies (44/50) reported significant differences between those with MTBIs and control subjects on DTI. Some studies examined the relation between DTI and cognitive functioning (31 studies; 62%), symptom reporting (9 studies; 18%), mental health (7 studies; 14%), or return to work (1 study; 2%). Of the studies that assessed clinical outcome, 87.1% (27/31) reported that DTI findings were related to reduced cognitive functioning, and 66.7% (6/9) reported that DTI findings were related to greater symptom reporting. It was uncommon for researchers to address mental health outcomes, and only one study addressed return to work.

The present study was designed to address significant gaps in the literature relating DTI and functional outcome following MTBI. The study is large, carefully controlled, and prospective. There were six primary hypotheses. First, patients with MTBIs will report more postconcussion symptoms than healthy controls. Second, there will be no differences between patients who have sustained an MTBI and healthy controls on neuropsychological testing. Third, patients who have sustained uncomplicated MTBIs will have reduced white matter integrity in a greater number of regions of interest compared to healthy controls. Fourth, consistent with the results of the recent meta-analysis,[63] reduced white matter integrity will be present in the corpus callosum. Fifth, MTBI patients identified as having abnormal white matter on DTI will show deficits on cognitive testing and will take longer to return to work than patients who do not show evidence of abnormal white matter. Finally, MTBI patients identified as having abnormal white matter on DTI will report more postconcussion symptoms than patients who do not show evidence of abnormal white matter.

Methods

Participants

Participants were 48 patients (Age: M = 36.4 years, SD = 12.4; Education: M = 12.7 years, SD = 2.5, female 60.4%) who were admitted to Tampere University Hospital Emergency Department (ED) between September 2007 and May 2009 after an MTBI. Participants were included if they had sustained an uncomplicated MTBI (no evidence of acute intracranial abnormalities on day-of-injury CT scan or post-acute 3T MRI scan). Classification of MTBI was defined according to the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine[73] and the World Health Organization (WHO) Collaborating Center Task Force on Mild Traumatic Brain Injury (page 115).[74]

Inclusion criteria was as follows: (a) biomechanical force applied to the head, (b) loss of consciousness, if present, for less than

Table 1. Association Between DTI Findings and Outcome Following MTBI

First author	Year	Country	Civilian, Sports, Military	MTBI N	CTRL N	MRI	DTI method	Time following injury	Significant DTI findings	DTI findings related to outcome			
										Return to work, school, or sports	Cognitive functioning	PCS symptoms	Mental health
Arfanakis[55]	2002	USA	Civilian	5	10	1.5 T	ROI	≤24h	Yes	N/R	N/R	N/R	N/R
Inglese[58]	2005			46	29	1.5T	ROI, WBHA	4 days ($n=20$), 5.7 years ($n=26$)	Yes	N/R	N/R	N/R	N/R
Salmond[97]	2006	UK	Civilian	16	16	3 T	VBA	≥6 months	Yes	N/R	Yes	N/R	N/R
Bazarian[56]	2007	USA	Civilian	6	6	3 T	WBA	≤72 hours	Yes	N/R	Yes	Yes	Yes
Benson[125]	2007	USA	Civilian	20 (6 mild, 14 moderate-sever)	14	1.5 T	Whole brain histogram	Mean 35.3 months (range: 3 days–15 years)	Yes	N/R	N/R	N/R	N/R
Kraus[59]	2007	USA	Civilian	37 (20 mild,17 moderate-severe)	18	3 T	ROI	≥6 months	Yes	N/R	Yes	N/R	N/R
Lipton[98]	2008	USA	Civilian	17	10	1.5 T	WBHA, Voxelwise analysis	8 months to 3 years	Yes	N/R	Yes	N/R	N/R
Miles[99]	2008	USA	Civilian	17	29	1.5 T	ROI	Mean 4.0 days (range: 1–10 days)	Yes	N/R	Yes	N/R	N/R
Niogi[100]	2008a	USA	Civilian	43	23	3 T	ROI	Mean 16.9 months (range: 1–53 months)	Yes	N/R	Yes	N/R	N/R
Niogi[100]	2008b	USA	Civilian	34	26	3 T	ROI	≥1 month post injury (range: 1–65 months)	Yes	N/R	Yes	N/R	N/R
Rutgers[101]	2008a	France	Civilian	21	11	1.5 T	ROI, Tractography	Mean 5.5 months (range: 0.1–109.3 months)	Yes	N/R	N/R	N/R	N/R
Rutgers[101]	2008b	France	Civilian	39 (24 mild, 9 moderate, 6 severe)	10	1.5 T	ROI	Mean 2.8. months	Yes	N/R	N/R	N/R	N/R
Wilde[60]	2008	USA	Civilian	10	10	3 T	Tractography	Mean 2.7 days (range: 1–6 days)	Yes	N/R	N/R	Yes	N/R
Huang[127]	2009	USA	Civilian, Sport, MIlitary	10	14	1.5 T	TBSS, Probabilistic tractocraphy	Mean 11.6 months (range: 1–46 months	Yes	N/R	N/R	N/R	N/R
Kumar[102]	2009	India	Civilian	83 (26 mild, 57 moderate)	33	1.5 T	ROI	Mean 8.9 days (range: 5–14 months)	Yes	N/R	Yes	N/R	N/R
Lipton[101]	2009	USA	Civilian	20	20	3 T	Voxelwise analysis	≤2 weeks	Yes	N/R	Yes	N/R	N/R
Lo[67]	2009	USA	Civilian	10	10	1.5 T	ROI	≥2 years (range:1.2–9.3 years)	Yes	N/R	Yes	N/R	N/R
Geary[103]	2010	USA	Civilian	40	35	3 T	ROI	≥6 months	Yes	N/R	Yes	N/R	N/R

Table 1. (Continued)

First author	Year	Country	Civilian, Sports, Military	MTBI N	CTRL N	MRI	DTI method	Time following injury	Significant DTI findings	DTI findings related to outcome			
										Return to work, school, or sports	Cognitive functioning	PCS symptoms	Mental health
Holli (b)[104]	2010	Finland	Civilian	42	10	1.5 T	Texture analysis, ROI	≤3 weeks	Yes	N/R	Yes	N/R	N/R
Hartikainen[113]	2010	Finland	Civilian	18 (13 mild, 5 moderate)	0	1.5 T	ROI	≤3 weeks	Yes	N/R	Yes	Yes	N/R
Levin[114]	2010	USA	Military	37 (28 mild, 9 moderate)	15	3 T	VBA, ROI, Quantitative tractography	Mean 2.4 years (SD 343.1 days)	No	N/R	Yes	No	N/R
Little[105]	2010	USA	Civilian	24 (12 mild, 12 moderate-severe)	12	3T	ROI	Mean 55.5 months (range: 12–149 months)	Yes	N/R	Yes	N/R	N/R
Maruta[106]	2010	USA	Civilian	17	9	3 T	ROI	Mean 2.7 years (range: 1.4 months–5.4 years)	Yes	N/R	Yes	N/R	N/R
Mayer[65]	2010	USA	Civilian	22	21	3 T	ROI	≤21 days post injury (3 to 5month follow-up, $n=10$ mTBIs, 15 controls)	Yes	N/R	Yes	N/R	N/R
Warner[107]	2010	USA	Civilian	24	0	3 T	Tractography (FreeSurfer), automated segmentation and volumetric analysis	≤1 week (range: 1–9 days), follow-up MRI at 8 months (range: 6–14 months)	Yes	N/R	Yes	N/R	N/R
Zhang[61]	2010	USA	Sports	15	15	3 T	ROI	Mean 30 days ± 2 days	No	N/R	No	N/R	N/R
Cubon[108]	2011	USA	Sports	15 (10 concussion, 2 moderate, 3 severe)	10	3 T	TBSS, whole brain WM skeleton	≥1 month (mean 115 days, SD 104 days), ≥1 year for subjects with moderate and severe TBI	Yes	N/R	No	N/R	N/R
Henry[64]	2011	Canada	Sports	18	10	3 T	VBA	1–6 days, follow-up 6 months (patients) or 18 months (controls)	Yes	N/R	N/R	N/R	N/R
Lange[13]	2011	Canada	Civilian	60	34	3 T	ROI	Mean 47 days, (SD = 6.3, range = 31–66)	No	N/R	N/R	No	N/R
MacDonald[130]	2011	USA	Military	63	21	1.5 T	ROI	≤90 days	Yes	N/R	N/R	N/R	N/R
Matthews[131]	2011	USA	Military	22	0	3 T	VBA	Self-reported history of concussions	Yes	N/R	N/R	N/R	Yes

(*continued*)

TABLE 1. (CONTINUED)

First author	Year	Country	Civilian, Sports, Military	MTBI N	CTRL N	MRI	DTI method	Time following injury	Significant DTI findings	DTI findings related to outcome: Return to work, school, or sports	Cognitive functioning	PCS symptoms	Mental health
Matsushita[110]	2011	Japan	Civilian	20 (9 mild, 11 moderate)	27	1.5 T	ROI	Median 3.5 days (range: 0–20 days)	Yes	N/R	Yes	N/R	N/R
Messe[115]	2011	France	Civilian	23	23	1.5 T	VBA, TBSS	7–28 days, follow-up 3–4 months	Yes	N/R	Yes	Yes	Yes
Smits[112]	2011	Netherlands	Civilian	19	12	3 T	TBSS	30.6 days	Yes	N/R	N/R	Yes	N/R
Sponheim[111]	2011	USA	Military	9	8	1.5 T	ROI	32.7 months (SD 9.26 months)	No	N/R	No	N/R	N/R
Bazarian[114]	2012	USA	Sports	9	8	3 T	WBA	≤72 hours	Yes	N/R	Yes	Yes	N/R
Davenport[126]	2012	USA	Military	25	33	3 T	Standard probabilistic tractography-based ROIs	2–5 years	Yes	N/R	N/R	N/R	N/R
Grossman[109]	2012	USA	Civilian	22	14	3 T	ROI	Group 1 ($n=7$) ≤1 year, (mean 0.18 years) Group 2 ($n=15$) ≥1 year, (mean 3.9 years)	Yes	N/R	Yes	N/R	N/R
Jorge[128]	2012	USA	Military	72	35: 21 veteransand 14 civilians	3 T	VBA, pothole analysis	Mean 49.9 months (SD 19.7)	No in VBA, Yes in pothole analysis	N/R	Yes	N/R	No
Lipton[66]	2012	USA	Civilian	34	30	3 T	VBA	3 serial assessments: 2 weeks, 3 and 6 months	Yes	N/R	N/R	N/R	N/R
McAllister[129]	2012	USA	Sports	10	0	3 T	FreeSurfer segmentation, strain and strain rate calculations	Preseason and ≤10 days of concussion	Yes	N/R	N/R	N/R	N/R
Matthews[132]	2012	USA	Military	46	0	3 T	TBSS	Mean 3.6 years (SD 1.5)	Yes	N/R	N/R	N/R	No
Maugans[123]	2012	USA	Sports	9	12	3 T	ROI	≤72 hours and 14 days and ≥30 days	No	N/R	N/R	N/R	N/R
Toth[68]	2013	Hungary	Civilian	14	14	3 T	TBSS and volumetric analysis	2 serial assessments: 72 h and 1 month	Yes	N/R	N/R	N/R	N/R
Wilde[136]	2012	USA	Civilian	8	0	3 T	ROI	4 serial assessments within 8 days postinjury (0–192 h)	Yes	N/R	Yes	N/R	N/R

(*continued*)

Table 1. (Continued)

First author	Year	Country	Civilian, Sports, Military	MTBI N	CTRL N	MRI	DTI method	Time following injury	Significant DTI findings	DTI findings related to outcome: Return to work, school, or sports	Cognitive functioning	PCS symptoms	Mental health
Virji-Babul	2013	Canada	Sports	12	10	3 T	WBA	≤2 months (range: 18–61 days)	Yes	N/R	N/R	N/R	N/R
Arenth	2013	USA	Civilian	12 (5 mild, 7 moderate-severe)	12	3 T	VBA (only CC)	1.7 years	Yes	N/R	Yes	N/R	N/R
Spitz	2013	Australia	Civilian	68 (10 mild, 14 moderate, 44 severe)	25	3 T	TBSS and ROI tractogaphy	Mean 18 months (SD 14.01)	No for MTBI, Yes for moderate-severe TBI	N/R	Yes	N/R	N/R
Sorg	2013	USA	Military	30	15	3 T	TBSS	2–4 years	Yes	N/R	Yes	N/R	No
Waljas	2013	Finland	Civilian	48	30	3 T	ROI	Mean 27.4 days (SD 8.9 days)	Yes	No	No	No	No
									Yes = 44 No = 6	Yes = 0 No = 1 N/R = 49	Yes = 27 No = 4 N/R = 19	Yes = 6 No = 3 N/R = 41	Yes = 3 No = 4 N/R = 43

*Reported in Table 3 of Shenton et al.;[52] ^Reported in Table 2–7 of Gardner et al.[72]

CC, corpus callosum; CTRL, control; MRI, magnetic resonance imaging; mTBI, mild traumatic brain injury; N/R, Not reported; TBI, traumatic brain injury; TBSS, Tract Based Spatial Statistics; VBA, voxel based approach; WBA, whole brain analysis; WBHA, whole brain histogram analysis; WM, white matter.

References: Arenth[124]; Arfanakis [55]; Bazarian[56]; Bazarian[116]; Benson[125]; Cubon[108]; Davenport[126]; Geary [103]; Grossman[109]; Henry[64]; Hartikainen[113]; Holli[104]; Huang [127]; Inglese[58]; Jorge[128]; Kraus[59]; Kumar[102]; Lange [62]; Levin[114]; Lipton [98]; Lipton[70]; Lipton[66]; Little[105]; Lo [67]; Maruta[106]; Matsushita[110]; Maugans[123]; Mayer[65]; McAllister[129]; Mac Donald[130]; Matthews[131]; Matthews[132]; Messé[115]; Miles[99]; Niogi[71]; Niogi[100]; Rutgers[101]; Rutgers[122]; Salmond[97]; Smits[112]; Sorg[133]; Spitz[134]; Sponheim[111]; Toth[68]; Warner[107]; Virji-Babul[135]; Waljas, 2013 (current study); Wilde[60]; Wilde[136]; Zhang.[61]

30 min, (c) Glasgow Coma Scale score between 13 and 15 after 30 min following injury, and (d) post-traumatic amnesia, if present, of less than 24 h. Exclusion criteria was as follows: (a) MRI performed under 2 weeks (13 days) or over 2 months (60 days), (b) age under 16 or over 65, (c) previous symptomatic brain injury, (d) history of psychiatric disorder, and (e) history of major substance abuse or other medical condition (frequently) associated with cognitive changes, and major incidental (not trauma related) neuroradiological findings (such as tumor, cysts, demyelinating disease, enlargement of cortical sulci, ventricular enlargement, ischemic lesions, multiple subcortical signal changes). Minor incidental findings, such as isolated white matter hyperintensities, were not considered as abnormal and were retained in the sample. A substantial minority ($n = 15$; 31.3%) had what appeared to be incidental white matter hyperintensities on MRI (with normal acute CT imaging, and no hemosiderin or other findings on MRI). It is possible, but unknowable, that some of these hyperintensities could have been trauma related. Neuroradiological data were evaluated by an expert radiologist (PD) and all decisions about inclusion and exclusion were based on his professional opinion. None of the patients were involved in litigation.

Two separate healthy control groups were also recruited from the community for the study: (a) neuroimaging control group, and (b) neuropsychological control group. The *neuroimaging control group* initially consisted of 30 age- and gender-matched participants with no history of brain injury, neurological disease, or psychiatric disorders who completed a neuroimaging protocol using MRI. In the control sample, 26.7% (8/30) had incidental MRI findings. Of the 8, 6 participants were excluded due to major incidental findings (e.g., ischemic lesions, numerous white matter hyperintensities, or enlarged lateral ventricles). Twenty-four neuroimaging control subjects were included in the final sample (Age: M = 36.6 years, SD = 10.1, female 66.7%). Of those 24, 2 had incidental white matter hyperintensities (8.3%). The *neuropsychological control group* consisted of 36 age- and gender-matched participants with no previous history of brain injury, neurological disease, or psychiatric disorders (Age: M = 36.9 years, SD = 13.6, female 64%, Education: M = 15.1 years, SD = 2.5) who completed a battery of self-report (e.g., postconcussion symptoms, depression, and fatigue) and neurocognitive measures (e.g., verbal learning and memory).

All participants provided written informed consent according to the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Tampere University Hospital.

Measures and procedure

For the uncomplicated MTBI group, MRI scanning was conducted at 2 weeks to 2 months post-injury for the majority of participants (M = 27.4 days, SD = 8.9 days; IQR = 21–32.5 days, Range = 16–60 days). All MTBI patients completed self-report measures and neurocognitive testing within 35 days post injury (M = 25.5, SD = 3.3, IQR = 24–27 days, Range = 17–34 days). For both control groups, MRI scanning and neuropsychological testing was completed as soon as possible following enrolment in the study.

Neuroimaging. MRI was performed on a 3T Siemens Trio (Siemens AG Medical Solutions, Erlangen, Germany) machine. MRI sequences were evaluated by a certified neuroradiologist. The MRI protocol included sagittal T1-weighted 3D IR prepared gradient echo, axial T2 turbo spin echo, conventional axial and high resolution sagittal fluid-attenuated inversion recovery (FLAIR), axial T2*, and axial susceptibility weighted imaging (SWI) series. White matter hyperintensities (WMHI) were recorded from FLAIR sequences. The parameters for FLAIR sequences were TI 2216 ms, TR 7000 ms, TE 87 ms, FOV 199 × 220 ms, matrix 232 × 256, slice/gap 4.0/1.2 mm. The DTI sequence was single-shot diffusion-weighted echo planar imaging. The parameters for DTI were TR 5144 ms, TE 92 ms, FOV 230 mm, matrix 128 × 128, 3 averages, slice/gap 3.0/0.9 mm, voxel dimension 1.8 × 1.8 × 3.0 mm, b-factor 0 and 1000 s/mm^2, and 20 diffusion gradient orientations. A 12-channel head matrix coil was used.

Region-of-interest (ROI) based DTI measurements were performed in eight different anatomical locations of each hemisphere and in three locations within the corpus callosum. Quantitative DTI parameters, including apparent diffusion coefficient (ADC) and fractional anisotropy (FA), were calculated symmetrically for multiple ROIs in the pyramidal tract (i.e., basal pons, cerebral peduncle, posterior limb of the internal capsule, corona radiata, and centrum semiovale) and frontobasal area (i.e., uncinate fasciculus, forceps minor, and anterior corona radiata). In the corpus callosum, the ROIs included three regions: the genu, body, and splenium. ROIs were selected on the basis of prior studies that have demonstrated abnormalities on DTI parameters in these areas.[55–60]

All diffusion parameter analyses were performed by one observer (a physicist with long experience of brain ROI measurements; UH) on a workstation using commercially available software (Neuro 3D; Siemens Medical Solution, Malvern, USA). Circular ROIs were manually placed on color-coded axial fractional anisotropy (FA) maps and automatically transferred on the nondiffusion-weighted b_0 and ADC maps. The ROIs of the corpus callosum were drawn onto the median-line sagittal images. The size of the ROI was modified to the axial structure of each fiber tract. The circular ROIs were centered in the region taking care to avoid border areas, such as overlapping with cerebrospinal fluid spaces and neighboring tracts. The data quality was excellent in most cases, except in certain regions that had artifacts caused by air cavities and fluid flow. Mean values for FA and ADC for each region were calculated from the mean values of the right and left hemispheres.

A reliability study of this method was undertaken using the control sample ($n = 30$).[75] Each ROI was sampled twice by the same rater to evaluate intrarater reliability. Intraclass correlation coefficients (ICCs) were calculated for all FA and ADC using a two-way random-model analysis with absolute agreement. The ICC values were considered as excellent agreement if greater than 0.8, as substantial agreement if they were from 0.60 to 0.79, and as fair/poor agreement if below 0.6. All ROIs that did not met criteria for substantial agreement for intrarater reliability (> 0.65) were excluded from the analyses, including the cerebral peduncle-ADC (0.19), centrum semiovale-FA (0.48), centrum semiovale-ADC (0.63), forceps minor-ADC (0.64), anterior corona radiata-ADC (0.27), corpus callosum body-FA (0.23), and corpus callosum body-ADC (0.26).

Initially, 19 ROIs were measured and ADC and FA values were calculated symmetrically for each ROI. Based on results from the reliability study, two regions were excluded for FA analysis (centrum semiovale and corpus callosum body). Five regions were excluded for ADC analysis (cerebral peduncle, centrum semiovale, forceps minor, anterior corona radiata, and corpus callosum body). The number of ROIs retained for the analysis was 16 ROIs for FA and 10 ROIs for ADC.

Self-report questionnaires. Self-reported fatigue was examined using the Barrow Neurological Institute Fatigue Scale (BNI-FS) and the Fatigue Impact Scale (FIS). The BNI-FS is an 11-item self-report questionnaire designed to assess fatigue during the early stages of recovery after brain injury.[76] Participants are asked to rate the extent to which each of the 10 primary items has been a problem for them since the injury on a 7-point scale (0–1 = rarely a problem; 2–3 = occasional problem, but not frequent; 4–5 = frequent problem; 6–7 = a problem most of the time). The final item (item 11) asks participants to provide an overall rating of their level of fatigue on a scale from 0 (no problem) to 10 (severe problem). In this study the total BNI-FS score was used, which is the sum of all 10 scores (min = 0, max = 70).

The FIS is a structured 40-item self-report questionnaire that focuses on the ways in which fatigue affects everyday life.[77] There are three separate subscales (10 physical items, 10 cognitive items, and 20 psychosocial items). Participants are asked to rate how much of a problem fatigue has been for them during the past month, including the day of testing on a 5-point Likert scale (0 = no problem, 1 = small problem, 2 = moderate problem, 3 = big problem, and 4 = extreme problem). In this study, the total FIS score was used. The total score is the sum of all 40 items (range: 0–160).

Postconcussion symptoms were assessed with the Rivermead Postconcussion Symptom Questionnaire (RPSQ).[78] The RPSQ is a 16-item self-report questionnaire that measures the presence and severity of common postconcussion symptoms on a 5-point Likert scale. The patients rated the presence of the symptoms over the past 24 hours on a scale from 0 to 4 (0 = not experienced at all after the injury, 1 = experienced but no more of a problem compared with before the injury, 2 = mild problem, 3 = moderate problem, and 4 = severe problem). A total score was calculated by adding all items with a score greater than 1 (not present anymore or no worse than prior to the injury).

Depressive symptoms were assessed using the Beck Depression Inventory-Second Edition (BDI-II), a 21-item self-report questionnaire.[79] Subjects are asked to rate each item on a 4-point scale ranging from zero to three. In this study, we used the total score which is the sum of all 21 items, giving a range from 0 to 63.

The EuroQol Five Dimension (EQ-5D™) Visual Analogue Scale (VAS) was used to evaluate general health-related quality of life. EQ-5D™ is a standardized instrument for use as a measure of health outcome.[80] The EQ-5D™ VAS is a visual scale that asks the respondent to consider and rate his/her health "today" on a vertical scale calibrated from 0 (worst imaginable health state) to 100 (best imaginable health state). Note that the EQ-5D™ was not completed by the neuropsychological control group.

Neurocognitive measures. The Rey Auditory Verbal Learning Test (RAVLT)[81] and Four Word Short Term Memory Test (FWSTMT)[82] were used to assess verbal memory. RAVLT is a widely used test for learning and memory. In this study, immediate recall (total number of words recalled in trials 1–5), recall after interference word list, and delayed recall and recognition after 30 minutes were used. FWSTMT is a test of working memory based on the Brown-Peterson paradigm.[81] In this study, total scores for each three distractor intervals (5'', 15'', 30'') were used, which is the sum of 5 trials (min = 0, max = 20). Visual memory was assessed with the Rey-Osterrieth Complex Figure Test (ROCFT) immediate recall version.[83] Verbal intelligence was assessed with Wechsler Adult Intelligence Scale (WAIS)–Third Edition[84] information subtest. Executive functions were assessed with a Stroop Test Golden version (color-word interference trial, number of items completed),[81] Trail Making Test Part A and Part B (TMT, time in seconds),[85] tests of phonemic (P/A/S) and semantic (animals) verbal fluency (total number of words in 1 minute),[86] and ROCFT copy version (sum of correct responses).[86] Raw scores were used in all analyses. Note that not all neurocognitive tests were completed by the neuropsychological control group (i.e., ROCFT, WAIS-III Information, Stroop, TMT, and verbal fluency tasks).

Data analyses

Prior to the analyses, all variables were examined for departures from normality and heterogeneity of variance (Levene's test). Group differences were assessed using chi-square analyses for categorical variables (e.g., gender). Fishers Exact test statistics were interpreted when cell sizes were less than five. Independent *t*-tests or Mann Whitney U tests were used for all continuous variables (e.g., age, education, neuroradiological results, neurocognitive tests, self-report measures). Nonparametric analyses (Mann Whitney U tests) were conducted for those variables that were not normally distributed. Alpha was adjusted for sets of analyses dealing with specific hypotheses. It was not corrected for some of the exploratory multiple comparisons due to the small sample sizes (resulting in reduced power)—although the implications of adjusting versus not adjusting alpha are discussed for some specific findings. Effect sizes (Cohen's d) are also reported as a measure of clinical significance. Correlations between demographic variables (age, years of education), injury-related variables (duration of post-traumatic amnesia (PTA), duration of retrograde amnesia (RTA), duration of loss of consciousness (LOC), self-reported measures (BNI-FS, FIS, BDI, RPSQ), and neurocognitive measures (RAVLT, FWSTMT) were calculated by using Spearman's rank correlation coefficient analyses. Linear regression analysis was conducted to determine whether time post injury predicts FA scores. This regression analysis used total number of low FA's as a dependent factor and time post injury as an independent factor. Statistical analyses were conducted using SPSS for Windows version 20.0.

Results

Demographic and injury variables

There were no significant differences between the MTBI and neuroimaging control group for age ($t(70) = 0.530$, $p = 0.598$) or gender ($X^2 = 0.267$, $p = 0.606$). Similarly, there were no significant differences between the MTBI and neuropsychological control group for age ($t(82) = -0.158$, $p = 0.875$) or gender ($X^2 = 0.105$, $p = 0.746$). However, the MTBI group was less educated (Mean = 12.7 years, SD = 2.5) compared to the neuropsychological control group [Mean = 15.1 years, SD = 2.5; $t(82) = -4.381$, $p < 0.01$; d = 0.96, very large effect size]. Years of education were not available for the neuroradiological control group.

In the MTBI group, the mean duration of PTA was 197.5 minutes (Median = 0.0, SD = 373.6, Range = 0–1440.0). More than 50% of the MTBI group had no PTA. The mean duration of retrograde amnesia (RTA) was 6.8 minutes (Median = 0.0, SD = 20.2, Range = 0–120). Loss of consciousness (LOC) was present in 11 of 48 patients (8 missing), and all patients had a duration of LOC for 10 minutes or less. The mechanisms of injury were as follows: 20.8% motor vehicle accident (MVA), 4.2% pedestrian hit by motor vehicle, 12.5% sports-related, 41.7% fall (low), 4.2% fall (high), 10.4% assault, and 6.3% other.

Spearman correlations were used to examine the relations between demographic and injury-related variables and the neurocognitive and self-report measures. In the MTBI group, there were no significant correlations between age, education, LOC, PTA, or RTA and the self-report measures or the majority of the neurocognitive measures. There were a few significant positive correlations between education and RAVLT total ($r = 0.449$, $p < 0.01$), education and FWSTMT 30'' ($r = 0.369$, $p < 0.05$), duration of LOC and FWSTMT 30'' ($r = 0.337$, $p < 0.05$), and duration of PTA and FWSTMT 15'' ($r = 0.306$, $p < 0.05$). In the neuropsychological control group, there were no significant correlations between education and the self-report or neurocognitive measures. For age, significant negative correlations were found for all neurocognitive measures [range: $r = -0.356$ to $r = -0.551$; except FWSTMT 5'' ($r = -0.288$)], but not for any of the self-report measures.

Neurocognitive and self-report measures

Descriptive statistics, group comparisons, and effect sizes for the neurocognitive and self-report measures by group are presented in Table 2. In support of hypothesis #1, compared to the neuropsychological control group, the MTBI group reported a greater

Table 2. Comparison of Memory, Postconcussion Symptoms, Depression, and Fatigue Measures by Group

	Uncomplicated MTBI (n=48)		*Neuropsychological healthy controls (n=36)*			
	M	*SD*	*M*	*SD*	*p*	*Cohen's Effect Size (d)*
Neurocognitive measures						
RAVLT total recall	55.40	8.02	55.58	9.03	.920	0.02
RAVLT post-interference recall	11.13	2.66	11.75	2.93	.310	0.22
RAVLT delayed recall	10.71	2.90	11.75	3.10	.118	0.35
RAVLT recognition	13.42	1.99	13.72	1.92	.481	0.15
FWSMT 5"	15.51	2.72	16.11	2.96	.340	0.21
FWSMT 15"	12.32	3.68	13.58	3.16	.103	0.37
FWSMT 30"	11.11	3.65	11.08	3.38	.977	0.01
Self-report measures						
RPSQ total score	10.73	12.42	3.72	4.89	.001	0.76
BDI-II total score	5.25	4.65	4.03	3.59	.193	0.29
BNI-total score	13.85	13.07	10.33	7.44	.123	0.33
FIS: total sum score	22.48	26.49	13.28	11.30	.034	0.46

BDI-II, Beck Depression Inventory – II; BNI, Barrow Neurological Institute Fatigue Scale; FIS, The Fatigue Impact Scale; FWSMT, Four Word Short Term Memory Test; RAVLT, Rey Auditory Verbal Learning Test; RPSQ, The Rivermead Post-Concussion Symptoms Questionnaire.

number of postconcussion symptoms ($p<0.01$, d=0.76, medium effect size). In addition, the MTBI group reported more difficulty with fatigue ($p=0.03$, d=0.46, medium effect size), but not depression. Adjusting alpha for multiple comparisons, the groups did not differ in their ratings of fatigue. In support of hypothesis #2, there were no significant differences between the MTBI and neuropsychological control group on any measure of working memory, learning, or memory. Effect sizes ranged from very small (d=0.01) to small (d=0.37).

Diffusion tensor imaging measures

A multivariate ROI analysis was used to examine hypothesis #3. This methodology is described in detail by Iverson and colleagues.[87] For these analyses, the 16 ROIs for FA and 10 ROIs for ADC were considered simultaneously. To examine the prevalence of low or high scores, when all ROIs were considered simultaneously, a cut-off score for each ROI was set at 1.28 SDs below or above the mean of control values. The 1.28 SDs below the mean for each FA score for each ROI was selected as a cutoff score for abnormally low FA scores (i.e., 10th percentile) and 1.28 SDs above the mean for each ADC score for each ROI was selected as a cutoff score for abnormally high ADC scores (i.e., 90th percentile). The 10th and 90th percentiles were selected because the control sample was relatively small and this would create more variability, and mediate the effects of possible outliers, in the control sample. The cumulative percentages of the number of low FA scores and high ADC scores by group are presented in Table 3.

Overall, there were a greater number of low FA scores in the MTBI group compared to the control group. Chi-square analyses revealed that there was a significantly greater number of low FA scores when using 2 or more low scores as the criterion ($p=0.003$, 66.7% MTBI, 29.2% controls). Although not statistically significant, there was a trend towards a greater number of low FA scores in the MTBI group when using 3 or more low scores as the criterion ($p=0.063$, 39.6% MTBI, 16.7% controls). Similarly, there were also a greater number of high ADC scores in the MTBI group compared to the control group. Chi-square analyses revealed that there was a significantly greater number of high ADC scores when using 2 or more high scores ($p=0.011$, 47.9% MTBI, 16.7% controls) and 3 or more high scores ($p=0.007$, 33.3% MTBI, 4.2% controls) as the criterion.

To further examine hypothesis #3, a multifocal abnormal WM group was defined as follows: 4 or more areas of abnormally low

Table 3. Cumulative Frequency Distribution of 16 Low FA and 10 High ADC Scores Considered Simultaneously

	FA						*ADC*				
	MTBI patients (N=48)		*Neuroimaging healthy controls (N=24)*				*MTBI patients (N=48)*		*Neuroimaging healthy controls (N=24)*		
Low Scores	*f*	*cp*	*f*	*cp*	p	*High Scores*	*f*	*cp*	*f*	*cp*	p
6	1	2.1	0	–	1.00	6	0	–	0	–	–
5	5	12.5	1	4.2	0.412	5	1	2.1	0	–	1.00
4	4	20.8	1	8.4	0.314	4	5	12.5	0	–	0.169
3	9	39.6	2	16.7	0.063	3	10	33.3	1	4.2	0.007**
2	13	66.7	3	29.2	0.003**	2	7	47.9	3	16.7	0.011
1	11	89.6	12	79.2	0.228	1	13	75.0	12	66.7	0.457
0	5	100.0	5	100.0		0	12	100	8	100	

cp, cumulative percentage; f, Frequency; *p* based on X^2 –test.

FA values OR 3 or more areas of abnormally high ADC values. The broadly normal WM group was defined as follows: <4 areas of abnormally low FA values AND <3 areas of abnormally high ADC values. Classification of multifocal abnormal WM was found in 12.5% of the control group (3/24) and 52.1% of the MTBI group (25/48). Patients in the MTBI group were more likely to show evidence of multifocal diminished white matter than participants in the control group ($X^2 = 10.549$, $p = 0.002$). To examine whether presumed pre-existing white matter hyperintensities accounted for this finding, subgroup analyses were conducted on the 33 MTBI subjects and 22 control subjects who had no hyperintensities. Multifocal abnormal WM was found in 13.6% of the control group (3/22) and 48.5% of the MTBI group (16/33). Patients in the MTBI group were more likely to show evidence of multifocal diminished white matter than participants in the control group ($X^2 = 7.09$, $p = 0.010$).

Descriptive statistics, group comparisons, and effect sizes for the 26 DTI measures, by group, are presented in Table 4. Exploratory analyses revealed no significant differences between the MTBI and neuroimaging control group on 24 of 26 DTI measures. In regards to hypothesis #4, there were significant differences for ADC in the genu of the corpus callosum ($p = 0.022$, d = 0.58, medium effect size) and FA in splenium of the corpus callosum ($p = 0.027$, d = 0.56, medium effect size). These medium differences between groups would not be significant if alpha was adjusted for multiple comparisons. For both ROIs, there was increased ADC (genu) and increased FA (splenium) in the MTBI group compared to controls. Increased FA is the splenium is the opposite of what is expected based on the literature. Although not significantly different, medium effect sizes were also found for ADC in the basilar pons-right ($p = 0.105$, d = 0.42) and right posterior corona radiata ($p = 0.109$, d = 0.41), and for the FA in the left basilar pons ($p = 0.111$, d = 0.41) and right posterior corona radiata ($p = 0.073$, d = 0.40). For these ROIs, there was increased ADC and decreased FA in the uncomplicated MTBI group compared to controls (with the exception of ADC in the right basilar pons).

Clinical correlates of DTI abnormalities

To examine the relation between DTI abnormalities and clinical outcome, the MTBI sample was divided into two groups based on the presence or absence of multiple areas of abnormally low FA values or abnormally high ADC values: (a) broadly normal white matter (WM) group ($n = 23$, 47.9%), and (b) multifocal abnormal WM group ($n = 25$, 52.1%). As described above, the multifocal abnormal WM group was defined as follows: 4 or more areas of abnormally low FA values OR 3 or more areas of abnormally high ADC values. The broadly normal WM group was defined as follows: <4 areas of abnormally low FA values AND <3 areas of abnormally high ADC values.

Descriptive statistics, group comparisons, and effect sizes for the demographic, injury-related, self-report, neurocognitive, and return

Table 4. Exploratory Comparisons of Apparent Diffusion Coefficient and Fractional Anisotropy of the Mild Traumatic Injury Patients and Control Subjects

	Uncomplicated MTBI (n = *48*)		*Neuroimaging Healthy Controls* (n = *24*)			
	M	*SD*	*M*	*SD*	p	*Cohen's Effect Size (d)*
ADC (10^{-3} mm^2/sec)						
Basilar pons right	0.692	0.069	0.723	0.084	0.105	0.42
Basilar pons left	0.720	0.099	0.709	0.047	0.520	0.14
Internal capsule right	0.689	0.034	0.696	0.029	0.402	0.22
Internal capsule left	0.679	0.038	0.672	0.026	0.396	0.21
Corona radiata posterior right	0.664	0.041	0.649	0.027	0.109	0.41
Corona radiata posterior left	0.649	0.073	0.637	0.036	0.339	0.20
Uncinate fasciculus right	0.776	0.044	0.778	0.041	0.864	0.05
Uncinate fasciculus left	0.774	0.048	0.769	0.045	0.693	0.11
Corpus callosum: genu	0.796	0.084	0.750	0.070	0.022	0.58
Corpus callosum: splenium	0.711	0.063	0.721	0.053	0.510	0.17
FA						
Basilar pons right	0.626	0.079	0.644	0.086	0.393	0.22
Basilar pons left	0.622	0.082	0.653	0.064	0.111	0.41
Cerebral peduncle right	0.857	0.052	0.863	0.051	0.691	0.12
Cerebral peduncle left	0.854	0.057	0.863	0.049	0.523	0.17
Internal capsule right	0.725	0.044	0.735	0.053	0.394	0.21
Internal capsule left	0.722	0.043	0.731	0.046	0.408	0.21
Corona radiata posterior right	0.444	0.073	0.469	0.042	0.073	0.40
Corona radiata posterior left	0.516	0.077	0.524	0.060	0.646	0.11
Anterior corona radiata right	0.554	0.072	0.558	0.077	0.855	0.05
Anterior corona radiata left	0.558	0.077	0.574	0.076	0.160	0.21
Uncinate fasciculus right	0.537	0.071	0.538	0.062	0.953	0.02
Uncinate fasciculus left	0.533	0.072	0.545	0.058	0.485	0.18
Forceps minor right	0.548	0.086	0.533	0.066	0.458	0.19
Forceps minor left	0.567	0.092	0.552	0.081	0.485	0.17
Corpus callosum: genu	0.826	0.058	0.840	0.042	0.310	0.27
Corpus callosum: gplenium	0.877	0.044	0.850	0.056	0.027	0.56

ADC, apparent diffusion coefficient ; FA, fractional anisotropy.

to work variables, by group, are presented in Table 5. For the demographic and injury-related variables, there were no significant differences between groups for age, education, gender, RTA, or LOC (all $p > 0.05$). However, the broadly normal WM group had a significantly longer duration of PTA compared to the multifocal abnormal WM group ($p = 0.034$, d = 0.75, large effect size). To address hypothesis #5, the two groups were compared on the neurocognitive measures and number of days to return to work. There were no significant differences between groups for the majority of measures, with the exception of the 15'' and 30'' retention interval trials on the FWSTMT. For these two measures, the multifocal abnormal WM group had higher (better) scores compared to the broadly normal WM group (15'' retention trial, $p = 0.035$; d = 0.64; 30'' retention trial, p = 0.026, d = 0.68). If alpha was adjusted downward for multiple comparisons, there would be no difference between the two groups on cognitive testing. The multifocal abnormal white matter group did not take longer to return to work than the broadly normal white matter group ($p = 0.939$). Consistent with hypothesis #6, the two groups did not differ on postconcussion symptom reporting.

Clinical correlates of postconcussion syndrome

To examine the relation between self-reported postconcussion symptoms and neuropsychological and DTI measures, the MTBI sample was divided into two groups based on International Classification of Diseases (ICD-10; World Health Organization, 1992) Category C symptom criteria for Postconcussion Syndrome (PCS): (a) PCS-Present ($n = 11$), and (b) PCS-Absent ($n = 37$). PCS was classified using symptoms endorsed as moderate or higher on the RPSQ.

Descriptive statistics, group comparisons, and effect sizes for the demographic variables, injury-related variables, self-report measures, neurocognitive measures, and DTI measures by group are presented in Table 6. There were no significant differences between groups on all demographic (gender, age, education) and injury related variables (LOC, PTA, RTA), and for the majority of neurocognitive measures.

Table 5. Comparison of Demographic Variables, Injury-Related Measures, Neurocognitive Measures, and Self-Report Measures by Group

	Broadly normal (n = *23*)		*Multifocal abnormal* (n = *25*)			
	M	*SD*	*M*	*SD*	p	*d*
Demographic variables						
Age	33.13	11.40	39.48	12.79	0.077	0.52
Education	12.65	2.40	12.72	2.59	0.925	0.03
Gender (female)	F = 15[+]	% = 65.2[‡]	F = 14[+]	% = 56.0[‡]		
Injury-related measures						
PTA in minutes	318.48	484.92	81.46	159.74	0.034	0.75
RTA in minutes	6.61	14.69	6.88	24.62	0.964	0.01
LOC[†] in minutes	.61	1.32	0.91	2.35	0.629	0.16
Functional outcome						
Return to Work (days)[††]	10.81	14.39	10.48	14.35	0.939	0.02
Neurocognitive measures						
RAVLT total recall	56.17	6.93	54.68	8.99	0.525	0.19
RAVLT post-int recall	11.04	2.38	11.20	2.93	0.841	0.06
RAVLT delayed recall	10.91	2.52	10.52	3.26	0.644	0.13
RAVLT recognition	13.35	1.92	13.48	2.08	0.821	0.07
FWSMT 5"	14.87	2.51	16.13	2.82	0.114	0.47
FWSMT 15"	11.17	3.55	13.42	3.53	0.035	0.64
FWSMT 30"	9.91	2.91	12.25	3.97	0.026	0.68
ROCFT copy	35.52	0.79	35.52	0.71	0.994	0.00
ROCFT immediate memory	22.72	4.88	23.50	6.38	0.638	0.14
WAIS-III Information	11.17	2.31	10.68	3.26	0.551	0.17
STROOP color-word total	43.74	7.30	39.88	8.17	0.092	0.50
Phonemic naming (letter)	42.87	13.42	40.68	10.88	0.536	0.18
Semantic naming (animal)	24.74	6.05	24.68	5.17	0.971	0.01
TMT A time in seconds	30.83	10.44	28.52	8.51	0.404	0.25
TMT B time in seconds	62.39	22.77	69.48	20.96	0.267	0.33
Self-report measures						
BDI-II total score	5.87	4.45	4.68	4.85	0.381	0.26
BNI-FS total score	17.30	16.04	10.68	8.77	0.089	0.54
FIS total sum score	27.96	31.34	17.44	20.46	0.181	0.41
RPCSQ total score	13.57	13.20	8.12	11.29	0.130	0.45
EQ-5D™	73.83	16.66	76.68	11.96	0.496	0.20

BDI-II, Beck Depression Inventory – Second Edition; BNI, Barrow Neurological Institute Fatigue Scale; EQ-5D™, EuroQol 5D; d, Cohen's Effect Size; FIS, Fatigue Impact Scale; FWSMT, Four Word Short Term Memory Test; LOC, loss of consciousness; PTA, post-traumatic amnesia; RTA, retrograde amnesia; RAVLT, Rey Auditory Verbal Learning Test; ROCFT, Rey Osterrieth Complex Figure Test; RPCSQ, Rivermead Post-Concussion Symptoms Questionnaire ; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition.

[+]f, frequency, [‡]p, percentage, [†]n, 18 broadly normal group, and n, 22 multifocal abnormal group, [††]n, 21 broadly normal group, and n, 25 multifocal abnormal group.

Table 6. Comparison of Demographic Variables, Injury-Related Measures, Neurocognitive Measures, and Selected Self-Reported Measures by PCS Group

	PCS- (n=37)		*PCS+ (n=11)*			
	M	*SD*	*M*	*SD*	p	*d*
Demographic variables						
Age	35.41	13.18	39.91	9.22	0.297	0.37
Education	12.54	2.52	13.18	2.32	0.455	0.26
Gender (female)	f=21[+]	%=56.8[‡]	f=8[+]	%=72.7[‡]		
Injury-related measures						
PTA in minutes	146.11	297.73	365.46	539.64	0.222	0.62
RTA in minutes	6.73	22.15	6.82	12.30	0.989	0.01
LOC[†] in minutes	.75	2.03	.89	1.69	0.848	0.07
Neurocognitive measures						
RAVLT total recall	55.27	8.06	55.82	8.27	0.845	0.07
RAVLT post-int recall	11.00	2.72	11.55	2.51	0.555	0.21
RAVLT delayed recall	10.65	2.95	10.91	2.88	0.797	0.09
RAVLT recognition	13.49	2.01	13.18	1.99	0.660	0.16
FWSMT 5"	15.58	2.76	15.27	2.69	0.744	0.11
FWSMT 15"	13.03	3.45	10.00	3.58	0 .015	0.87
FWSMT 30"	11.11	3.85	11.09	3.05	0.987	0.01
ROCFT copy	35.49	0.77	35.64	0.67	0.563	0.20
ROCFT immediate memory	23.22	5.99	22.82	4.64	0.840	0.07
WAIS-III Information	11.16	3.00	10.09	2.07	0.274	0.38
STROOP color-word total	42.35	8.23	39.64	6.73	0.324	0.34
Phonemic naming (letter)	42.32	11.87	39.73	13.15	0.537	0.21
Semantic naming (animal)	24.62	5.84	25.00	4.67	0.845	0.07
TMT A time in seconds	29.49	8.84	30.09	11.77	0.855	0.06
TMT B time in seconds	67.84	21.91	60.18	21.86	0.314	0.35
Self-report measures						
BDI-II total score	3.86	3.66	9.91	4.75	<0.001	1.55
BNI-FS total score	10.08	9.99	26.55	14.62	<0.001	1.49
FIS total sum score	14.41	20.40	49.64	27.33	<0.001	1.60
EQ-5D™	77.76	12.26	67.09	18.08	0.028	0.79

BDI-II, Beck Depression Inventory – II; BNI, Barrow Neurological Institute Fatigue Scale; EQ-5D™, EuroQol 5D; D, Cohen's Effect Size; FIS, Fatigue Impact Scale; FWSMT, Four Word Short Term Memory Test; LOC, loss of consciousness; PTA, post-traumatic amnesia; RTA, retrograde amnesia; RAVLT, Rey Auditory Verbal Learning Test; ROCFT, Rey Osterrieth Complex Figure Test; RPCSQ, Rivermead Post-Concussion Symptoms Questionnaire; TMT, Trail Making Test ; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition.

[+]f, frequency; [‡]*p*, percentage; [†]*n*, 31 PCS- group and *n*, 9 PCS+ group.

The one exception to this was the 15'' retention interval trial in FWSTMT in which the PCS-Absent group had higher (better) scores compared to the PCS-Present group ($p=0.015$; $d=0.87$; if alpha was adjusted for multiple comparisons, this large effect would not be considered statistically significant. There were significant differences and very large effect sizes between groups on both measures of fatigue (FIS total score, $p<.01$; d=1.60; BNI-FS total score, $p<0.01$; d=1.49), depression (BDI-II total score, $p<0.01$; d=1.55), and general health (EQ-5D™ VAS score, $p=0.028$, d=0.79; although this finding for general health would not be considered statistically significant if alpha was adjusted for multiple comparisons. For the DTI measures, there were no significant differences between the two groups for all ROIs for FA and ADC (all $p>0.05$, see Table 7). In addition, when all ROIs were considered simultaneously, the prevalence of low FA scores or high ADC scores did not differ between groups (data not shown; available from MW on request).

Discussion

It is difficult to predict who will have a good or poor outcome following MTBI. Some risk factors for slow or incomplete recovery include pre-injury mental health problems,[20,88–90] sustaining a complicated MTBI,[43,45,50,91] acute psychological distress associated with the injury event or developing in the first two weeks,[18,92] involvement in litigation,[30,93] and ongoing problems with depression,[14,90,94,95] chronic pain,[15,96] or both. Psychosocial factors, such as expectations and misattribution[23–26] and retrospective recall biases,[24,25,27–29] are associated with greater symptom reporting. There has been tremendous interest in the past few years in determining whether microstructural changes in white matter integrity, as measured by DTI, occur in patients across the spectrum of MTBI severity—and whether these changes are associated with worse functional outcome. A summary of this literature is provided in Table 1. Many studies to date are based on small and nonrepresentative samples. Some studies have examined the relation between DTI findings and cognition,[59,61,65,67,70,71,97–111] symptoms,[13,60,112] or both.[56,113–116] However, no studies have examined the relation between DTI findings and time to return to work.

The present study was large, carefully controlled, and prospective. It is the first study to examine the relation between DTI findings and functional outcome in a comprehensive way (i.e., postconcussion symptoms, cognition, mental health, and return to work). However, this study has several methodological limitations and issues that should be considered. First, the study included

age- and gender-matched community controls as a comparison group instead of an orthopedically-injured trauma control group. In general, trauma control subjects are a better and more generalizable control group. Second, the imaging control group was a convenience sample that did not undergo psychological and neuropsychological testing. Using separate comparison groups for outcome measures and imaging is a weakness that needs to be taken into account when interpreting results. Third, some newer DTI analysis techniques, such as tract-based spatial statistics, were not conducted as a preliminary step prior to the ROI analyses. The ROI method is the most commonly used in the literature, the present results were fairly consistent with the majority of the literature, and this study examined numerous outcome variables (i.e., symptoms, cognition, return to work, and neuroimaging). Therefore, additional analyses of the DTI data were not undertaken. Other methodological limitations are discussed in relation to specific hypotheses.

Six hypotheses were addressed. In support of hypothesis #1, patients with MTBIs reported more postconcussion symptoms than healthy controls ($d = 0.76$, large effect). This is not surprising given that symptoms were measured at approximately 3 weeks post injury. Consistent with the second hypothesis, patients with MTBIs did not perform more poorly than healthy controls on neuropsychological testing. This finding is consistent with some past studies illustrating that cognitive deficits resolve in most people within the first month following injury, as reported in meta-analyses.[35,38,41,117] It is inconsistent, however, with some studies that have reported differences between those with MTBIs and control subjects at 1 or 3 months following injury.[118–121]

Consistent with the third hypothesis, patients with uncomplicated MTBIs had reduced white matter integrity in a greater number of regions of interest compared to healthy controls. For example, a multifocal abnormal white matter group was defined as follows: 4 or more areas of abnormally low FA values or 3 or more areas of abnormally high ADC values. Based on this criterion, 52.1% of the MTBI group and only 12.5% of the control group showed evidence of multifocal white matter findings ($X^2 = 10.55$, $p = 0.002$). For hypothesis #4, we predicted that those with MTBIs would show reduced white matter integrity in the corpus callosum. This hypothesis was not supported. A significant difference, in the predicted direction, was found in only one of four of the corpus callosum variables. Moreover, a significant difference was found in the opposite direction, with control subjects having lower FA, in one region of the corpus callosum. Adjusting alpha for multiple comparisons (0.05/4 DTI measures = 0.0125) results in no significant differences between groups in the corpus callosum. There is recent evidence from longitudinal studies that DTI abnormalities are related to time since injury.[66,68] Also, the present study used a cross-sectional design that is a limitation in relation to identifying possible transient MRI findings. Therefore, we ran exploratory regression analysis to examine whether time post injury predicts FA scores. In the present study, time post injury did not predict total number of low FA scores ($R = 0.141$, $R2 = 0.020$, $p = 0.339$). Many[55,56,58,64,65,67,98–102,106,110,115,122] but not all[13,59,61,123] past studies have found differences in the corpus callosum. Exploratory analyses on all regions of interest revealed differences in only two regions of interest, and in one of those regions the difference was in the opposite direction than predicted (i.e., control subjects had lower FA scores than those with MTBIs). Correcting for multiple comparisons, there would be no statistically significant differences between groups in any ROI. Although somewhat inconsistent with several previous studies, this is not a particularly surprising finding if one considers that MTBIs are heterogeneous in regards to mechanisms of injury, biomechanics, and severity. This heterogeneity reduces the likelihood of finding abnormalities, at the group level, in specific brain regions.

To address the fifth and sixth hypotheses, we examined whether MTBI patients with multifocal white matter findings had worse functional outcome than patients with broadly normal white matter. Inconsistent with hypothesis #5, those with multifocal white matter changes did not perform more poorly on any neuropsychological test. Moreover, those with multifocal white matter changes did not take longer to return to work. In the present study, there was not enough subjects who met possible DSM-IV criteria for postconcussional disorder to be analyzed statistically (i.e., those with psychometric evidence of impairment in attention or memory and impairment in social or occupational functioning).

For hypothesis #6, we predicted that white matter changes would be associated with postconcussion symptom reporting because there is a large literature, as indicated in Table 1, indicating that postconcussion symptoms are associated with DTI findings. Inconsistent with hypothesis #6, those with multifocal white matter changes did not report more symptoms than those with broadly normal white matter. Only a few studies to date have not reported a relation between DTI findings and postconcussion symptom reporting;[62,114] the majority have found this association (see Table 1). Although inconsistent with many past DTI studies, the present results are consistent with a large literature indicating that (i) postconcussion symptom reporting is influenced by a wide range of factors, and (ii) some researchers have reported that those with complicated MTBIs do not report more symptoms than those with uncomplicated MTBIs.[46–50]

In conclusion, this study advances knowledge regarding biopsychosocial outcome from uncomplicated MTBI. This is the first study to examine multiple outcome measures (i.e., symptoms, cognitive functioning, mental health, and return to work) in a large sample of patients with uncomplicated MTBIs. Some findings were expected and some were unexpected. At approximately 3 weeks following injury, those with uncomplicated MTBIs reported more postconcussion symptoms than healthy controls but did not perform more poorly on cognitive testing. Those with MTBIs were significantly more likely to show multifocal areas of diminished white matter on DTI compared to control subjects. It is possible that some of these MTBI patients had pre-injury differences in white matter integrity, but we have no way of knowing this. We tried to control for this by excluding subjects with pre-existing developmental, psychiatric, or neurological problems; head trauma; substance abuse; and major incidental abnormalities. Therefore, it is reasonable to conclude that the white matter differences were due mostly to MTBI. The most important finding was that white matter changes were not associated with functional outcome. MTBI patients with multifocal white matter changes did not show evidence of worse symptoms, cognitive impairment, or slower return to work compared to MTBI patients with broadly normal white matter.

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Author Disclosure Statement

The authors report no clear competing financial interests. Grant Iverson, PhD, has been reimbursed by the government, professional scientific bodies, and commercial organizations for discussing or presenting research relating to mild TBI and sports-related concussion at meetings, scientific conferences, and symposiums. He has a clinical and consulting practice in forensic neuropsychology involving individuals who have sustained mild TBIs. He has received research funding from several test publishing companies. He is a co-investigator, collaborator, or consultant on grants relating to mild TBI funded by several organizations.

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A Prospective Biopsychosocial Study of the Persistent Post-Concussion Symptoms Following Mild Traumatic Brain Injury

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Abstract

This study examined multiple biopsychosocial factors relating to post-concussion symptom (PCS) reporting in patients with mild traumatic brain injuries (MTBI), including structural (CT and MRI) and microstructural neuroimaging (diffusion tensor imaging; DTI).

Patients with MTBIs completed several questionnaires and cognitive testing at approximately one month (N=126) and one year post injury (N=103). At approximately three weeks post injury, DTI was undertaken using a Siemens 3T scanner in a subgroup (N=71). Measures of fractional anisotropy (FA) were calculated for 16 regions of interest (ROIs) and measures of apparent diffusion coefficient (ADC) were calculated for 10 ROIs. Patients were compared to healthy control subjects.

Using ICD-10 postconcussional syndrome (PCS) criteria and mild or greater symptom reporting, 59% of the MTBI sample met criteria at one month and 38% met criteria at one year. However, 31% of the healthy control sample also met criteria for the syndrome—illustrating a high false positive rate. Significant predictors of ICD-10 PCS at one month were pre-injury mental health problems and the presence of extra-cranial bodily injuries. Being symptomatic at one month was a significant predictor of being symptomatic at one year, and depression was significantly related to PCS at both one month and one year. Intracranial abnormalities visible on MRI were present in 12.1% of this sample, and multifocal areas of unusual white matter as measured by DTI were present in 50.7% (compared to 12.4% of controls). Structural MRI abnormalities and microstructural white matter findings were not significantly associated with greater post-concussion symptom reporting.

The personal experience and reporting of post-concussion symptoms is likely individualized, representing the cumulative

effect of multiple variables, such as genetics, mental health history, current life stress, medical problems, chronic pain, depression, personality factors, and other psychosocial and environmental factors. The extent to which damage to the structure of the brain contributes to the persistence of post-concussion symptoms remains unclear.

Key words: cognitive function, diffusion tensor imaging, traumatic brain injury, outcome measures, prospective study

Introduction

It is well established that mild traumatic brain injury (MTBI) is associated with cognitive impairment in the initial days following injury in athletes and civilians,[1-3] and by three months post injury there is substantial recovery and cognitive deficits are no longer present in group studies.[4-8] A minority of patients with MTBIs who undergo day-of-injury computed tomography (CT) show evidence of macroscopic abnormalities [e.g., 5% in patients with a Glasgow Coma Scale Score (GCS) of 15, 20% for those with a GCS of 14, and 30% for those with GCS of 13[9]]. The term complicated MTBI has been used to refer this subgroup of patients who have evidence of trauma-related intracranial abnormality (e.g., hemorrhage, contusion, or edema).[10] Some studies have shown that those with complicated MTBIs, as a group, have worse short-term (i.e., 1 week to 3 months)[11-14] and long-term outcome.[15-17] Some researchers, however, have reported that patients with complicated MTBIs do not report more post-concussion symptoms at one month,[18] three months,[19] or six months[20] following injury than those with uncomplicated MTBIs.

The rate at which people recover subjectively, in regards to post-concussion symptoms, varies from study to study—but it is clear that a substantial minority of people continue to report symptoms at one,[21-23] three,[24-27] six,[28] and 12 months[29-31] following injury. Post-concussion-like symptoms tend to be persistent in some people; many of those who are highly symptomatic at one month will also be highly symptomatic at one year.[21,31,32] Of course, there is considerable individual variability in how people endorse their symptoms over time.[27,31,33] There is even evidence that some people who do not report significant post-concussion symptoms shortly following the injury report post-concussion-like symptoms many months or year post-injury.[33,34] The situation is complicated because these symptoms are non-specific; they are reported fairly frequently by healthy adults[35,36] and people with chronic pain,[37,38] post-traumatic stress disorder,[39,40] and depression.[41-46] Therefore, it is not surprising that in clinical practice and research it is difficult to predict the rate at which a person will improve and recover following an MTBI. The etiology of persistent symptoms is likely diverse, multifactorial, and characterized by considerable individual variability. Therefore, a perspective that integrates biological, social, cognitive, affective, and behavioral factors into a biopsychosocial framework might be useful for conceptualizing rapid, typical, or slow recovery in individual patients.[47-53]

The purpose of this study was to adopt a biopsychosocial perspective for examining the natural history of post-concussion symptom reporting using a prospective, longitudinal, inception cohort design. A biopsychosocial approach facilitates the integration and synthesis of a large and diverse literature into a set of specific hypotheses that can be tested on a single large prospective cohort. Numerous clinical and methodological factors that are relevant to studying outcome from MTBI will be controlled or statistically analyzed, such as pre-existing mental health problems,[4,35,54-59] injury severity and structural neuroimaging,[10,13,15,60-62] the nonspecificity of post-concussion-like symptoms,[35,55,56,63] and

the role of post-injury mental health.[49,64,65] Researchers have reported that pre-injury psychiatric problems[55,57] are associated with persistent post-concussion symptom reporting in some people. Moreover, brain injuries of all severities are associated with increased risk for developing depression,[41-46] especially in those with pre-existing mental health problems.[66] Therefore, the relationship between depression and post-concussion symptom reporting is important to analyze. Studies examining the relationship between persistent symptom reporting and macrostructural intracranial abnormalities (e.g., complicated vs. uncomplicated MTBI)[11-20] and microstructural changes in white matter (diffusion tensor imaging; DTI) have yielded mixed results. Waljas and colleagues[67] summarized the findings from 50 studies involving DTI in MTBI. They reported that 88% of authors reported DTI abnormalities associated with MTBI. However, 82% of the studies did not study the relation between the abnormalities and post-concussion symptoms. Most published studies have found a relationship between white matter abnormalities and PCS,[68-74] although some reported no association.[46,67,75]

This prospective study will include diverse outcome measures, including structural (CT and MRI) and microstructural neuroimaging (DTI), cognition, depression, and post-concussion symptom reporting. There are five primary hypotheses. First, patients who sustain complicated MTBIs (i.e., those with trauma-related abnormalities on day of injury CT or subacute MRI), compared to those with uncomplicated MTBIs, will perform more poorly on memory testing and report greater post-concussion symptoms at one month, but not at one year, following injury. Second, patients with pre-existing mental health problems will report greater post-concussion symptoms than those without pre-injury mental health problems following MTBI. Third, post-concussion-like symptoms at both one month and one year following MTBI will have a medium to high correlation with affective symptoms of depression. Fourth, patients with MTBIs will show more areas of abnormality on diffusion tensor imaging (DTI) than control subjects. Finally, patients with abnormalities on DTI will endorse more symptoms than patients with broadly normal DTI findings following MTBI at three weeks but not one year following injury.

Method

Participants

Participants were 126 consecutively enrolled patients who were evaluated in the Emergency Department (ED) of Tampere University Hospital, Finland. All patients fulfilled the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine[76] and the World Health Organization (WHO) Collaborating Center Task Force on Mild Traumatic Brain Injury (page 115) criteria for an MTBI[59]). Inclusion criteria were (i) biomechanical force applied to the head, (ii) loss of consciousness, if present, for less than 30 minutes, (ii) GCS score between 13 and 15 after 30 minutes following injury, and (iii) post-traumatic amnesia, if present, of less than 24 hours. Exclusion criteria were: age under 16 or over 65, history of previous major substance abuse, history of psychiatric disorder, or past neurological condition or disease. MTBI patients underwent day-of-injury head computed tomography (CT) and magnetic resonance imaging (MRI) at average 29 days (SD = 19.9 days) post injury. This sample included patients (N=17; 13.5%) who had an intracranial trauma-related abnormality on day-of-injury CT or follow-up MRI (i.e., a complicated MTBI).

The average age of the MTBI sample was 37.8 years (SD = 13.5; Range = 16-64),

their average education was 12.6 years (SD = 2.7; Range = 8-22), and 56.3% of the sample was female. At the time of injury, the employment status of the sample was as follows: 67.5% working full time, 2.4% working part time, 15.9% students, 4.0% retired/partly retired, 9.5% unemployed, and 0.8% on sick leave. The percentages of patients with previous MTBIs were as follows: none = 65.1%, one = 32.5%, two = 2.4%. The psychiatric history of this sample was as follows: 90.5% none, 7.1% yes, 2.4% unknown. The mechanisms of injury were as follows: 32.5% motor vehicle accident (MVA), 4.0% pedestrian-MVA, 8.7% sports, 36.5% fall (low), 7.1% fall (high), 7.1% assault, and 4.0% other. Their average GCS score was 14.96 (SD = 0.20, Range = 14-15, 96% = 15). Duration of loss of consciousness (LOC) was as follows: 71.6% no LOC, 12.0% LOC ≤ 1 min, 13.8% LOC > 1min ≤ 5 min, 1.8% LOC > 5 min ≤ 10 min, and 0.9% LOC > 10 min; the average duration of LOC was 0.8 min (SD = 2.2, Range = 0 – 15). Duration of post-traumatic amnesia was as follows: 48% no PTA, 22% PTA ≤ 2hours, 30% PTA > 2 hours, average duration of PTA was 196.2 minutes (SD = 353.2 minutes, Range = 0-1440 minutes). The average duration of sick leave after the injury was 42.1 days (SD = 112.1, IQR = 3.0 – 30.5, Range = 0 – 729). Four patients were missing data of duration of sick leave. None of the patients were involved in litigation. All participants were Caucasian. This sample was also used in a recent study examining return to work following MTBI,[77] and a subgroup of this sample was used to examine short-term outcome from uncomplicated MTBI.[67]

Two separate healthy control groups were recruited from the community for the study: (a) a neuroimaging control group, and (b) a neuropsychological control group. The neuroimaging control group initially consisted of 30 age- and gender-matched participants with no history of brain injury, neurological disease, or psychiatric disorders who completed a neuroimaging protocol using MRI with diffusion tensor imaging (DTI). In the control sample, 26.7% (8/30) had incidental MRI findings. Of the 8, 6 participants were excluded due to major incidental findings [e.g., cavernotic angioma with hemosiderin or numerous white matter hyperintensities (e.g., more than 10)]. Twenty-four neuroimaging control subjects were included in the final sample (Age: M=36.6 years, SD=10.1, female 66.7%). Of those 24, two had incidental white matter hyperintensities (8.3%; one had a single nonspecific hyperintensity and the other had two).

The neuropsychological control group consisted of 36 age and sex matched individuals (63.9% female) with no history of head injury or psychiatric disorders. The mean age of the controls was 36.9 years (SD = 13.6 years, Range = 17-61) and their average education was 15.1 (SD = 2.5 years, Range = 8-19) years. The employment status of the control sample was as follows: 64% of the participants were working full time, 33% were full-time students and 3% were unemployed. Participants in the neuropsychological control group completed self-report measures (e.g., post-concussion symptoms and depression) and a test of verbal learning and memory. The MTBI and control group did not differ on age ($t[160] = .336$, $p = .737$) or gender ($\chi 2 = .654$, $p = .419$). The MTBI group differed from the control group on education ($t[160] = -4.890$, $p = .001$). The mean years of education for MTBI patients and control subjects were 12.6 (SD = 2.7) and 15.1 (SD = 2.5), respectively.

All participants provided written informed consent according to the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Tampere University Hospital, Finland

Procedures

All the MTBI patients in this study were recruited from the ED of Tampere University Hospital. Brain CT scans were

performed in all patients within 24 hours of admission. For the MTBI group, MRI scanning was conducted between two weeks and two months post injury for the majority of participants (n= 119, 7 individuals missing MRI) (M=29.1 days, SD=19.9 days; IQR = 21.0-32.0 days, Range=1-159 days). MTBI patients participated in an interview and completed several questionnaires at approximately one month (N=126) and one year post injury (N=103). The average number of days from injury to the first interview and questionnaires was 24.1 days (SD = 5.4, Range = 8-38). Most of the patients (n = 103, 82%) were seen for an annual follow-up. This session occurred on average 12.6 months post injury (Mean = 383.8 days, SD = 30.6 days, Range = 316 – 488 days). For the control group, testing was completed as soon as possible following enrolment in the study.

Measures

Neuroimaging: MRI was performed either on a 1.5 Tesla (Magnetom Avanto A TIM system Siemens Medical Solutions, Erlangen, Germany) (n = 37, 29.4%) or a 3T Siemens Trio (Siemens AG Medical Solutions, Erlangen, Germany) (n = 89, 70.6%) machine. MRI sequences were evaluated by a certified neuroradiologist. The MRI protocol included sagittal T1-weighted 3D IR prepared gradient echo, axial T2 turbo spin echo, conventional axial and high resolution sagittal fluid-attenuated inversion recovery (FLAIR), axial T2*, and axial susceptibility weighted imaging (SWI) series. White matter hyperintensities (WMHI) were recorded from FLAIR sequences. The parameters for FLAIR sequences were TI 2216 ms, TR 7000 ms, TE 87 ms, FOV 199 × 220 ms, matrix 232 × 256, slice/gap 4.0/1.2 mm. The DTI sequence was single-shot diffusion-weighted echo planar imaging. The parameters for DTI were TR 5144 ms, TE 92 ms, FOV 230 mm, matrix 128 × 128, 3 averages, slice/gap 3.0/0.9 mm, voxel dimension 1.8 x 1.8 x 3.0 mm, b-factor 0 and 1000 s/mm^2, and 20 diffusion gradient orientations. A 12-channel head matrix coil was used. Only trauma related findings in CT and MRI were counted as abnormal; minor incidental findings, such as isolated white matter hyperintensities, were not considered as abnormal.

Of the 89 patients who underwent 3T MRI, DTI was acquired on 84 of them. A subset of these subjects (n=13) were excluded due to the presence of major incidental findings (e.g., ischemic lesions, numerous white matter hyperintensities, or enlarged lateral ventricles); 3 for incidental findings on CT, and 10 for incidental findings on MRI. The final subsample consisted of 71 MTBI patients (at one year follow-up n= 60). Those who had 1.5T did not differ from those with 3T on age (p=.106), education (p=.980), PTA (p=.603), RA (p=.858) LOC (p=.723), BDI-II at one month (p=.269), BDI-II at one year (p=.396), AUDIT at one month (p=.170), AUDIT at one year (p=.082), sex (p=.214), previous psychiatric symptoms (p=.726), previous brain injuries (p=.204), or previous diseases (p=.564). There was a significant difference in duration of time off work: the 1.5T group has a significantly greater number of days off work (mean 87.4, SD=182.4) than the 3T group (mean 23.1, SD=54.5) (t[120]=2.08, p=.044).

Region-of-interest (ROI) based DTI measurements were performed in eight different anatomical locations of each hemisphere and in three locations within the corpus callosum. Quantitative DTI parameters, including apparent diffusion coefficient (ADC) and fractional anisotropy (FA), were calculated symmetrically for multiple ROIs in the pyramidal tract (i.e., basal pons, cerebral peduncle, posterior limb of the internal capsule, corona radiata, and centrum semiovale) and frontobasal area (i.e., uncinate fasciculus, forceps minor, and anterior corona radiata). In the corpus callosum, the ROIs included three regions: the genu, body, and

splenium. ROIs were selected on the basis of prior studies that have demonstrated abnormalities on DTI parameters in these areas.[69,70,78-81]

All diffusion parameter analyses were performed by one observer (a physicist with long experience of brain ROI measurements; UH) on a workstation using commercially available software (Neuro 3D; Siemens Medical Solution, Malvern, USA). Circular ROIs were manually placed on color-coded axial fractional anisotropy (FA) maps and automatically transferred on the non-diffusion-weighted b_0 and ADC maps. The ROIs of the corpus callosum were drawn onto the median-line sagittal images. The size of the ROI was modified to the axial structure of each fiber tract. The circular ROIs were centered in the region taking care to avoid border areas, such as overlapping with cerebrospinal fluid spaces and neighboring tracts. The data quality was excellent in most cases, except in certain regions that had artifacts caused by air cavities and fluid flow. Mean values for FA and ADC for each region were calculated from the mean values of the right and left hemispheres.

A reliability study of this method was undertaken using the control sample (n=30).[82] Each ROI was sampled twice by the same rater to evaluate intrarater reliability. Intraclass correlation coefficients (ICCs) were calculated for all FA and ADC using a two-way random-model analysis with absolute agreement. The ICC values were considered as excellent agreement if greater than 0.8, as substantial agreement if they were from 0.60 to 0.79, and as fair/poor agreement if below 0.6. All ROIs that did not met criteria for substantial agreement for intrarater reliability (>0.65) were excluded from the analyses, including the Cerebral Peduncle-ADC (0.19), Centrum Semiovale-FA (0.48), Centrum Semiovale-ADC (0.63), Forceps Minor-ADC (0.64), Anterior Corona Radiata-ADC (0.27), Corpus Callosum Body-FA (0.23), Corpus Callosum-Body-ADC (0.26).

Initially, 19 ROIs were measured and ADC and FA values were calculated symmetrically for each ROI. Based on results from the reliability study, two regions were excluded for FA analysis (Centrum Semiovale, Corpus Callosum Body). Five regions were excluded for ADC analysis (Cerebral Peduncle, Centrum Semiovale, Forceps Minor, Anterior Corona Radiata, and Corpus Callosum Body). The number of ROIs retained for the analysis was 16 ROIs for FA and 10 ROIs for ADC.

Self-Report Questionnaires: Post-concussion symptoms were assessed with the Rivermead Post Concussion Questionnaire (RPSQ).[83] The RPSQ is a 16-item self-report questionnaire that measures the severity of common post-concussion symptoms on a 5-point Likert scale. The patients rated the presence of the symptoms over the past 24 hours on a scale from 0 to 4 (0 = not experienced at all after the injury, 1 = experienced but no more of a problem compared with before the injury, 2 = a mild problem, 3 = a moderate problem, and 4 = a severe problem). A total score was calculated by adding all items with a score greater than 1. High test-retest reliability has been reported for 7-10 day (r=.90) and 6-month (r= .87) intervals.[83]

Depressive symptoms were assessed using the Beck Depression Inventory-Second Edition (BDI II [84] a 21-item self-report questionnaire). Subjects are asked to rate each item on a four-point scale ranging from zero to three. It should be noted that many symptoms on this questionnaire overlap with post-concussion symptom measured by the RPSQ and clinically it is often not possible to differentiate depression from persistent post-concussion symptoms. Therefore, 10 of the 21 symptoms from the BDI-II, believed to have the least overlap with symptoms of MTBI and being most representative of depression, were selected. These symptoms were: sadness, loss of interest, loss of pleasure, pessimism, past failure, guilt feelings, punishment feelings,

self-criticalness, crying, and suicidal thoughts or wishes. In this study, we used the total score which is the sum of all 10 items, giving a range from zero to 30. Higher total scores indicate more severe depressive symptoms.

The Alcohol Use Disorders Identification Test (AUDIT) was used to detect alcohol problems.[85] The AUDIT is a widely used brief screening test to identify persons who have risky drinking, harmful drinking, or alcohol dependence. The AUDIT is a self-report measure that consists of 10 questions. Each of the questions has a set of responses to choose from, and each response has a score ranging from 0 to 4 (questions 1 – 8). Questions 9 and 10 are scored 0, 2, or 4 only. All the response scores are added to create a total score. Total score of ≥ 10 on the AUDIT is considered indicative of harmful or hazardous drinking. One subject did not complete this questionnaire.

Neurocognitive measure: The Rey Auditory Verbal Learning Test (RAVLT)[86] was used to assess verbal memory. RAVLT is a widely used test for learning and memory. In this study, immediate recall (total number of words recalled in trials 1-5) was used. The normative data applied in this study were from Mitrushina and co-workers.[87]

Postconcussion Symptom Classification

Classification of the ICD-10 symptom criteria for the post-concussion syndrome (PCS) was based on the Rivermead Post Concussion Symptoms Questionnaire. We defined the syndrome, based on ICD-10 criteria, two ways: (a) based on mild or greater symptom reporting in each domain, and (b) based on moderate or greater symptom reporting in each domain.

We defined the DSM-IV criteria for postconcussion disorder (PCD) two ways as follows: (a) mild cognitive impairment AND mild or greater report of 3 Category C symptoms AND not having returned to work by one month (30 days); or (b) mild cognitive impairment AND moderate or greater report of 3 Category C symptoms AND not having returned to work by approximately one month (30 days). The methodology of this study did not permit an exact application of the DSM-IV criteria at 3 months because the symptom and cognition data were collected prior to that point in time. In the total sample, 75.4% had returned to work by one month and 93.4% had returned to work by three months following injury. We operationally defined mild cognitive impairment in memory as scoring more than 1.5 standard deviations below the normative mean on the Rey Auditory Verbal Learning Test total score.[87] The RAVLT is recommended as a common data element for TBI research.[88] Using 1.5 standard deviations below the normative mean cut-off score, the percentages of the MTBI sample with low scores were as follows: RAVLT total score = 7.1% at one month following injury and 1.9% at one year. Applying this cut-off to the control sample, the percentages with low scores were as follows: RAVLT total score = 5.6%.

Withdrawal During the Study

Twenty three patients (18.3%) dropped out of the study during the one-year follow-up. Those who did not come to the follow-up (i.e., Attrition group) were compared to those who came to the follow-up (i.e., Follow-up group). The Attrition group did not differ from the Follow-up group on age (p=.205), education (p=.211), AUDIT at one month (p=.397), BDI-II at one month (p=.302), RAVLT total score at one month (p=.113), RPSQ total score at one month (p=.609), gender (p=.342), previous psychiatric symptoms (p=1.0) previous brain injuries (p=.456), abnormal CT findings (p=.206), abnormal MRI findings (p=.737), or duration of time off work (p=.325). There was a significant difference in PTA, retrograde amnesia (RA), and LOC: the Attrition group had a significantly shorter PTA (mean=30.8 minutes, SD=81.5) than the Follow-up group [mean=232.2 minutes, SD=378.7; t(121)=4.85, p<.001]. Also, the Attrition group had a

significantly shorter RA (mean=.03 minutes, SD=.11) than the Follow-up group [mean=9.5 minutes, SD=36.5; t(101)=2.61, p=.010]. On LOC, the Attrition group had a significantly shorter duration (mean=.16 minutes, SD=.47) than the Follow-up group [mean=.96 minutes, SD=2.39; t(107)=2.94, p=.004]. Therefore, by traditional injury severity criteria, those who completed the study had more severe MTBIs than those who dropped out.

Results

Complicated Versus Uncomplicated MTBI

The MTBI group's RAVLT total score mean 53.3 (SD=9.3) did not differ from the healthy control's RAVLT total score mean 55.6 (SD=9.0) at one month post injury [t(160)=-1.31, p=.193; Cohen's d=.25] or one year post injury [t(137)=1.04, p=.300; d=.20] (RAVLT total score mean=57.4, SD=9.0 for the MTBI group at one year). Alpha was adjusted for the four primary comparisons for the first hypothesis (.05/4=.0125). The RAVLT total score for those with complicated MTBIs (n=17, mean=55.5, SD=12.8) did not differ from those with uncomplicated MTBIs (n=109, mean=52.9, SD=8.7) at one month following injury [t(124)=-1.06, p=.299; d=.28]. Similarly, the total score for those with complicated MTBIs (n=15, mean=59.8, SD=10.7) did not differ from those with uncomplicated MTBIs (n=88, mean=57.0, SD=8.7) at one year following injury [t(101)=-1.12, p=.266; d=.31].

Regarding symptoms, the RPSQ total score for those with complicated MTBIs (mean=7.3, SD=6.3) did not differ from those with uncomplicated MTBIs (mean=10.9, SD=11.2) at one month following injury [t(34)=1.92, p=.064; d=.34]. Similarly, the total score for those with complicated MTBIs (mean=4.0, SD=4.3) did not differ from those with uncomplicated MTBIs (mean=7.3, SD=10.2) at one year following injury [t(46)=2.11, p=.040; d=.35]. The percentages of patients who met ICD-10 criteria, using "mild or greater" symptom reporting, for a PCS at one month and one year post injury were as follows: uncomplicated MTBI=59.8% and 39.8%, and complicated MTBI (MRI abnormality)=52.9% and 26.7%, respectively. The percentages of patients who met ICD-10 criteria, using "moderate or greater" symptom reporting, for a PCS at one month and one year post injury were as follows: uncomplicated MTBI=21.9% and 13.6%, and complicated MTBI (MRI abnormality)=5.9% and 0%, respectively. Chi square analyses did not reveal any significant differences in the rates of the ICD-10 diagnosis in relation to the presence or absence of MRI abnormalities. Also, the effect sizes (phi-coefficient; φ) for this finding were very small (φ ranged from .05 to .15 indicating little or no association).

Depression

There was a significant positive Pearson correlation between the BDI-II subscale scores and the RPSQ total scores in the MTBI group at one month post injury (r=.51; p<.001) and at one year post injury (r=.59; p<.001). The correlation between BDI-II subscale scores and RPSQ total scores in the control group was .48 (p=.003). At one month, the MTBI group had higher mean BDI-II subscale scores (sum of all 10 selected items; mean=2.2, SD=3.3) than the control group [mean=1.3, SD=1.8; t(101)=2.10, p=.042, d=.30] – but this finding is not significant after considering multiple comparisons. At one year, the MTBI group's BDI-II subscale scores (mean=1.7, SD=3.4, d=.13) did not differ from the control group mean subscale BDI-II score (p=.548). Patients who met ICD-10 criteria for postconcussional syndrome had significantly higher BDI-II subscale total scores than those patients who did not meet the ICD-10 criteria at one month based on "mild or greater" symptom reporting [t(94)=-5.59, p<.001, Cohen's d=.96] and "moderate or greater" symptom reporting [t(27)=-3.59, p=.001, Cohen's d=1.19]. Similarly, at one year post-

injury, patients who met ICD-10 criteria for the syndrome had significantly higher BDI-II subscale total scores than those patients who did not meet the ICD-10 criteria using both "mild or greater" symptom reporting [t(56)=-2.68, p=.010, Cohen's d=.63] and "moderate or greater" symptom reporting [t(12)=-3.59, p=.004, Cohen's d=2.01]. Correcting for multiple comparisons (.05/4=.0125), three of the four above mentioned findings are statistically significant.

Regarding pre-injury history of mental health problems, the RPSQ total score for those with pre-injury mental health problems (n=9, mean=21.0, SD=11.1) was much higher than for those without mental health problems (n=117, mean=9.6, SD=10.3) at one month following injury [t(124)=-3.19, p=.002; d=1.10]. At one year, the RPSQ total score for those with pre-injury mental health problems (n=7, mean=12.9, SD=16.9) did not differ from those without mental health problems [n=96, mean=6.4, SD=8.83; t(6)=-1.01, p=.351; d=.69], most likely due to small sample size. Of the 73 patients who met ICD-10 criteria for PCS at one month post injury based on "mild or greater" symptom reporting, 10.9% (n=8) had previous mental health problems [$\chi 2$ (1,126)=3.61, p=.080]. Of those 8 patients, who had a history of mental health problems, 88.9% met the ICD-10 criteria for PCS based on "mild or greater" symptom reporting. Using symptom endorsement as "moderate or greater" in those with a pre-injury mental health problem (n=8), 62.5% [$\chi 2$ (1,122)=9.94, p=.007] met the PCS criteria at one month. At one year, there was not a significant association between PCS group membership and previous mental health problems.

Descriptive Analysis of Post-Concussion Symptoms

Descriptive statistics, percentages, and group comparisons for the RPSQ total score and individual symptoms at one month and one year post injury are presented in Table 1. The RPSQ total score was significantly higher in the MTBI group compared to controls at both one month [t(129)=5.32, p<.001, d=.71] and one year [t(119)=2.48, p=.015, d=.36] following injury. In the MTBI group, significantly lower RPSQ total scores were found at one year post injury compared to one month post injury [t(102)=3.57, p<.001, d=.35]. At one month, the individual symptoms that differentiated the MTBI group from the control group with the largest effect sizes were fatigue, taking longer to think, dizziness, headaches, blurred vision, and nausea. At one year, the individual symptoms that differentiated the MTBI group from the control group, with the largest effect sizes, were fatigue, taking longer to think, and blurred vision.

Insert Table 1 About Here

Considering the total number of symptoms endorsed by the MTBI and the control group, two important issues emerge (see Figure 1). First, it is typical for control patients to endorse post-concussion-like symptoms. When using the criteria "mild or greater" symptom reporting, over 50% of controls endorsed one to five symptoms and approximately 6% endorsed six to ten symptoms. Commonly reported symptoms included feeling frustrated or impatient, sleep disturbance, being irritable, and headaches. Second, there is a subgroup of MTBI patients who endorse an extremely high number of symptoms (11 or more) at both one month and one year following injury. None of the controls endorsed this level of symptoms.

Insert Figure 1 About Here

Diagnostic Rates for the Post-Concussion Syndrome

The percentages of the sample that met ICD-10 symptom criteria for postconcussion syndrome (PCS) and DSM-IV criteria for postconcussional disorder (PCD) are presented in Table 2. Using the mild or greater ICD-10 criteria for PCS, 59% of the MTBI cases met criteria at one month post injury and 38% met

criteria at one year post injury. In the control group, 31% met the criteria. Using the moderate or greater ICD-10 criteria for the PCS, 20% of the MTBI cases met criteria at one month post injury and 12% met criteria at one year. In the control group, 0% met the criteria. At one month post injury, a significantly greater proportion of MTBI patients met PCS criteria than control participants using symptom endorsement as "mild or greater" [$\chi 2(1,160) = 8.97$, $p=.003$] and "moderate or greater" [$\chi 2(1,158) = 8.35$, $p=.007$]. At one year post-injury, a significantly greater proportion of MTBI patients met PCS criteria compared to controls when using "moderate or greater" criterion [$\chi 2(1,139) = 4.59$, $p=.036$].

Using the mild or greater DSM-IV criteria for PCD, only 1.6% of the MTBI cases met criteria at one month post injury, and 1.0% met criteria at one year. In the control group, 0% met the criteria. Using the moderate or greater DSM-IV criteria for the syndrome, 0% of the MTBI cases met criteria one month post injury, and 1.0% met criteria at one year. None of the controls met the criteria. There were too few cases of PCD to run statistical analysis. All patients who met DSM-IV PCD criteria also fulfilled ICD-10 PCS criteria.

Insert Table 2 About Here

Postconcussion Symptom Reporting Trajectory

The natural history of post-concussion symptom reporting from one month to one year post-injury was examined in each individual MTBI subject (n=101). Of the 58 patients who met criteria for ICD-10 PCS at one month based on "mild or greater" symptom reporting, 53.4% (31 patients) met and 46.6% (27 patients) did not meet the PCS criteria at one year. Of those 43 patients who did not meet the ICD-10 PCS criteria ("mild or greater" symptom reporting") at one month, 16.3% (7 patients) met and 83.7% (36 patients) did not meet the PCS criteria at one year. Thus, of those who initially met the criteria ICD-10 criteria for PCS (n=58), 46.6% improved and 53.4% remained symptomatic. Of those who did not meet ICD-10 criteria at one month (n=43), 16.3% worsened and met criteria at one year.

Correlates of Post-Concussion Symptom Reporting (Exploratory Analyses)

Descriptive statistics and group comparisons for numerous demographic and injury variables by ICD-10 PCS groups (e.g., mild or greater vs. moderate or greater) are presented in Table 3 for exploratory purposes. There were no significant differences for age, sex, or education across PCS groups at one month or one year post injury. The duration of post-traumatic amnesia was not related to PCS group membership at one month or one year post injury. Those with previous head trauma were not more likely to meet PCS criteria at one month or one year. Those with multiple bodily injuries were more likely to have PCS (based on "mild or greater" symptom reporting) at one month [$\chi 2(1,124)=5.99$, $p=.014$]. Presence of multiple bodily injuries was not related to PCS group membership at one month based on "moderate or greater" symptom reporting or at one year post injury. Those with structural abnormalities on day-of-injury CT or four-week MRI were not more likely to meet PCS criteria at one month or one year. Post-injury alcohol abuse at one month was not associated with post-concussion symptom reporting at one month or one year.

Insert Table 3 About Here

Diffusion Tensor Imaging and Post-Concussion Symptom Reporting

To examine the relation between self-reported post-concussion symptoms and DTI measures, the MTBI subsample was divided into four groups based on ICD-10 criteria for PCS: (a) PCS-Present at one month, mild or greater symptom reporting (n=39), (b) PCS-Absent at one month, mild or greater symptom reporting (n=32), (c) PCS-Present at one year, mild or greater symptom reporting (n=18), and (d)

PCS-Absent at one year, mild or greater symptom reporting (n=42).

A multivariate ROI analysis was used to examine the relation between post-concussion symptoms and DTI measures. This methodology is described in detail by Iverson and colleagues.[89] For these analyses, the 16 ROIs for FA and 10 ROIs for ADC were considered simultaneously. To examine the prevalence of low (FA) or high (ADC) scores, when all ROIs were considered simultaneously, a cut-off score for each ROI was set at 1.28 SDs below or above the mean of control values. The 1.28 SDs below the mean for each FA score for each ROI was selected as a cutoff score for unusually low FA scores (i.e., 10th percentile) and 1.28 SDs above the mean for each ADC score for each ROI was selected as a cutoff score for unusually high ADC scores (i.e., 90th percentile). The 10th and 90th percentiles were selected because the control sample was relatively small and this would create more variability, and mediate the effects of possible outliers, in the control sample. The cumulative percentages of the number of low FA scores and high ADC scores by group are presented in Table 4.

Insert Table 4 About Here

Overall, there were a greater number of low FA scores in the MTBI group compared to the control group. Chi-square analyses revealed that there was a significantly greater number of low FA scores when using 2 or more low scores as the criterion [$X^2(1,95)$ = 12.72, p<.001; 70.4% MTBI, 29.2% controls]. Also, there was a greater number of low FA scores in the MTBI group when using 3 or more low scores as the criterion [$X^2(1,95)$ = 4.63, p=.046; 40.9% MTBI, 16.7% controls]. Similarly, there were also a greater number of high ADC scores in the MTBI group compared to the control group. Chi-square analyses revealed that there was a significantly greater number of high ADC scores when using 2 or more high scores [$X^2(1,95)$ = 10.60, p= .002; 54.9% MTBI, 16.7% controls] and 3 or more high scores [$X^2(1,95)$ = 7.57, p=.006; 32.4% MTBI, 4.2% controls] as the criterion. However, there were no significant differences in DTI measures between those who met ICD-10 criteria for PCS and those who did not meet criteria for PCS.

To further examine the relation between post-concussion symptoms and DTI measures, a multifocal abnormal WM group was defined as follows: 4 or more areas of abnormally low FA values or 3 or more areas of abnormally high ADC values. The broadly normal WM group was defined as follows: less than 4 areas of abnormally low FA values and less than 3 areas of abnormally high ADC values. Based on this definition, multifocal abnormal WM was found in 12.5% of the control group (3/24) and 50.7% of the MTBI group (36/71). Patients in the MTBI group were significantly more likely to show evidence of multifocal diminished white matter than participants in the control group [$X^2(1,95)$=10.82, p=.001; RR=4.06, 95% CI (1.44-16.01)]. However, the presence of multifocal diminished white matter was not significantly associated with the presence or absence of ICD-10 PCS (see Table 5).

Insert Table 5 About Here

Multivariable Prediction of ICD-10 Postconcussional Syndrome

Two logistic regression analyses were used to determine the extent to which ICD-10 PCS, based on mild or greater symptom reporting, could be predicted at one month and one year following injury. To predict PCS at one month post injury, the variables entered into the model were: (a) pre-injury mental health problems, (b) presence/absence of MRI abnormality, (c) presence/absence of bodily injuries, (d) one-month BDI-II subscale score, and (e) total number of low FA scores and high ADC scores on DTI. The only significant predictor of ICD-10 PCS (mild or greater symptom reporting) was the one-month BDI-II subscale score [p<.001, 95% CI (1.75-7.20)].

Presence of bodily injuries neared significance (p=.052). The overall classification rate was 81.7% (74.4% PCS Present, 90.6% PCS Absent; Cox & Snell R^2=.397, Nagelkerke R^2=.531).

To predict PCS at one year post injury, the variables entered into the model were: (a) pre-injury mental health problems, (b) presence/absence of MRI abnormality, (c) presence/absence of bodily injuries, (d) one-month BDI-II subscale score, (e) one-month RPSQ total score, (f) total number of low FA scores and high ADC scores on DTI, and (e) one-year BDI-II subscale score. At one year, only one-month symptom reporting [RPSQ total score, p=.001, 95% CI (1.10-1.48)] was a significant predictor of ICD-10 PCS (mild or greater symptom reporting). The overall classification rate was 81.7% (66.7% PCS Present, 88.1% PCS Absent; Cox & Snell R^2=.391, Nagelkerke R^2=.555).

Discussion

This study prospectively examined the prevalence of, and factors related to, persistent postconcussion symptom reporting following MTBI. We hypothesized that patients who sustained complicated MTBIs would perform more poorly on memory testing and report more post-concussion symptoms at one month but not one year following injury. Those with complicated MTBIs did not perform more poorly on memory testing and they did not report more post-concussion symptoms at one month or one year post injury. Also, patients with longer periods of post-traumatic amnesia were not more likely to report more post-concussion symptoms. Thus, our results do not provide support for the hypothesis that patients with greater injury severity will report more post-concussion symptoms than patients with milder injuries.

To address the second and third hypotheses, we examined whether MTBI patients with pre-existing mental health problems or current affective symptoms of depression would report greater post-concussion symptoms than those without pre-injury mental health problems or current problems with depression. Pre-injury mental health problems[54-57] and ongoing problems with depression[57,58,90,91] have been identified as risk factors for slow or incomplete recovery following MTBI. In fact, it is well established in the literature that people who sustain a MTBI are at increased risk for developing depression,[41,92] with prevalence rates varying from 12% to 44% in the first three months following injury.[19,93-97] In this study, the prevalence of pre-injury mental health problems was low because patients with a known psychiatric history were initially excluded during recruitment. However, some patients brought up some pre-injury problems with depression and anxiety in the neuropsychological evaluation only after recruiting them into the study.

In the current study, and consistent with our second hypothesis and previous studies,[41,92,98] those with a pre-injury history of mental health problems were more likely to have postconcussion symptoms at one month. At one year follow-up, pre-injury mental health problems were not significantly associated with postconcussion symptom reporting. We tried to reduce the overlap between post-concussion symptom reporting and depression symptom reporting by conducting the analyses with a reduced item set for the BDI-II. Only ten of the 21 symptoms from the BDI-II, believed to have the least overlap with symptoms of MTBI and being most representative of depression, were selected. As a group, MTBI patients reported more depressive symptoms at one month post-injury compared to controls. At one year, the groups did not differ in depression symptom reporting. In support of the third hypothesis, post-concussion-like symptoms had a significant positive correlation with affective symptoms of depression at both one month

and one year following injury. Similar to previous studies,[92,94] our results lend support to the view that depression should be evaluated as part of the assessment protocol after MTBI.

In the present study, the MTBI patients were significantly more likely to show multifocal areas of diminished white matter on DTI compared to control subjects—which is consistent with our fourth hypothesis. Thus, this study is consistent with many previous studies showing that patients with MTBIs show differences on DTI relative to controls.[for a review see 67,99,100] For the fifth hypothesis, we predicted that white matter changes would be associated with post-concussion symptom reporting because some studies have suggested that compromised microstructural white matter might be associated with increased post-concussion symptom reporting following MTBI.[69,101-104] However, inconsistent with the final hypothesis, those MTBI patients who had multifocal white matter changes on DTI did not report more symptoms than those with broadly normal white matter. In other words, the presence of multifocal white matter changes was not associated with the presence of the persistent post-concussion symptoms. Several published studies have found a relationship between white matter abnormalities and PCS,[68-74] although some reported no association.[46,67,75]

The present study was large, carefully controlled, and prospective. We carefully excluded most obvious premorbid conditions (substance abuse, psychiatric disorders, previous moderate-severe brain injuries, developmental cognitive disorders, and other medical conditions resulting in cognitive changes) to rule out the possible influence of premorbid moderator variables and to avoid possible bias due to these confounding factors. Furthermore, we ensured that none of the patients were involved in litigation, and had no financial incentives to exaggerate their symptoms.

This study has some methodological limitations and issues that should be considered. First, the majority (96%) of patients in the sample had a GCS of 15 with only a few having a GCS of 14. Thus, the sample can be considered to be skewed toward the less severe end of injury severity spectrum in MTBI. Second, the study included age and gender matched community controls as a comparison group instead of an orthopedically-injured trauma control group. In general, trauma control subjects are a better and more generalizable control group. Third, self-reported pain was not examined in the current study. Post-concussion-like symptoms are often endorsed by patients with chronic pain,[37,38] so it is important that pain be taken into account in future studies. Fourth, the imaging control group was a convenience sample that did not undergo psychological testing. Using separate comparison groups for outcome measures and imaging is a weakness that needs to be taken into account when interpreting results. Fifth, the inclusion/exclusion criteria were very strict and resulted in a slight female majority. For this study, a total of 2,479 consecutive patients from the ER were screened for inclusion between October 2006 and May 2009. As expected based on previous literature, the total sample had a male preponderance (males 1,406, females 1,073). However, applying strict inclusion/exclusion criteria excluded 94.8% of MTBI patients, leaving only 126 patients in the final sample. Finally, in this study a cross-sectional, not prospective, design was used for DTI (i.e., subjects were imaged only once).

In conclusion, the rate at which the post-concussion syndrome is diagnosed varies greatly based on whether ICD-10 or DSM-IV criteria are used,[98,105-107] and whether the researcher or clinician requires the symptoms to be mild or greater or moderate or greater on the rating scale. Using ICD-10 criteria and mild or greater symptom reporting, 59% of the

MTBI sample met criteria at one month and 38% met criteria at one year. However, 31% of the healthy control sample also met criteria for the syndrome—illustrating a high false positive rate. Of those who met criteria at one month, 47% improved and 53% remained symptomatic at one year. Notably, of those who did not meet criteria at one month, 16% worsened and met criteria at one year. Significant predictors of ICD-10 PCS at one month were pre-injury mental health problems and the presence of extra-cranial bodily injuries. Age, gender, and prior MTBI were not significant predictors. Being symptomatic at one month was as significant predictor of being symptomatic at one year, and depression was related to PCS at both one month and one year. Intracranial abnormalities visible on MRI were present in 12.1% (15/124) of this sample, and multifocal areas of unusual white matter were present in 50.7% of the subgroup who underwent DTI (compared to 12.4% of controls). However, these structural MRI abnormalities and microstructural white matter findings were not associated with greater post-concussion symptom reporting. Simply put, greater putative damage to the brain was not associated with greater symptom reporting. Clearly, no simple theory relating to the etiology of post-concussion symptom reporting following MTBI has strong explanatory value. The manifestation of post-concussion symptoms likely represents the cumulative effect of multiple variables, such as genetics, mental health history, current life stress, general medical problems, chronic pain, depression, and substance abuse. How people report their symptoms also can be influenced by personality factors and the presence of possible future financial gain (e.g., personal injury litigation or disability determinations). The extent to which damage to the structure of the brain contributes to the persistence of post-concussion (or post-concussion-like) symptoms following MTBI remains unclear.

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Declaration of Interest

Dr. Iverson has received past research funding from several test publishing companies, including ImPACT Applications, Inc., CNS Vital Signs, and Psychological Assessment Resources (PAR, Inc.). He receives royalties for two books in neuropsychology and one test (WCST-64). He has a clinical practice in forensic neuropsychology involving individuals who have sustained mild TBIs (including athletes). He is a co-investigator, collaborator, or consultant on grants relating to mild TBI funded by several organizations. The authors report no declarations of interest.

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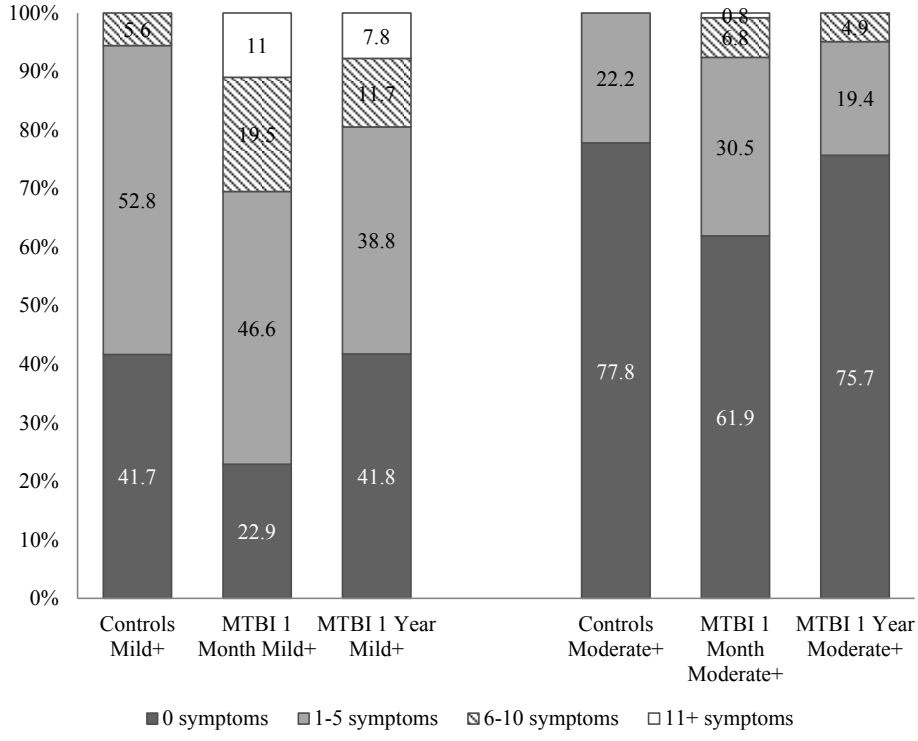

Figure 1. Total number of symptoms endorsed by MTBI and control group presented in percentages

Table 1. Individual RPSQ symptom reporting at one month and one year post injury.

	MTBI 1 Month N = 126		Mild+	Mod+	MTBI 1 Year N = 103		Mild+	Mod+	Controls N = 36		Mild+	Mod+	1 month vs. 1 year		1 month vs. controls		1 year vs. controls	
Symptom	M	SD	%	%	M	SD	%	%	M	SD	%	%	p†	d	p‡	d	p‡	d
1. Headaches	1.33	.99	40.5	11.1	.76	.93	26.2	3.9	.50	.94	19.4	5.6	<.001	.60	<.001	.85	.158	.28
2. Feelings of Dizziness	1.21	.96	34.9	9.5	.76	.91	21.4	3.9	.36	.76	16.7	0.0	<.001	.48	<.001	.93	.021	.46
3. Nausea and/or Vomiting	.66	.83	14.3	3.2	.25	.50	2.9	0.0	.11	.40	2.8	0.0	<.001	.60	<.001	.75	.091	.30
4. Noise Sensitivity	.67	.92	15.9	6.3	.54	.92	15.5	3.9	.11	.52	2.8	2.8	.123	.14	<.001	.67	.001	.53
5. Sleep Disturbance	1.03	1.20	34.1	13.5	.71	1.04	24.3	9.7	.44	.91	16.7	5.6	.007	.28	.002	.52	.179	.27
6. Fatigue, tiring more easily	1.56	1.21	51.6	23.0	.98	1.16	30.1	11.7	.19	.58	8.3	0.0	<.001	.49	<.001	1.28	<.001	.78
7. Being Irritable, easily angered	.98	1.06	33.3	9.5	.64	.95	20.4	4.9	.61	1.05	22.2	5.6	.017	.34	.064	.35	.875	.03
8. Feeling Depressed or Tearful	.67	.94	21.4	5.6	.52	.99	15.5	5.8	.14	.54	2.8	2.8	.192	.16	<.001	.62	.005	.44
9. Feeling Frustrated or Impatient	.87	1.09	30.9	11.4	.54	.93	15.5	5.8	.58	1.08	19.4	8.3	.004	.32	.167	.27	.833	.04
10. Forgetfulness, poor memory	1.02	1.06	36.0	8.0	.86	1.03	32.0	5.8	.39	.69	11.1	0.0	.275	.12	<.001	.64	.003	.50
11. Poor Concentration	1.02	1.07	36.3	9.7	.75	1.04	22.3	7.8	.39	.77	16.7	0.0	.019	.26	<.001	.63	.031	.37
12. Taking Longer to Think	.91	.98	31.2	6.4	.58	.95	17.5	5.8	.06	.23	0.0	0.0	.003	.34	<.001	1.05	<.001	.68
13. Blurred Vision	.49	.81	13.5	3.2	.37	.74	11.7	1.9	.00	.00	0.0	0.0	.113	.15	<.001	.78	<.001	.68
14. Light Sensitivity	.54	.82	14.3	3.2	.44	.81	13.6	1.9	.11	.47	5.6	0.0	.174	.12	<.001	.58	.004	.46
15. Double Vision	.23	.53	4.8	0.0	.15	.41	1.9	0.0	.00	.00	0.0	0.0	.131	.17	<.001	.56	<.001	.49
16. Restlessness	.68	.93	25.4	3.2	.42	.81	11.7	2.9	.39	.77	16.7	0.0	.013	.30	.058	.32	.854	.04
Total score	10.4	10.7	---	---	6.8	9.6	---	---	3.7	4.9	---	---	<.001	.36	<.001	.71	.015	.36

Note: † p values based on Paired Samples T Test, ‡ p values based on Independent Samples T Test; M=mean; MTBI=mild traumatic brain injury; RPSQ=Rivermead Postconcussion Symptom Questionnaire; SD=standard deviation

Table 2. Rates of participants who meet the criteria for post-concussion syndrome (PCS) depending on different diagnostic criteria

	MTBI group				Control group	
	1 Month n (%)		1 Year n (%)		n (%)	
Criteria	PCS Absent	PCS Present	PCS Absent	PCS Present	PCS Absent	PCS Present
ICD-10 Mild or greater symptoms	51 (41.1)	73 (58.9)	64 (62.1)	39 (37.9)	25 (69.4)	11 (30.6)
ICD-10 Moderate or greater symptoms	98 (80.3)	24 (19.7)	91 (88.3)	12 (11.7)	36 (100)	0 (0)
DSM-IV Mild + RTW >30 days	120 (98.4)	2 (1.6)	100 (99.0)	1 (1.0)	36 (100)	0 (0)
DSM-IV Moderate + RTW >30 days	0 (0)	0 (0)	100 (99.0)	1 (1.0)	36 (100)	0 (0)

Note: Sample size for 1 month: n = 124 for ICD-10 mild, 122 for ICD-10 moderate, n= 122 for DSM-IV; Sample size for 1 year: n = 103 for ICD-10; n = 101 for DSM-IV; Sample size for control group: n=36; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders-IV, ICD-10= International Classification of Diseases-10th edition, MTBI= Mild Traumatic Brain Injury, PPCS=Persistent Post-Concussion Syndrome, RTW=Return to Work.

Table 3. Demographic, pre-injury, and injury characteristics of the MTBI patients

	MTBI group											
	1 Month (N=126)						1 Year (N=103)					
	Mild + n=124			Moderate + n=122			Mild + n=103			Moderate + n=103		
	PCS+ n=73, 58.9 %	PCS- n=51, 41.1%	p	PCS+ n=24, 19.7%	PCS- n= 98, 80.3%	p	PCS+ n=39, 37.9%	PCS- n=64, 62.1%	p	PCS+ n=12, 11.7%	PCS- n= 91, 88.3%	p
Women, n (%)	45 (61.6)	25 (49.0)	.163	16 (66.7)	53 (54.1)	.265	22 (56.4)	34 (53.1)	.745	6 (50.0)	50 (54.9)	.747
Age, mean years (SD)	38.9 (13.4)	36.2 (13.6)	.275	39.1 (13.7)	37.4 (13.6)	.583	39.8 (13.6)	37.7 (13.3)	.435	37.8 (13.9)	38.6 (13.4)	.863
Education, years (SD)	12.8 (2.9)	12.3 (2.4)	.281	12.5 (2.3)	12.7 (2.9)	.763	12.8 (3.0)	12.7 (2.7)	.898	12.3 (3.2)	12.8 (2.7)	.500
PTA, minutes (SD)	164.4 (333.2)	234.7 (377.6)	.281	206.2 (397.4)	194.3 (345.1)	.884	147.8 (269.7)	283.1 (425.4)	.053	146.4 (252.2)	243.73 (392.3)	.406
BDI-II subscale score, mean (SD)	3.34 (3.8)	.63 (1.3)	<.001	4.83 (4.4)	1.49 (2.5)	.001	2.91 (4.1)	.95 (2.53)	.010	6.54 (5.2)	1.06 (2.4)	.004
AUDIT												
0-9	56	43	.299	18	79	.542	32	56	.446	8	80	.072
≥ 10	17	8		6	19		7	8		4	11	
CT												
Normal	67	47	1.00	23	89	.685	36	53	.737	12	81	.364
Abnormal	6	4		1	9		3	7		0	10	
MRI												
Normal	65	44	.642	23	84	.299	37	53	.736	12	78	.222
Abnormal	8	7		1	14		2	11		0	13	
Previous psychiatric symptoms												
No	65	50	.080	19	95	.007	36	60	1.00	10	86	.188
Yes	8	1		5	3		3	4		2	5	
Previous head trauma												
No	47	37	.339	14	68	.301	27	44	.959	8	63	1.00
Yes	26	14		10	30		12	20		4	28	
Multiple injury												
No	47	43	.014	14	75	.072	28	48	.719	8	68	.727
Yes	26	8		10	23		11	16		4	23	

Note: AUDIT= The Alcohol Use Disorders Identification Test, CT=computed tomography, PCS += postconcussional syndrome present, PCS - = postconcussional syndrome absent, Mild + = mild or greater symptom reporting, Moderate + = moderate or greater symptom reporting, MRI=magnetic resonance imaging, MTBI = mild traumatic brain injury, PTA=posttraumatic amnesia, SD=standard deviation

Table 4. Cumulative frequency distributions of low FA and high ADC scores, by group, and stratified by the presence or absence of ICD-10 Postconcussional Syndrome (based on symptom rating of "mild or greater").

	Low FA Scores				High ADC Scores				Low FA Scores By ICD-10 Dx At One Month				High ADC Scores By ICD-10 Dx At One Month				Low FA Scores By ICD-10 Dx At One Year				High ADC Scores By ICD-10 Dx At One Year			
	MTBI FA Scores (n = 71)		Controls FA Scores (n = 24)		MTBI ADC Scores (n = 71)		Controls ADC Scores (n = 24)		PCS + (n = 39)		PCS - (n = 32)		PCS + (n = 39)		PCS - (n = 32)		PCS + (n = 18)		PCS – (n = 42)		PCS + (n = 18)		PCS – (n = 42)	
Unusual Scores	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp
6	5	7.0	0	-	1	1.4	0	-	3	7.7	2	6.3	0	-	1	3.1	0	-	3	7.1	0	-	1	2.4
5	6	15.5	1	4.2	1	2.8	0	-	3	15.4	3	15.6	0	-	1	6.3	1	5.6	4	16.7	1	5.6	0	-
4	7	25.4	1	8.4	7	12.7	0	-	4	25.6	3	25.0	4	10.3	3	15.6	3	22.2	4	26.2	1	11.1	5	14.3
3	11	40.9	2	16.7	14	32.4	1	4.2	7	43.6	4	37.5	8	30.8	6	34.4	6	50.0	4	35.7	4	33.3	10	38.1
2	21	70.4	3	29.2	16	54.9	3	16.7	14	79.5	7	59.4	9	53.9	7	56.3	6	88.9	11	61.9	4	55.6	10	61.9
1	15	91.6	12	79.2	19	81.7	12	66.7	6	94.9	9	87.5	12	84.6	7	78.1	2	100.0	11	88.1	5	83.3	7	78.6
0	6	100.0	5	100.0	13	100.0	8	100.0	2	100.0	4	100.0	6	100.0	7	100.0	0	-	5	100.0	3	100.0	9	100.0

Note: dx = diagnosis, cp = cumulative percentage, f = Frequency; FA = fractional anisotropy, ADC=apparent diffusion coefficient, PCS += postconcussional syndrome present, PCS - = postconcussional syndrome absent, MTBI = mild traumatic brain injury

Table 5. The presence of multifocal abnormal white matter by group.

				1 Month ICD-10 Mild or Greater (MTBI)			1 Month ICD-10 Moderate or Greater (MTBI)			1 Year ICD-10 Mild or Greater (MTBI)			1 Year ICD-10 Moderate or Greater (MTBI)		
	MTBI (n=71)	Controls (n=24)	p	PCS + (n=39)	PCS – (n=32)	p	PCS + (n=15)	PCS – (n=56)	p	PCS + (n=18)	PCS – (n=42)	p	PCS+ (n=5)	PCS – (n=55)	p
Broadly Normal WM	35 (49.3%)	21 (87.5%)	.001; RR 4.06, 95% CI	20 (51.3%)	15 (46.9%)	.712; RR 1.09, 95% CI	9 (60.0%)	26 (46.4%)	.351; RR 0.75, 95% CI	9 (50.0%)	19 (45.2%)	.740; RR 0.91, 95% CI	4 (80%)	24 (43.6%)	.175; RR 0.36, CI
Abnormal WM	36 (50.7%)	3 (12.5%)	1.44-16.01	19 (48.7%)	17 (53.1%)	0.68-1.77	6 (40.0%)	30 (53.6%)	0.38-1.45	9 (50.0%)	23 (54.8%)	0.53-1.56	1 (20%)	31 (56.4%)	0.06-2.08

Abbreviations: ADC=apparent diffusion coefficient, CI= confidence interval; FA=fractional anisotropy, PCS=postconcussional syndrome, RR=relative risk, WM=white matter