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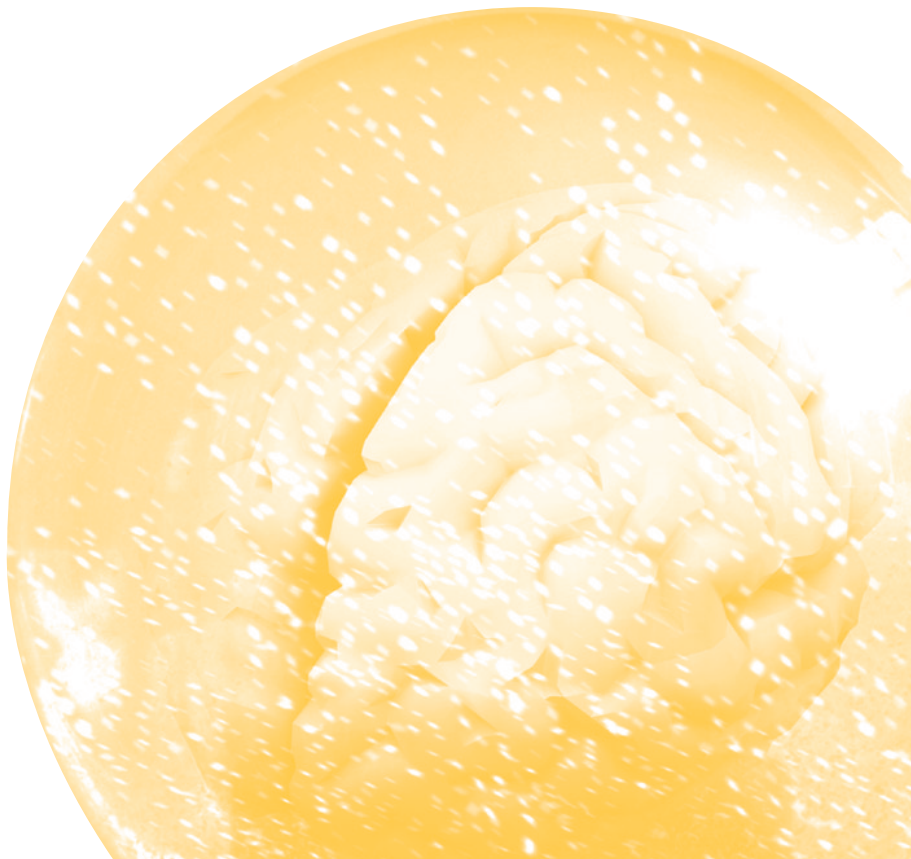For additional information about this publication click this link.
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Maja Stulemeijer

Recovery after Mild Traumatic Brain Injury

An integrative approach on understanding complaints,
performance and functional outcome

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Een wetenschappelijke proeve op het gebied
van de Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het college van decanen
in het openbaar te verdedigen op vrijdag 4 november 2009
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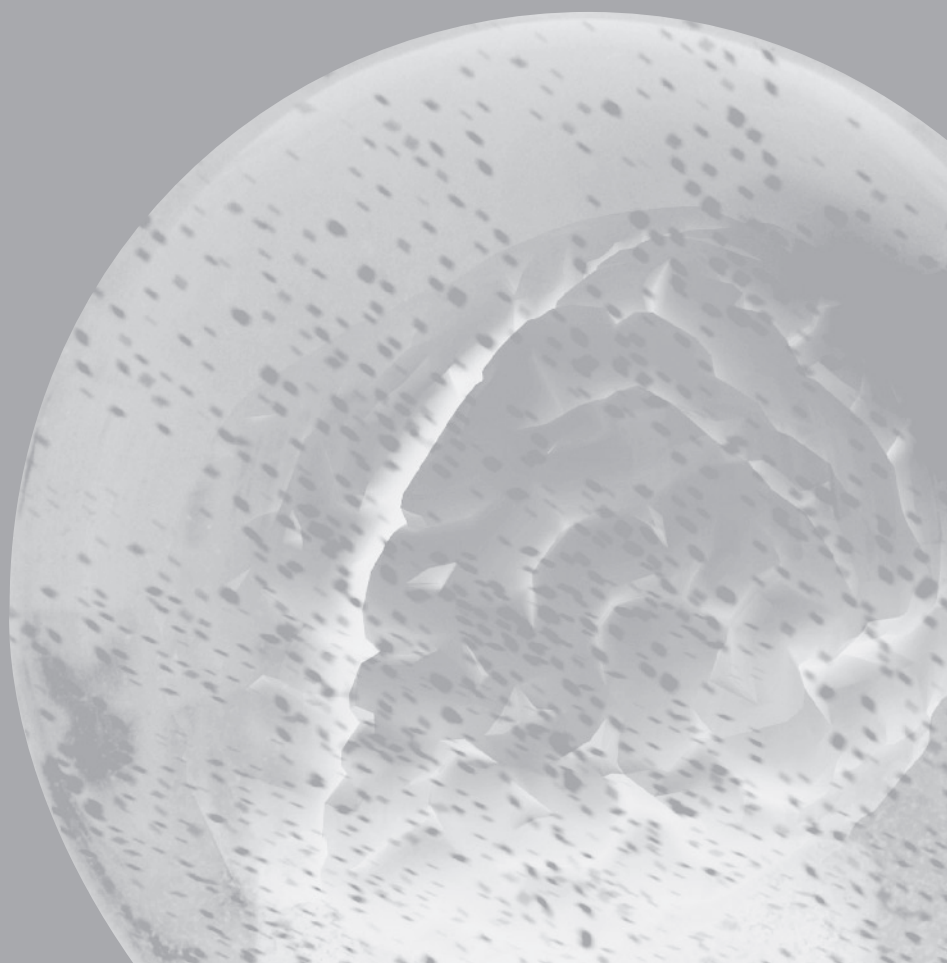
geboren op 13 oktober 1977
te Utrecht

Opgedragen aan twee vrouwen die mij zijn voorgegaan in de zoektocht: mijn oma Christina Stulemeijer-Hagemeijer (1910- 2000) en mijn moeder Vera Stulemeijer-van der Laan.

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Chapter I

General Introduction

Mild Traumatic Brain Injury (MTBI) is one of the most prevalent neurological conditions world-wide. Mortality in this population is very low, neurosurgical interventions are rarely needed and most patients show a spontaneous, quick and full recovery. Nevertheless, MTBI is considered to be an important public-health concern as a minority of patients will develop debilitating symptoms that may persist for up to years after injury. Typically, these so-called 'post-concussional symptoms' are present without evidence of gross cognitive impairments or other neurological abnormalities, an observation that gave rise to a continuing debate about possible causes for this apparent discrepancy. One point of agreement, however, is that to fully understand why some MTBI patients do not recover favourably, we need to know more about these patients than simply the characteristics of their injury. Already in 1937 the British neurologist Sir Charles Symonds stated that "it is not only the kind of injury that matters, but the kind of head that is injured that determines recovery of function" (Symonds 1937). With this statement in mind, the studies presented in the current thesis were designed. This general introductory chapter starts with providing some basic facts and figures about MTBI and its natural course. To provide the background for our study, current knowledge and open questions regarding patients in which post-concussional symptoms persist will be discussed. Finally, a description of the research setting will be provided as well as a brief overview of the aim and contents of each chapter. The studies in this thesis aim to gain more insight in determinants of post-concussional symptoms (especially fatigue and cognitive complaints), neuropsychological test performance and return to work six months after MTBI by integrating neurological characteristics of the injury with a patients' physical and psychological functioning.

1.1 Mild Traumatic Brain Injury: basic facts and figures

1.1.1 TBI severity grading and terminology
Traditionally, TBI severity is classified along a continuum from mild to moderate to severe. The Glasgow Coma Scale (GCS) is by far the most recognized and widely used method for grading TBI severity (Teasdale 1974). As outlined in Table 1.1, the GCS assesses gross neurological status across three core areas of motor function, verbal responding, and the patients' ability to open the eyes voluntarily or in response to external commands and stimuli. The most basic approach to scoring TBI severity is based solely on the GCS score on admission to the Emergency Department; the injury of patients with an admission GCS of 13 – 15 is classified as 'mild', a score of 9 – 12 as 'moderate', and 3 – 8 as 'severe'. However, the GCS was not developed to assess mild TBI, but rather the depth of coma following severe TBI, and it has limited utility and sensitivity in the detection of MTBI (discussed in McCrea 2008, Chapter 3). An overwhelming majority of patients with MTBI have an admission score of 15 and the GCS score is largely unaffected by defining MTBI characteristics like symptoms (e.g. headache and nausea) or alterations in mental status (e.g. confusion and disorientation). Therefore other classification systems have been developed to grade milder TBI. In this thesis, the criteria of the European Federation of Neurology (EFNS) are used to define MTBI. Following this criterion, MTBI is defined as a history of impact to the head with or without loss of consciousness (LOC) ≤30 minutes and with or without PTA and a hospital admission GCS of 13-15. MTBI severity can be further specified into three grades, developed to guide for performing acute CT imaging such that patients at risk for

intracranial complications requiring surgery are identified (see Table 1.2) (Vos 2002). There is large overlap between the EFNS criteria and others widely used operational definitions but there are differences as well. For example, in the criteria developed by the American Congress of Rehabilitation a patient will be classified as 'moderate' when the duration of PTA is greater than 24 hours (Kay 1993). We use the term Mild Traumatic Brain Injury, but other terms such as minor/mild head injury, mild/minor closed head injury and concussion are used in other studies and describe more or less the same category of patients.

1.1.2 Epidemiology and impact

Traumatic brain injury is one of the most prevalent neurological conditions world-wide (Hirtz 2007). Based on traditional case definitions and acute injury characteristic criteria (see Table 1.1), it is estimated that 80-90% of all treated TBIs are considered mild (Tagliaferri 2006). In a 2004 report, the WHO Collaborating Centre Task Force on MTBI estimated the incidence of hospital-treated MTBI to be 100-300 per 100.000 (Cassidy 2004). This estimation is clearly an underestimation of the true incidence of people with a mild head injury, as patients that are discharged from the Emergency Department (ED) were not included in this estimation, neither were those who sought treatment in non-hospital settings (e.g. general practitioner) and the many patients that did not seek medical contact at all (Hyder 2007, Jennett 2006, Langlois 2006, Sosin, 1991). Several factors affect an individual's risk of suffering MTBI. For example, incidence rates in men, are approximately twice that of females and are highest in people younger than 24 and older than 74 (Bazarian 2005, Jennet 2006, Meerhoff 2000.). In terms of lifestyle

Table 1.1. Assessment of level of consciousness: Glasgow Coma Scale (GCS).

Motor (M)		Verbal (V)	
6	Obeys verbal commands	5	Fully oriented and converses
5	Localizes to noxious stimuli	4	Disoriented and converses
4	Normal flexion to noxious stimuli	3	Voices appropriate words
3	Abnormal flexion to noxious stimuli	2	Makes incomprehensible sounds
2	Extension to noxious stimuli	1	No vocalization
1	No response to noxious stimuli		
Eye opening (E)		**Scoring**	
4	Opens eyes spontaneously		GCS = E + M + V
3	Opens eyes to verbal commands		Mild = 13-15
2	Opens eyes to noxious stimuli		Moderate = 9-12
1	No eye opening		Severe = 3-8

Table 1.2. European Federation of Neurological Societies classification of MTBI based on risk factors for acute intracranial complications (Vos 2002). †

Category 1:	Category 2:	Category 3:
GCS 15 no LOC no PTA no risk factors*	GCS 15 LOC < 15 minutes PTA < 60 min no risk factors*	GCS 13-14 or GCS 15 with risk factors*

† GCS = Glasgow Coma Scale; PTA = Post Traumatic Amnesia; LOC = Loss of Consciousness
* Risk factors for intracranial complications: ambiguous accident history, high-energy accident, trauma above clavicles, focal neurological deficits, seizure, coagulation disorders, vomiting, severe headache, intoxication with alcohol/drugs, continued post traumatic amnesia, retrograde amnesia more than 30 minutes

factors, substance abusers are at significantly higher risk of TBI, as are people with certain professions (such as military personnel), and those performing high risk sports (in McCrea 2008). Leading causes of MTBI are related to transportation (motor vehicle crashes, bicycle accidents, and pedestrian injuries), followed by falls, assaults, and sports. The total economic costs and health care consumption associated with MTBI are substantial. While the intensity of care is less than in moderate and severe TBI (e.g. no intensive care, surgery or lengthy hospitalization), the cost equation is balanced by its sheer volume (Max 1991). The one existing epidemiologic study in the Netherlands estimated the population incidence of TBI to be 836/ 100.000, with a hospital-admission incidence of 88/100.000 (Meerhoff 2000). In this study, 99% of the ED-admitted patients suffered a mild TBI. Despite its favourable natural course, 'skull-brain injuries', are estimated to be the forth most costly injuries in the Netherlands (Meerdink 2006).

1.1.3 Natural history
TBI results from an external mechanical force causing acceleration, deceleration or rotation of the head and neck. This force causes abrupt displacement of the brain in the skull, and generates intracranial pressure waves which may deform brain tissue and depress skull bone (Bayly 2005, Giza 2004, Shaw 2002). These pressure waves trigger a multilayered neurometabolic cascade including ionic shifts, abnormal energy metabolism, diminished cerebral blood flow, and impaired neurotransmission. The time course of return to normal cerebral function is not entirely clear, but the bulk of evidence suggests a gradual reversal of physiologic abnormalities and return to normal brain metabolic function within days or weeks after MTBI. (e.g. Bergsneider 2001, Jacobs 1994, Umile, 2002). In case of MTBI, the impact to the head results in a brief period of unconsciousness, usually seconds to minutes. In some cases there is no loss of consciousness but simply a brief period of dazed consciousness. Amnesia for the accident itself and some period before (retrograde amnesia) and after the impact (anterograde or post-traumatic amnesia) are other hallmark characteristics of TBI. Commonly, the inability to lay down continuous memories ranges from minutes to a few hours in MTBI patients. In addition, MTBI is accompanied by rapid onset of temporary neurological impairment and acute clinical symptoms such as nausea, dizziness and a raised sensitivity to light and sound. Although MTBI is essentially a temporary dysfunction of the brain, it may cause structural damage to the brain or skull in some patients. Due to its sensitivity to detect lesions requiring surgical interventions, CT-imaging is routinely applied on the ED. An estimated 3-10% of these CT scans reveal a traumatic abnormality (Jagoda 2002, Smits 2005). The most common abnormalities on CT include cerebral contusions, subdural hematomas, and oedema. More sensitive neuroimaging techniques, such as magnetic resonance imaging (MRI) show abnormalities in 10-57 % of patients (Bazarian 2006). MTBI-related mortality is very low (< 0.5%) and neurosurgical interventions are seldom required ($\approx$ 1%) (Alexander 1995, Iverson 2005, Geijerstam af 2003). Generally, patients return home directly from the ED or after an overnight stay at the hospital. We now know that the adage that one should take bed rest after suffering MTBI is no more effective in reducing complaints than no bed rest at all (Kruijk de 2002). Nowadays, patients are instructed to rest only for a couple of days as needed and then start with gradually resuming their daily activities including work (Nederlandse Vereniging voor Neurologie 2001, Vos 2002). Patients typically report a cluster of physical (including headache, dizziness, nausea, noise and light sensitivity, disturbed vision, sleep disturbance and fatigue), cognitive (including forgetfulness, poor concentration and needing longer to think) and emotional symptoms (including

irritability, depressed mood, frustration and restlessness) after suffering an MTBI (King 1995). Together these symptoms are often referred to as 'post-concussional symptoms'. Typically, the symptoms decrease over time, and the majority of patients recovers fully and spontaneously within a few months (e.g. Belanger 2005a, McCrea 2008, McHugh 2006). When symptoms do linger, they are usually mild and do not interfere with daily functioning of the patient. To understand why MTBI continues to be the subject of intense debate among clinicians, researchers and health-care policy makers alike, we have to turn to those patients that do not follow this favourable course of recovery– sometimes referred to as the miserable minority.

1.1.4 The 'miserable minority'

A minority of MTBI patients continues to experience symptoms for months to years after injury. Fatigue and cognitive complaints are almost invariable in the Top 5 of most frequent symptoms (e.g. Eyres 2005, King 1998, Røe 2006). In these patients, the persisting complaints are perceived as severe and distressing. They affect many aspects of life, and may result in substantial decline in social and occupational functioning. Generally, this subgroup of patients becomes progressively preoccupied with the symptoms and attributes them to a neurological cause. Medical consumption is usually high (Nolin 2006a). The prevalence rates of such 'post-concussional syndrome' at six months vary widely, from <5% to 25% depending on the operational criteria used, the methodology of the study and the population examined (e.g. Bohnen 1992b, Ingebritsen 1998, Kashluba 2004, McHugh, 2006, Paniak 2002, 2003). Left untreated, the prognosis seems rather poor. Studies on the time course of recovery have shown that symptoms that persist at three months after injury tend to become chronic (e.g. Bohnen 1994). Early interventions aimed at promoting adequate coping-skills and adjusting catastrophic interpretations

of benign bodily symptoms, may have great value in reducing complaints and/or prevent them from becoming chronic (Bryant 2005, Paniak 2000, in Carr 2007). Unfortunately, the scientific foundations for reliable early identification of patients at risk for developing persisting complaints are weak (Perel, 2006). Which factors account for the development and persistence of post-concussional symptoms is the subject of an intense debate that started back in the 19th century and continues to stir the emotions of clinicians and researchers alike today (see Box 1 on page 17 for an overview). Although the notion that any health problem – including MTBI- is influenced by biological, psychological and social factors has gained wide acceptance among researchers in the field of TBI, there is a lack of consensus about the relative importance of these factors for understanding post-concussional symptoms and its course (reviewed in King 2003, Iverson 2005). To provide the background for the studies in this thesis, several dilemmas and caveats in current knowledge on MTBI outcome in general and post-concussional symptoms specifically, will be briefly discussed.

1.2 MTBI outcome: dilemmas and caveats

1.2.1 Assessment of outcome

Often outcome assessment is limited to brief self-report questionnaires containing only generic complaints. Using correlational analysis, the strength of the association between late complaints and traditional injury characteristics (such as CT abnormalities or the duration of PTA) is then tested in order to draw inferences about the role of trauma on outcome (e.g. Ingebritsen 2003, McCullagh 2001, Røe 2006, Sadowski-Cron 2006). This approach is highly questionable as many of the symptoms reported by MTBI patients, such as fatigue or concentration difficulties, also occur frequently in other patient populations without head injury, have high

base rates in the general population and are part of the criteria of psychiatric disorders like depression and post-traumatic stress disorders (Gouvier 1988, Iverson 1997). Also, it has been shown that the relationship between trauma-induced neurophysiological disturbances and perceived symptoms usually weakens markedly in the hours to days after injury (reviewed by McCrea 2008). Even if subtle structural or functional disturbances would persist beyond this time-point, as experimental and animal studies suggest (e.g. Bergsneider 2001, Jacobs 1994, Umile 2002), more advanced techniques then standard CT will be required to detect them (Belanger 2007). Then again, even though advances in imaging techniques will undoubtedly augment our understanding of how MTBI impacts the brain, it will probably not be sufficient to fully understand the impairments reported by 'the miserable minority'. Thus, to better understand the 'bio', 'psycho' and 'social' correlates of post-concussional symptoms, simultaneous assessment of various health dimensions is required (covering at least injury severity, physical functioning, cognitive functioning and emotional functioning), as well as the use of various methods such as a neuropsychogical test battery and Magnetic Resonance Imaging (MRI) (see 1.2.2). Regarding injury severity there is preliminary evidence that physical limitations or pain associated with concurrently sustained injuries to other parts of the body might also lead to increased levels of post-concussion-like symptoms (Binder 1986, Iverson 1997, Kibby 1997, Satz 1999). The inclusion of a control group therefore is also imperative when one aims to answer questions regarding the prevalence or specificity of post-concussional symptoms.

1.2.2 The case of cognitive complaints
Whether or not MTBI can have a detrimental effect on cognitive functioning beyond the acute stage, and whether the self-perceived cognitive complaints reflect such underlying deficits are among the most central questions

in MTBI research today. It is known that the temporal and frontal brain regions that are vulnerable for traumatic impact due to their anatomical location play a critical role in learning and memory (Bigler 2007, Fernandez 2001, Salmond 2005). Possibly, dysfunction of these regions may underlie the experienced cognitive difficulties. Several studies using neuropsychological tests found small but significant decrements in cognitive functioning (Barth 1983, Leininger 1990, Vanderploeg 2005), but the interpretation of these findings is complicated as injury characteristics have shown only very weak relations to test performance. Furthermore, cognitive complaints are generally more prominent than the impairments found on neuropsychological tests. However, the reverse pattern has also been found, and the strength of the association differs considerably between studies (Belanger 2005b, Binder 1997, Gfeller 1994, Hofman 2002, Leiniger 1990, McHugh 2006). Previous studies have shown that poor effort (= the non-specific allocation of energy to mental activities) can be a major contributor to poor neuropsychological test performance in MTBI patients (Binder 2003, Green 2001, Keller 2000, Moore 2004, Ross 2006) If patients do not exert sufficient effort during the performance of a neuropsychological test, the obtained results might be invalid. Measuring effort however, is no a straightforward task. Although many advances are made in the development of measures that enable discrimination between poor and adequate effort, a 'gold standard' is still lacking. Most of these tests, usually referred to as 'effort tests' or 'validity tests', are based on principles such as performing under chance level or performing under a norm-based criterion. (Rogers 1993) Unfortunately, outside the mediolegal, effort tests are rarely used, implicitly assuming that effort level will be adequate if no external gain is expected. However, this assumption has not yet been examined. Also, there is little known about the impact of other factors

such as pain, anxiety or fatigue that potentially may affect the amount of effort a patient is able and willing to exert during testing (Leininger 1990, Ross 2006, Suhr 1997). Thus, further investigation of test validity and its correlates is warranted. In addition, the use of advanced neuro-imaging techniques such as functional Magnetic Imaging (fMRI) might add information above and beyond that provided by traditional techniques (e.g. Belanger 2007). fMRI works by detecting the changes in blood oxygenation and flow that occur in response to neural activity. fMRI is sensitive to deficits related to dynamic aspects of neural function that may be evident only under conditions of cognitive load or information processing (Jantzen 2005). An influential paper by McAllister and colleagues, demonstrated that, despite comparable performance outcomes on a working memory task, the prefrontal cortex of MTBI patients showed more activity during task performance than it did in healthy controls (McAllister 1999). Therefore, it may be possible that the non-specific cognitive complaints after MTBI result from such a 'compensatory activation' at the cerebral level. Speculatively, such compensatory effort might result in feelings of (mental) fatigue. However, as mentioned earlier, there are many other factors that might cause both fatigue and cognitive complaints, including pain related to extracranial injuries and emotional distress. Unfortunately, basic questions regarding the prevalence of fatigue after MTBI, its dimensions and its relation to general MTBI outcome, have scarcely been studied.

1.2.3 Early prediction of outcome after MTBI
Early identification of MTBI patients at risk for developing chronic symptoms has great clinical importance. In 2006, a review of prognostic models in TBI identified only few high quality studies concerning the prediction of MTBI outcome (Perel 2006). These studies were mainly directed at calculating the risk of post acute complications, rather than at long-term outcomes such as self-perceived symptoms

or return to work. Although hundreds of studies reported potential risk factors for poor outcome, few such factors are used in clinical practice. To a large extent this is due to a lack of adequate validation studies which demonstrate the therapeutic relevance and robustness of pre-specified predictors. As a result, evidence-based guidelines regarding long-term patient management cannot be developed and tested. Nevertheless, the existing literature does provide the ingredients for a potentially powerful prediction model. It is recognized that besides head injury indices, other injury characteristics (e.g. early symptoms (Dacey 1991, Kruijk de 2002, Savola 2003)), as well as pre- and post-injury physical functioning (e.g. pain, fatigue (Borgano 2005, Lundin 2006)), and psychological status (e.g. depressed mood (Cattelani 1996, Levin 2006), anxiety (Guerin 2006, Levin 2005), neurotic personality (Cattelani 2006), and negative outcome expectations (Mooney 2005) are considered important for understanding and predicting MTBI outcome. The overwhelming majority of papers on prediction of outcome have focussed on poor outcome. Given the high incidence of MTBI, and the good recovery in most patients, routine follow-up may not be feasible or needed. Thus, one might argue that *early* prediction of patients who have a high change of good recovery is also relevant. This could help clinicians to make evidence-based decisions about which patients are likely to recover fully without medical support, so that they can devote their resources to those patients that may in fact benefit from outpatient follow-up.

1.3 The present study

1.3.1 Framework
The work presented in this thesis is part of the Radboud University Brain Injury Cohort Study (RUBICS). RUBICS is issued at the department of Neurology of the Radboud University Medical Centre and works in close collaboration with several departments both

within (Top Centre Traumatology, Medical Psychology, Rehabilitation Medicine, Radiology, Antropogenetics, F.C. Donders Institute for Neuroimaging) and outside our hospital (through collaborations with the Nijmegen based municipal Canisius Wilhelmina Hospital and internationally with research centres in the United States of America and Germany). The RUBICS databank contains clinical records, radiological parameters and outcome scores of all patients with head injury admitted to the ED of the Radboud University Nijmegen Medical Centre. Clinical data are registered by the resident Neurology in the ED, and thereafter collected by a research nurse and registered on prespecified forms. All data are then manually entered in the electronic database. The Radboud University Nijmegen Medical Centre is a so-called 'Level 1 trauma centre', which means that it provides the highest level of specialty expertise and meets strict national standards including the requirement of having a certain number of surgeons and anaesthesiologists on duty 24 hours a day, seven days a week, promptly available specialists in a wide range of disciplines, and a highly trained nursing staff. It has a local and regional trauma function for a hinterland of 3.5 million inhabitants. Annually, on average, 800-900 patients with MTBI are admitted to the ED. Of those, 21% is younger than 18, 55% between 18-60, and 24% older than 60. Part of RUBICS is focused on patients with MTBI.

1.3.2 The studies
The work presented in this thesis is based on data from two prospective cohort studies. Both studies were comprised of consecutive patients who attended the ED of the Radboud University Medical Centre with a diagnosis of MTBI according to the guidelines of the European Federation of Neurological Societies (Vos 2002). Patients were eligible to participate in the study if they were between 18 and 60 years of age, able to speak and write in Dutch and did not suffer from premorbid

mental retardation or dementia. Participation was based on willingness, not on outcome characteristics. We aimed to assess patients' functioning in a stage of recovery when symptoms had become relatively stable and distinction could be made between patients with good versus suboptimal outcome. Based on the existing literature which shows that after 3-6 months little spontaneous improvement occurs, six-months post injury was considered an appropriate time point for this aim. Data of Study 1 were collected in the period November 2001 to October 2003. Patients were approached six months after injury and invited to complete a postal questionnaire and take part in a two-session (neuro)psychological assessment. In total 299 patients from a cohort of 618 patients filled out the six-months questionnaire and 110 of those patients underwent (neuro) psychological assessment six months after injury. This assessment included a two-week registration of physical activity and a daily self-monitoring of symptoms. The data of Study 2 were collected between October 2004 and August 2006. As soon as possible after ED admission, patients were informed about the study and asked to complete a questionnaire. Consenting patients were sent a follow-up questionnaire six months later. Six-months data of 201 patients were collected. Of those, 50 underwent functional and structural MRI, and performed a cognitive test battery. For this study, more stringent exclusion criteria applied (see Chapter 5) and several patients from the Canisius Wilhelmina Hospital were added to the study population. Details regarding the patient selection, inclusion rates and potential recruitment biases will be discussed in more detail in the individual research chapters.

1.4 General aim and outline of the thesis

The studies in this thesis aim to gain more insight in determinants of post-concussional

symptoms (especially fatigue and cognitive complaints), neuropsychological test performance and return to work six months after MTBI by integrating neurological characteristics of the injury with a range of non-neurological factors. The thesis is outlined as follows: Chapter 2 focuses on experienced fatigue six-months after injury. There is evidence that feelings of debilitating tiredness continue to be a problem even when most symptoms have resolved, but it has rarely been studied in a systematic fashion. We will examine the prevalence of severe fatigue, its association with other symptoms, functional outcome and injury severity indices. As post-concussional symptoms like fatigue have a high base-rate in the general population, the scores of MTBI patients are compared to those of patients with minor orthopaedic injuries. In the same line of reasoning, many of post-concussional symptoms and functional limitations may relate to the 'non-brain' characteristics of the injury. For example, many MTBI patients also suffer injuries to other parts of their body. Chapter 3 describes a study in which MTBI patients with and without concurrently sustained extracranial injuries are compared on functional outcome and post-concussional symptoms six months post injury. Chapters 4 -7 focus on cognitive outcome after MTBI. As described earlier, memory deficits are common early after injury, and disabling cognitive complaints persist in a minority of patients. In previous studies, the association between cognitive complaints and actual test performance has been weak and inconsistent, raising many unresolved questions on the impact of MTBI on cognitive functioning. Firstly, Chapter 4 describes a study on cognitive functioning early after MTBI. Patients and healthy controls will be compared on cognitive measures and a neurophysiological measure of region specific activation during a memory task using functional Magnetic Resonance Imaging. In Chapter 5, cognitive test performance is examined more closely. We present a cross-sectional study on the prevalence of poor test effort and its relationship with cognitive test performance. To better understand the factors associated with poor effort, we compare patients with and without sufficient test effort on a range of measures of psychological distress, personality, physical functioning and fatigue. Then, in Chapter 6, a more in-depth investigation of cognitive complaints and actual performance is performed. Besides comparing test scores of patients with and without cognitive complaints, differences in the frequency of self-observed cognitive problems during a two-week period are investigated. In Chapter 7, the findings of the previous chapters are interpreted from a health psychology perspective, and a tentative model of the development and persistence of cognitive complaints after MTBI is presented. After assessing long-term outcome from MTBI by means of cross-sectional comparisons in several previous chapters, Chapter 8 deals with the feasibility of predicting favourable outcome at six-months on the basis of pre-, peri- and early post-injury variables. We develop and internally validate a prediction model for the absence of post-concussional complaints and full return to work. In Chapter 9, the results presented in this thesis will be summarized. Finally, in Chapter 10 the findings are integrated and discussed, together with clinical implications and possible directions for future research.

Box 1. Controversies regarding the post-concussional syndrome; then and now.

The symptoms that occur after a MTBI have been known for centuries. According to Benton, the idea that this set of symptoms forms a distinct entity began to attain wide recognition in the latter part of the 19th century (Benton 1989). The controversy surrounding the cause of post-concussional syndrome was started in 1866 when Erichsen published a paper about persisting symptoms after sustaining mild head trauma.

He suggested that the condition was due to injury by "molecular disarrangement" to the spine, and the condition was originally called "railroad spine" because most of the injuries studied had happened to railroad workers. While some of his contemporaries agreed that the syndrome had an organic basis, others attributed the symptoms to

(in ref Miller 1961). A similar vigorous debate emerged during World War 1. By 1914, British doctors working in military hospitals noticed patients suffering from what came to be called "shell shock". Early symptoms included tiredness, irritability, giddiness, lack of concentration and headaches. Eventually the men suffered mental breakdowns making

Table 1.3. *DSM-IV and ICD-10 diagnostic criteria to classify symptomatic MTBI patients*

Name	DSM-IV Post-concussional Disorder	ICD-10 Post-concussion Syndrome
Code	294.9 Cognitive Disorder Not Otherwise Specified	310 Specific nonpsychotic mental disorders due to organic brain damage
	A syndrome following significant cerebral concussion* resulting in quantifiable deficits in memory (e.g., learning of recalling information) or attention (e.g., concentration, shifting focus of attention, performing simultaneous cognitive tasks)	History of head trauma with loss of consciousness precedes symptom onset by maximum of 4 weeks.
Required symptoms	Onset, or substantial postinjury worsening, of any three of the following symptoms: - Becoming fatigued easily. - Disordered sleep. - Headache. - Vertigo or dizziness. - Irritability or aggression with little or no provocation. - Anxiety. - Depression or affective ability. - Apathy or lack of spontaneity. - Other changes of personality (e.g., social or sexual inappropriateness).	Three or more symptom categories: - Headache, dizziness, malaise, fatigue, noise intolerance. - Irritability, depression, anxiety, emotional lability. - Subjective concentration, memory, or intellectual difficulties without neuropsychological evidence of marked impairment - Insomnia - Reduced alcohol tolerance
Consequences	The disturbances resulting from these symptoms must result in a substantial decline in socials or occupational functioning, and the symptoms should not be better accounted by other diagnostic categories. *manifestations of PCD include loss of consciousness, PTA and, less commonly, post-traumatic onset of seizures.	Preoccupation with above symptoms and fear of brain damage with hypochondrial concern and adoption of sick role

psychological factors or to outright feigning. For example, Rigle suggested that the cause of the persisting symptoms was actually "compensation neurosis": the railroad's practice of compensating workers who had been injured was bringing about the complaints

it impossible for them to remain in the front-line. Some came to the conclusion that the soldiers condition was caused by the enemy's heavy artillery. These doctors argued that a bursting shell creates a vacuum, and when the air rushes into this vacuum it disturbs

the cerebro-spinal fluid and, creating a concussive like head injury. For both railway spine and shell shock, the decision whether the complaints of an individual were primarily due to commotional injury or emotional reactions was an important matter, for only the former entitled the sufferer to a gratuity. In the current ´war on terror', soldiers and their families are well informed about MTBI and its consequences. For example, through the PTSD/MTBI Chain Teaching program and the creation of the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (http://www.dcoe.health.mil/default. aspx). The number of research papers in this population is growing fast (e.g. Hoge 2008).

Although the terms changed, and diagnostic labels as post-concussional syndrome and post-concussional disorder were introduced (see Table 1.3), the controversy about the syndrome continued through the 20th century. There is lack of consensus on any one definition and a rather high degree of professional scepticism of the disorder and its legitimacy (Boake 2005, Kashluba 2006, McCauley 2005, 2007). To date, the two most widely used classification systems for patients that remain symptomatic following an MTBI are those of the International Statistical Classification of Diseases and Related Health Problems (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM). As shown in Table 1.3, there are important differences between the criteria as to the required characteristics, the symptoms and its consequences.

Chapter 2

**Recovery from Mild Traumatic Brain Injury:
a focus on fatigue.**

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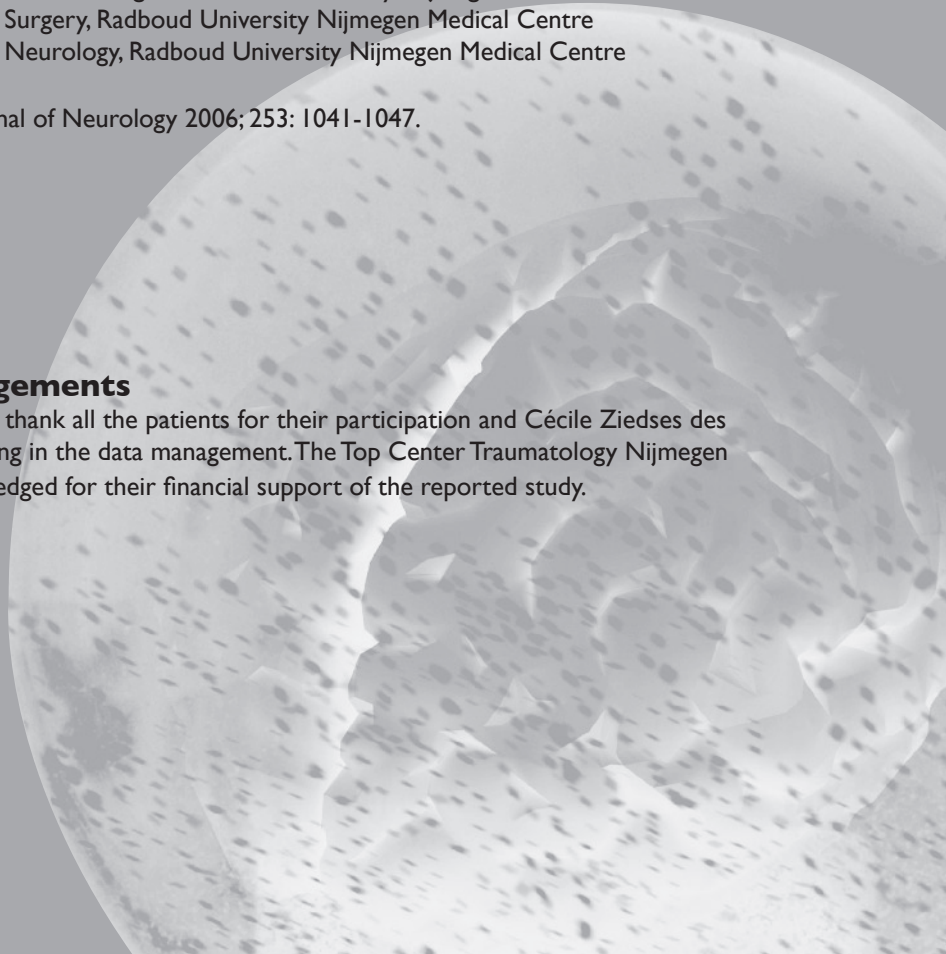2. Expert Centre Chronic Fatigue, Radboud University Nijmegen Medical Centre
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Acknowledgements

Abstract

Fatigue is one of the most frequently reported symptoms after Mild Traumatic Brain Injury (MTBI). To date, systematic and comparative studies on fatigue after MTBI are scarce, and knowledge on causal mechanisms is lacking. The objective of this study was to determine the severity of fatigue six months after Mild Traumatic Brain Injury and its relation to outcome. Furthermore, we tested whether injury indices, such as Glasgow Coma Scale scores, are related to higher levels of fatigue. Postal questionnaires were sent to a consecutive group of patients with an MTBI and a minor-injury control group, aged 18 – 60, six months after injury. Fatigue severity was measured with the Checklist Individual Strength. Postconcussional symptoms and limitations in daily functioning were assessed using the Rivermead Post Concussion Questionnaire and the SF-36. Our results show that a total of 299 out of 618 eligible (response rate 52%) MTBI patients and 287 out of 482 eligible (response rate 62%) minor-injury patients returned the questionnaire. Ninety-five MTBI patients (32%) and 35 control patients (12%) were severely fatigued. Severe fatigue was highly associated with the experience of other symptoms, limitations in physical and social functioning, and fatigue related problems like reduced activity. Of various trauma severity indices, nausea and headache experienced on the ED were significantly related to higher levels of fatigue at six months. We conclude that one third of a large sample of MTBI patients experience severe fatigue six months after injury, and this experience is associated with limitations in daily functioning. Our finding that acute symptoms and mechanism of injury rather than injury severity indices appear to be related to higher levels of fatigue warrants further investigation.

Introduction

Every year 100-300/100,000 people sustain a Mild Traumatic Brain Injury (MTBI) (Cassidy 2004). Although most patients are able to return to their former level of functioning within three months, some patients report a variety of symptoms up to years after injury (Evans 1992, Levin 1987, Naalt van der 1999). Fatigue is one of the most frequently reported symptoms within the first month after injury as well as on the longer term, often experienced as being the most bothersome of all postconcussional sequealae (Ingebrigtsen 1998, King 1995, LaChapelle 1998, McCullagh 2001, Paniak 2002b, Ponsford 2000). In addition, there is evidence that feelings of debilitating tiredness continue to be a problem even when most symptoms have resolved (Kashluba 2004, Mickeviciene 2004). Research in other neurological populations like stroke and Multiple Sclerosis show that prolonged severe fatigue interferes with daily functioning and is associated with diminished quality of life (Chaudhuri 2004, Groot de 2003).

To date, systematic and comparative studies on fatigue after MTBI are lacking, and as a result knowledge on the severity and nature of fatigue, its relation to outcome and causal mechanisms is limited. In most studies on outcome after MTBI, fatigue is addressed with single items within the framework of related subjects such as post-concussional symptoms (Haboubi 2001, Ingebrigtsen 1998, Kashluba 2004, Naalt van der 1999, Paniak 2002b) or depression (Cicerone 1997, Seel 2003). These studies do not differentiate

Methods

Patients and procedure

All consecutive patients aged 18 – 60 who attended the ED of the Radboud University Medical Centre Nijmegen with a diagnosis of MTBI in the period November 2001 to October 2003 were eligible to participate in

the study. The comparison group consisted of patients aged 18 – 60 presented to the ED in the period January to November 2003 with an ankle or wrist distortion, without a blow to the head. Eligible patients were sent a letter which contained information on the study and a questionnaire six months post injury. Non-responders received a reminder after 3 weeks. The study was approved by the ethics committee of the University Medical Centre Nijmegen.

Definition MTBI
MTBI was defined as a history of impact to the head with or without loss of consciousness (LOC) ≤30 minutes and with or without posttraumatic amnesia (PTA) and a hospital admission Glasgow Coma Score (GCS) 13-15. Three injury severity categories were classified according to the EFNS guidelines (Table1) (Vos 2002).

Outcome measures
Fatigue severity and fatigue related dimensions were measured with the Checklist Individual Strength (CIS), a 20-item self-report questionnaire which measures four aspects of fatigue during the previous two weeks: fatigue severity (8 items, range 8-56), concentration problems (5 items, range 5-35), reduced motivation (4 items, range 4-28) and reduced activity (3 items, range 3-21). Each item was scored on a 7-point Likert scale. High scores indicate high level of fatigue, a high level of concentration problems, low motivation and low levels of physical activity. A CIS-fatigue score equal or higher than 40 was used to identify severe fatigue (Vercoulen 1994).
Post-concussional symptoms were assessed with the Rivermead Post Concussion Questionnaire which consists of 16 common postconcussion symptoms on a 5-point Likert scale. Patients were asked to rate how

Table 1. Classification of Mild Traumatic Brain Injury severity

MTBI		
Category 1:	**Category 2:**	**Category 3:**
GCS 15 no LOC no PTA no risk factors[*]	GCS 15 LOC < 15 minutes PTA < 60 min no risk factors[*]	GCS 13-14 (no) risk factors[*] *or* GCS 15 which is no cat. 1 or 2
[*]**Risk factors for intracranial complications:** ambiguous accident history, high-energy accident, trauma above clavicles, focal neurological deficits, seizure, coagulation disorders, vomiting, severe headache, intoxication with alcohol/drug, continued post traumatic amnesia, retrograde amnesia more than 30 minutes		

MTBI injury parameters
As part of a standardized registration, the following data were recorded by the neurologist on-call on the ED: age, sex, GCS, presence and duration of PTA, risk factors for intracranial damage and mechanism of injury. (Table 1) The CT scans were classified according to the Trauma Coma Data Bank criteria, by one rater (blinded from all outcome measures). In the present study CT scans were dichotomized as either normal or abnormal. An abnormal CT was defined as the presence of contusion, oedema, subdural hematoma, epidural hematoma or subarachnoid haemorrhage.

problematic, if at all, each symptom has been compared with before their head injury. The Rivermead Post Concussion Questionnaire is found to be reliable both when self-administered and clinician administered (King 1995). A total score was calculated by adding all items with a score greater than 1 (not present anymore). To prevent overlap the item on fatigue was left out.
Functional and social impairments were measured with two subscale of the Short Form-36; 'Physical functioning' (10 items, measuring the extent to which a person is limited by their health in performing a range of physical activities, from playing strenuous

sport to bathing and dressing) and 'Social functioning' (2 items, measuring the extent to which health or emotional problems impact on social activities with others). For each subscale, all items are summed and transformed to form a scale from 0 to 100, where a higher score indicates a better state of health or well-being. This widely used measure of impairments in daily living has shown good reliability and validity (Steward 1998). The questionnaire contained several additional questions on demographics, education and work and rehabilitation status.

Statistics
Data analyses were performed using SPSS 12.0. All effects were tested at the p < 0.05 level (two-tailed). Since responses on most outcome measures were not normally distributed, a natural log transformation was performed on the outcome measures to correct for skewness. Analyses of variance were used for between-group comparisons, all analyses were adjusted for age, gender and educational level. Chi-square analyses were used in case of dichotomous variables.

Results

Patient characteristics
MTBI patients: All 618 eligible MTBI patients presented at the ED during the study period were sent a questionnaire six months post-trauma. Forty-four envelopes were returned as undeliverable. Completed questionnaires were returned by 299 patients, an overall response rate of 52%. Responders were significantly older than non-responders (36.0 vs. 33.2, $F(1,572) = 7.7$, p = .006) and a higher proportion of those was female (34% vs. 23%, $Chi^2 = 8.3$, p = .004). Furthermore, alcohol or drug intoxication on admission was significantly less prevalent in responders than non-responders (responders 25% vs. non-responders 40%, $Chi^2 = 15.1$, p = .0001). No differences existed between the groups on Glasgow Coma Scale score on admission, MTBI category or type of injury.
Controls: questionnaires were sent to 483 consecutive patients presented at the ED with an ankle or wrist distortion. Four envelopes were returned as undeliverable. Completed questionnaires were returned by 287 patients, an overall response rate of 60%. Responders were significantly older than non-responders (34.0 vs. 31.1, $F(1,481) = 4.99$, p = .026) and a higher proportion was female (57 % vs. 38 %, $Chi^2 = 6.97$, p < 0.001). Patient characteristics are presented in Table 2.
Presence and severity of experienced fatigue
In both patient samples the internal consistency of all subscales was good to excellent, with Cronbach's alpha reliability coefficients ranging from .839 to .948. MTBI

Table 2. Patient characteristics					
	MTBI		**Controls**		**p-value**
N	299		287		
Age	36.0 (12.3)		33.7 (12.1)		.021
Male	201	67%	124	43%	.001
Higher education (>= 12 years)	90	30%	141	50%	.0001
Social status					.693
Married/ cohabiting	146	49%	139	48%	
Living alone	97	32%	102	36%	
With parents	56	19%	46	16%	
Changes in occupation due to injury %	60	20%	10	4%	.001
Current rehabilitation	69	23%	19	7%	.001

patients reported significantly higher levels of fatigue than the minor-injury controls; mean score 29.9 ± 15.3 compared to 22.1 ± 12.5 respectively (F (1,584) = 27.9, p < .0001). Ninety-five MTBI patients (32%) and 35 control patients (12%) reported a score of 40 or more, indicating severe fatigue (Chi^2 = 32.4, p < 0.001). In both groups, fatigue severity was unrelated to age, educational level and social status. A small gender difference was found in the control group only; females reported a higher level of fatigue than males (mean 22.2 ± 12.7 vs. 19.0 ± 12.2) respectively (F(1,286) = 6.97, p = .009).

Relationships between fatigue and other outcome variables

As shown in Table 3, when patients report severe fatigue, levels of fatigue-related problems in concentration, motivation and activity are also high. Moreover, in these patients postconcussional symptoms as well as limitations in physical and social functioning are frequent and mean scores deviate from the normal range. Less-fatigued patients on the other hand report hardly any problems on these variables. Regardless of fatigue-status, MTBI patients consistently reported more problems than the minor-injury orthopedic controls on all outcome domains, with the exception of physical functioning. Moreover, there was a significant interaction effect between group and fatigue for the severity of postconcussion symptoms and both physical and social limitations in daily functioning, with the difference in scores between severe fatigue patients and less fatigued patients being the greatest in MTBI patients.

Relationships between fatigue and MTBI injury characteristics

Both the presence of headache as well as the presence of nausea on the ED was associated with higher levels of fatigue at six months after injury. As shown in Table 4, no other significant relationships between any acute injury characteristics and fatigue severity were found. There was a trend for patients who were injured through violence to report higher levels of fatigue compared to other causes.

Table 3. Comparison of fatigue related problems (Checklist Individual Strength), postconcussional symptoms (Rivermead Postconcussion Questionnaire) and functional limitations (SF-36) in severely fatigued vs. not-severely fatigued MTBI patients and controls. Table displays uncorrected mean scores (SD).

	MTBI		Minor injury controls		Sign. Testing[1,2]
	Severe fatigue	No severe fatigue	Severe fatigue	No severe fatigue	
Fatigue related dimensions					
Concentration problems	25.0 (7.5)	12.3 (7.0)	19.2 (8.1)	10.0 (6.3)	1**;2 **
Reduced motivation	17.8 (6.1)	9.2 (5.1)	15.0 (6.4)	8.1 (4.1)	1**;2**;5*
Reduced activation	14.3 (5.9)	6.8 (4.7)	11.0 (5.5)	5.4 (3.2)	1**;2**
Postconcussional symptoms					
Rivermead total score	27.8 (14.7)	5.5 (8.5)	11.4 (12.7)	1.5 (4.4)	1**;2**;3**;5**
Limitations in daily functioning					
Physical functioning	62.1 (27.6)	90.1 (18.9)	71.7 (26.9)	91.6 (13.2)	2**;3*,5**;6**
Social functioning	48.7 (26.8)	85.6 (21.4)	66.4 (31.4)	92.0 (14.8)	1**;2**;3*

[1]Main effects: 1=group membership is significant, 2=fatigue vs. non-fatigue is significant. Interaction effect: 3= group x fatigue interaction significant. Covariates: 4= covariate gender is significant, 5 = covariate education is significant, 6 = covariate age is significant. [2] *p < 0.05, ** p < 0.01

Table 4. Relation between fatigue severity (Checklist Individual Strength) and acute injury characteristics

			Fatigue severity		
Injury characteristics[1]	N	%	mean (SD)	95% CI	p-value
Loss of consciousness					.103
no	105	35	27.5 (14.7)	24.7 to 30.4	
yes	132	44	31.0 (15.8)	28.2 to 33.7	
Post Traumatic Amnesia					.417
no	89	30	27.7 (14.7)	24.6 to 30.8	
yes	192	64	29.2 (15.6)	27.0 to 31.4	
Admission Glasgow Coma Score					.734
13	10	34	24.8 (14.3)	15.2 to 34.4	
14	30	10	29.5 (15.5)	24.0 to 35.1	
15	258	86	29.1 (15.4)	27.2 to 31.0	
MTBI category					.534
1	24	8	25.3 (12.7)	20.0 to 30.7	
2	21	7	30.7 (16.8)	23.1 to 38.4	
3	254	85	29.1 (15.5)	27.2 to 31.0	
Mechanism of injury					.076
traffic	162	54	27.6 (15.6)	25.1 to 30.0	
falls	78	26	29.7 (15.6)	26.2 to 33.3	
violence	27	9	35.4 (13.1)	30.3 to 40.6	
other	32	11	28.2 (14.7)	22.8 to 33.6	
CT[2]					.389
normal	186	81	30.0 (15.8)	27.7 to 32.3	
abnormal	41	18	27.6 (14.9)	22.8 to 32.4	
Headache on admission					.021
no	156	52	26.8 (15.1)	24.5 to 29.2	
yes	137	46	31.0 (15.4)	28.4 to 33.6	
Nausea on admission					.044
no	235	79	27.8 (15.3)	25.8 to 29.8	
yes	60	20	32.4 (14.8)	28.5 to 36.3	
Dizziness on admission					.206
no	274	92	28.5 (15.5)	26.7 to 30.3	
yes	20	7	33.0 (11.8)	26.3 to 39.7	
Additional major injury					.316
no	217	73	28.3 (15.3)	26.2 to 30.3	
yes	82	27	30.3 (15.4)	26.9 to 33.6	

[1] Numbers do not amount to 299 because in a number of cases variables were unknown or missing
[2] CT-scans were performed in 230 MTBI patients

Discussion

The results of our study show that fatigue is a frequent problem in patients six months after a MTBI. Almost one third of a large hospital-treated cohort of these patients report severe levels of fatigue, compared to 12% of patients who suffered a minor orthopedic injury. In both groups, prevalence rates were higher than to be expected in the general population (Vercoulen 199). Compared to other neurological conditions however, severe fatigue seems somewhat less of a problem. Using the same instrument in stroke patients, MS patients and patients with common neuromuscular diseases, other studies found prevalence rates of 51%, 57% and 64% respectively (Kalkman 2002, Werf van der 2001). Fatigue was unrelated to age and education in both groups. In the control group only, a small but significant gender effect was found, with woman reporting higher levels of fatigue than men.

To better understand the nature of fatigue in patients with MTBI, we used a dimensional questionnaire which also measured related problems in motivation, activity and concentration. Since cognitive and emotional problems are especially frequent after a MTBI, one could expect that fatigue would be highly associated with the concentration or motivational aspects and less with activity related problems whilst the opposite may be the case in the patients with a minor orthopedic injury. The results of the present study do not support this assumption, since in both patient groups none of the fatigue related domains showed to be dominantly affected in severely fatigued patients. Contrarily, the results of the study show that in both groups severely fatigued patients report higher scores on all three domains. Since all of these measures were based on self-report questionnaires these findings should be interpreted with caution however. Overall, the proportion of patients that showed persistent symptoms and limitations was considerably higher in the MTBI patients, which is in agreement with the common finding, that although many MTBI patients return to their former level of functioning within months, a considerable number of patients continue to report debilitating symptoms. Strong associations were found between the experience of severe fatigue and the experience of other symptoms, limitations in daily functioning and fatigue related problems. Interaction effects between fatigue status and group suggested that fatigue may be especially associated with postconcussional symptoms and functional limitations in severely fatigued MTBI patients and less in those with a minor orthopedic injury. The cross-sectional nature of these analyses however, does not allow to determine any temporal sequence, and longitudinal research is necessary to disentangle the causal relationship between the variables found to be associated with fatigue severity.

In the MTBI patients we investigated the association between injury characteristics and fatigue. Results showed that the presence of nausea and headache experienced at time of trauma were associated with higher levels of fatigue after six months. Interestingly, these symptoms have found to be related with worse outcome in other studies too, which suggest that these acute injury symptoms may have predictive value for the recovery after an MTBI (Kruijk de 2002a, Rutherford 1989, Stalnacke 2004b). None of the traditional markers of severity of the brain damage, like Post Traumatic Amnesia or Glasgow Coma Score were related to levels of fatigue after six months. Additionally, when the cause of the injury was violence-related, fatigue levels tended to be higher which suggests that post-traumatic stress might be involved the experience of fatigue. Since we did not include a measure of depression or post-traumatic stress in the questionnaire, we do not know to which extent these variables explain the high levels of fatigue reported in this study. It is unlikely however, that the fatigue levels are only a sign of underlying psychopathology

since various studies in other conditions like stroke or MS have shown that fatigue can constitute a major independent symptom as well (Ingles 1999).

Although the RPQ has a high test-retest reliability, high interrater reliability and has been validated against the diagnosis Postconcussional syndrome (PCS) of the International Classification of Diseases (Ingebrigtsen 1998, King 1995, WHO 1978), most symptoms of the RPQ have high rates in the normal population (Iverson 2003, McLean jr 1993). Accordingly, in our study important overlaps were found between the more varied symptoms and those who have not had a head injury, despite the fact that the differences between fatigued and less fatigued patients were greatest with the brain injured patients. This raises the issue as to the non specificity of questionnaires including the RPQ that measure the so called post-concussion symptoms as well as to the PCS diagnosis itself. Further research should aim for a true gold standard for the Post Concussion Syndrome which is what is needed most to disentangle the causes and pattern of emotional and organic reactions displayed by many who sustained an MTBI.

When interpreting the data one should be cautious with extrapolating the findings to the general population because of the response rate of $\approx$ 50%. Responders differed from non-responders on age, gender and intoxication on admission. Neither of these variables however, had substantial influence on the results. Other potentially important factors like premorbid health status were known in a subset of patients only, and may have influenced the results to an unknown degree. This is the first study that uses the CIS to assess fatigue in MTBI patients, although it has been used in several other neurological populations like MS and stroke (Kalkman 2002, Werf van der 2001). In the present study the internal consistency of all subscales was good to excellent. We believe that the levels of self-reported fatigue and fatigue related problems reported are reliably assessed by this questionnaire albeit more studies are needed to fully test the psychometric qualities of the CIS in TBI patients.

In conclusion, our study shows that almost one third of a large group of MTBI patients experience severe fatigue six months after injury, and that this experience is associated with limitations in daily functioning. Of all injury severity indices, only nausea and dizziness at time of injury were associated with higher levels of fatigue. Our finding that fatigue tends to be especially high in violence-related injuries warrants further investigation. Future studies could benefit from a longitudinal approach that includes behavioural measures (eg. actual registration of physical activity and neuropsychological test performance) and should focus on identifying predictive and perpetuating factors of severe fatigue in patients with MTBI.

Chapter 3

Impact of additional extracranial injuries on outcome after Mild Traumatic Brain Injury.

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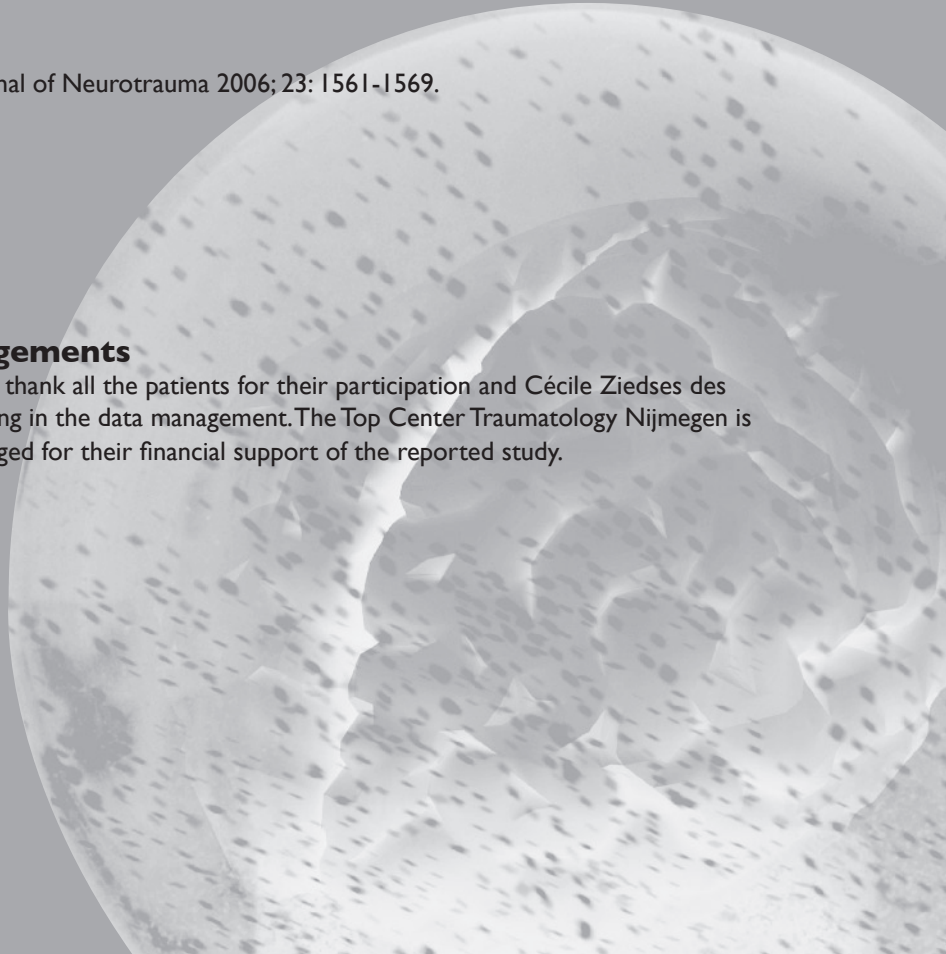1. Department of Medical Psychology, Radboud University Nijmegen Medical Centre
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Abstract

Many patients with Mild Traumatic Brain Injury (MTBI) concurrently sustain extracranial injuries, however, little is known about the impact of these additional injuries on outcome. We assessed the impact of additional injuries on the severity of postconcussional symptoms (PCS) and functional outcome six months post injury. A questionnaire (including the Rivermead Post-Concussion Questionnaire and SF-36) was sent to consecutive MTBI patients (hospital admission Glasgow Coma Score 13-15; age range 18-60 years) admitted to the Emergency Department of a level-I trauma center, and, to serve as a baseline for PCS, a control group of minor-injury patients (ankle or wrist distortion). Of the 299 MTBI respondents (response rate 52%), 89 had suffered additional injuries (mean Injury Severity Score 14.5 ± 7.4). After six months, 44% of the patients with additional injuries were still in some form of treatment, compared to 14% of patients with isolated MTBI and 0.5% of the controls. Compared to patients with isolated injury, MTBI patients with additional injuries had resumed work less frequently and reported more limitations in physical functioning. Overall, they did not report higher levels of PCS, despite somewhat more severe head injury. Regardless of the presence of additional injuries, patients that were still in treatment reported significantly more severe PCS, with highest rates in patients with isolated MTBI. In conclusion, many patients with additional extracranial injuries are still in the process of recovery at six months after injury. However, despite more severe impact to the head and inferior functional outcomes they do not report more severe PCS.

Introduction

With an incidence of 100-300/100,000 hospital-treated patients, Mild Traumatic Brain Injury (MTBI) is one of the most prevalent neurological disorders. Mortality is low and most patients are able to regain their former level of functioning within three months. (Cassidy 2004) Nevertheless, a subgroup of patients still reports debilitating symptoms up to years after injury and there is ongoing controversy regarding the mechanisms that cause these chronic postconcussional symptoms. (Binder 1997, Cassidy 2004, King 1999, Mooney 2005) A factor that may greatly delay the process of recovery after MTBI is the presence of concurrently sustained injuries to other parts of the body such as luxations, fractures or internal lesions. However, little is known about the impact of these additional injuries on long-term outcome and, more specifically, the development of postconcussional-like symptoms.

Many studies excluded patients with (severe) extracranial injuries to avoid potential bias. (Barth 1983, Bohnen 1995, de Kruijk 2002a, Hugenholtz 1988, Levin 1987, Macciocchi 1998, McCauley 2001) The few studies that did comment on the influence of non-brain injuries on outcome, either by including severity scores in a regression model (Bohnen 1994, Dikmen 1994, Savola 2003), or by comparing TBI patients to general trauma patients without head injury (Dacey 1991), consistently show that more severe additional injuries are associated with lower return-to-work rates, most likely reflecting slower physical recovery.(Dikmen 1994, Naalt van der 1999, Stambrook 1990) Several authors suggest that the presence of additional injuries might also lead to increased levels of postconcussion-like symptoms (e.g. through physical limitations, pain or fatigability)(Binder 1986, Iverson 1997, Kibby 1997, Satz 1999), but this assumption has not often been the subject of systematic research and current results are inconsistent. Whereas one study reports more cognitive and behavioral problems in patients with extracranial injuries compared to those without (Naalt van der 1999), others only found more physical symptoms (Bohnen 1994), or no influence of

non-brain injury severity on symptom report at all. (Paniak 2002b, Savola 2003)

To our knowledge, no studies have directly compared MTBI patients with and without additional injuries on long-term outcome or considered the impact of different types of additional injuries. As a result, the process of recovery of this category of patients is still poorly characterized. In the present study, we will evaluate MTBI patients with and without concurrently sustained extracranial injuries regarding functional outcome and postconcussional symptoms six months post injury, and assess the impact of the nature and severity of the additional injuries. Furthermore, as many MTBI patients with additional injuries will still be in the process of recovery, treatment status at time of the assessment will be considered.

Materials and Methods

Patients and procedure

All consecutive patients aged between 18 and 60 years who were admitted to the ED of the level-I trauma center of the Radboud University Nijmegen Medical Centre with a diagnosis of MTBI in the period between November 2001 and October 2003 were eligible to participate in the study. Six months post injury, all patients were sent a letter containing information about the study and a questionnaire booklet with a request to return the completed forms together with a written informed consent. The study was approved by the ethics committee of the Radboud University Medical Centre Nijmegen.

Definition MTBI

A history of impact to the head with or without loss of consciousness (LOC) ≤ 30 minutes and with or without posttraumatic amnesia (PTA) and a hospital admission Glasgow Coma Score (GCS) of 13-15.(Vos 2002)

MTBI injury parameters

As part of a standardized registration procedure, a range of clinical injury indices were recorded on admission to the ED (e.g. GCS, risk factors for intracranial complications and mechanism of injury). The presence and duration of LOC was based on reports of witnesses or ambulance personnel, and the presence and resolution of PTA was assessed by a resident of Neurology on the ED by a series of questions regarding short-term memory and orientation. A CT of the head was performed according to international guidelines.(Vos 2002) For the purpose of this study, CTs were classified as normal or abnormal where an abnormal CT was defined as showing signs of contusion, edema, subdural hematoma, epidural hematoma or subarachnoid hemorrhage, according to one rater blinded from all outcome measures (P.V.) In case alcohol or drug intoxication was suspected, a blood draw was conducted on the ED to determine blood-alcohol levels.

Additional injuries

Injury severity was scored with the Abbreviated Injury Score (AIS)/ Injury Severity Score (ISS) (Baker 1974), an anatomical scoring system that provides an overall severity score based on the three most severely injured body regions. Patients were categorized as having additional injuries when, in addition to an MTBI, they sustained significant injury, defined as an AIS-score of 2 or more, in one of the AIS-ISS body regions. Two ISS scores were calculated, i.e. the AIS-ISS, based on all six AIS body areas, and a modified score based on the three most severely injured body areas excluding injuries to the head. In this study, the location of the additional trauma was allocated to mutually exclusive AIS regions (Face, Chest/Abdomen, Extremities, or Multiple (significant injury to more than one AIS region besides the head)). Because of few patients per category, the categories Chest and Abdomen were grouped together. Only one patient had a score of 2 on the

AIS-External, and was consequently excluded from the subgroup analysis.

Outcome measures
In addition to general questions about the patient's demographics, education and rehabilitation status, the questionnaire booklet contained the following self-report scales:

The Rivermead Post-Concussion Questionnaire (RPCQ) assessing 16 common *post-concussional symptoms* on a 5-point Likert scale. Patients are asked to rate how problematic, if at all, each symptom is experienced compared with the situation before they sustained their head injury. (King 1995) In the present study symptoms were classified into three domains (physical, cognitive, affective) and, given that the number of items per domain was unequal, raw scores were transformed into a 1-100 scale. The three symptom domains were highly internally consistent, with Cronbach's alpha reliability coefficients ranging from .88 to .92. As the RPCQ rates symptom severity compared to before trauma, no population norms are available. Minor-injury orthopedic patients aged 18 – 60, who attended the ED in the period between January and November 2003 with an ankle or wrist distortion without any sign of a head injury, in whom speedy recovery was expected, served as a control for the severity and specificity of the postconcussional symptoms.

Two subscales of the Short Form-36 (Dutch version) to assess *limitations in activities of daily living (ADL)*: 'Physical functioning' (10 items measuring the extent to which a person is limited by his/her health in performing a range of physical activities, from playing strenuous sports to bathing and dressing) and 'Social functioning' (2 items measuring the extent to which health or emotional problems impact on social activities with others). All items of each subscale are summed and the total is transformed into a 1-100 score, with higher scores indicating a higher state of health or well-being. This widely used measure of impairments in ADL has shown good reliability and validity. (Aaronson 1998, Steward 1998)

The Extended Glasgow Outcome Scale (GOS-E) that scores *functional outcome* with a series of questions covering consciousness, independence inside and outside the home, major social roles (work, social and leisure activities, family and friendships), and return to normal life. The final rating is based on the lowest category of outcome indicated by the responses. Traditionally, the GOS-E is scored by a semi-structured interview but it was shown that reliable outcomes can also be obtained when the format of a self-report questionnaire is used. (Hudak 2005, Wilson 1998)

One item of the SF-36 ("Compared to one year ago, how would you rate your health in general now?") to rate *perceived health change*. Patients responded using a 5-point rating scale ranging from "much better" to "much worse". Scores were transformed into a 0-100 scale, where a score of 50 indicated no changes in health compared with one year ago. (Steward 1998)

Statistical analysis
Data analyses were performed using SPSS software version 12.0 (SPSS Inc., Chicago, IL, USA). All effects were tested at the $p < 0.05$ level (two-tailed). Since responses on most outcome measures were not normally distributed, a natural log transformation was performed on the outcome measures to correct for skewness. Analyses of variance were used for between-group comparisons. When a significant main effect was found, post-hoc analyses were performed using the Bonferroni correction. Because the groups were not matched, analyses were adjusted for age and gender. In the tables unadjusted scores are presented. Chi-square analyses were used in the case of dichotomous variables.

Table 1. Demographic and injury characteristics for the MTBI patients with and without additional injury[a]

	MTBI				p-value
	Additional injury		Isolated injury		
Demographics					
N	89		210		
Age	37.9 (12.0)		35.2 (12.3)		.078[b]
Male	66	74%	132	63%	.059[c]
Mechanism of injury					.0001[c]
Traffic	66	74%	96	46%	
Falls	17	19%	61	29%	
Violence	2	2%	25	12%	
Other	4	5%	28	13%	
Alcohol/drug intoxication (n = 296)	20/88	23%	54/208	26%	.557[c]
Admission to hospital	84	94%	83	40%	.0001[c]
Loss of Consciousness (n = 236)	30/59	51%	102/177	58%	.387[c]
Post Traumatic Amnesia (n = 281)	64/82	78%	128/199	64%	.025[c]
Retrograde Amnesia (n = 264)	34/73	47%	52/191	27%	.002[c]
Glasgow Coma Score					.042[c]
13	5	6%	5	2%	
14	14	16%	17	8%	
15	70	79%	188	90%	
Brain CT abnormalities (n = 231)	20/82	24%	21/149	14%	.047[c]
AIS head	2.3 (0.8) range 1-5		1.9 (0.7) range 1-4		.0001[b]
ISS Including Head	14.5 (7.4) range 5-41		4.7 (3.4) range 1-17		.0001[b]
ISS Excluding Head	8.8 (6.4) range 4-41		0.4 (0.5) range 0-2		.0001[b]
Headache (n = 293)	24/87	28%	113/206	55%	.0001[c]
Nausea (n = 294)	8/87	9%	52/207	25%	.002[c]
Dizziness (n = 294)	3/86	4%	17/208	8%	.147[c]

[a] In case data was unknown or missing, the number of patients with complete data is presented between brackets, and data are presented as number/total number known.
MTBI = Mild Traumatic Brain Injury; AIS = Abbreviated Injury Score; ISS = Injury Severity Score.
[b,c] P-value represents differences for patients with and without additional injuries by (b)Univariate Analysis of Variance (ISS and AIS scores are adjusted for age and gender) or (c) Chi^2 analysis

Results

Response analysis
MTBI patients: All 618 eligible MTBI patients presented at the ED during the study period were sent a questionnaire six months post trauma. Forty-four envelopes were returned as undeliverable. In total, 299 patients returned a completed questionnaire, which constitutes an overall response rate of 52%. Respondents were significantly older than non-responders (36.0 vs. 33.3, F(1,573) = 7.4, p = .007) and more often women (34% vs. 23%, Chi^2 = 8.9, p = .003). There were no differences between the groups with regard to the admission GCS and mechanism of injury.
Controls: Questionnaires were sent to 431 consecutive patients presented at the ED with

an ankle or wrist distortion during 2003. Four envelopes were returned as undeliverable. Completed questionnaires were returned by 261 patients, constituting an overall response rate of 61%. A higher proportion of the respondents was female (55% vs. 37 %, Chi^2 = 13.5, p < 0.001) but there were no age effects.

Patient characteristics

Table 1 shows the differences between the MTBI respondents with and those without additional injuries with respect to demographic variables and injury characteristics. Traffic-related accidents were common, especially in patients with additional injuries. Most patients with additional injuries had been admitted to the hospital, whereas this was less than half for the isolated MTBI patients. Besides more severe injuries to other parts of the body, the patients with additional injuries proved to have suffered more severe trauma to the head, as shown by a higher prevalence of PTA, retrograde amnesia (RA), a lower GCS on admission and more frequent brain CT abnormalities. To control for potential influence of MTBI severity on outcome we included the AIS Head score as a covariate in

Table 2a. Six-month outcomes for the MTBI patients with and without additional injuries and the minor-injury controls

	MTBI				Controls		p-value[b,c] post-ho[cd]	
	Additional		Isolated					
Global outcome								
Glasgow Outcome Scale-E							.0001 c	-
moderate disability (5/6)	29	33%	27	13%	n.a.[e]			
good recovery (7/8)	60	67%	183	87%	n.a.[e]			
Changes in occupation[a]	31	35%	29	14%	5	2%	.0001 c	-
Current treatment	39	44%	30	14%	14	5%	.0001 c	-
Psychosocial outcome								
SF-36 Physical functioning[f]	72.4 (28.7)		84.2 (22.6)		88.5 (17.6)		.0001[b]	2
SF-36 Social functioning[f]	65.9 (32.7)		74.6 (27.6)		87.8 (20.1)		.0001[b]	2
SF-36 Health changeg	32.4 (25.5)		41.0 (22.6)		50.4 (16.2)		.0001[b]	2
Rivermead symptom clusters								
Physical	23.7 (24.4)		23.0 (28.7)		4.8 (12.3)		.0001[b]	1
Affective	27.5 (32.5)		23.5 (30.2)		6.0 (15.9)		.0001[b]	1
Cognitive	31.4 (33.5)		27.4 (32.8)		4.7 (15.5)		.0001[b]	1

[a] Defined as loss of work or change of working status into partial employment or other lower-level occupation due to the accident
[b,c] P-values represent differences between patient groups by (b)Univariate Analysis of Variance adjusted for age, gender and AIS-Head. or (c) Chi² analysis
[d] Post-hoc comparisons: 1 = MTBI (Additional injury = Isolated) > controls (p < 0.001), 2 = MTBI Additional injury > MTBI Isolated > controls (p < 0.001)
[e] n.a. = data were not available.
[f] SF-36 Physical/ Social functioning: higher scores indicate a higher state functioning. SF-36 Dutch population norms (mean ± SD): Physical functioning = 85.2 ± 23.1/ Social functioning = 85.1 ± 21.5
[g] SF-36 Health change: a score of 50 indicates no change, lower scores indicate a decrease in perceived health compared to one year ago. SF-36 Dutch population norm (mean ± SD) = 52.6 ± 18.3
MTBI = Mild Traumatic Brain Injury

all further analysis. On ED admission, patients with isolated MTBI more frequently reported headache and nausea. The groups did not differ regarding the prevalence of LOC, dizziness or alcohol or drugs intoxication. Compared to the control group, the MTBI patients were significantly older (36.12 vs. 33.2, F (1,559) = 7.6, p = .006) and more patients were male (75% vs. 45%, Chi^2 = 25.9, p = .0001). All control patients had an AIS Extremities score of 1.

Six-month outcomes
Table 2a summarizes the scores of the three patient groups on all outcome measures. As a group, the MTBI patients reported higher impairments in daily functioning and more severe postconcussional symptoms than the controls. Limitations in physical, social and occupational functioning were especially prevalent in the MTBI patients with additional injuries. In contrast, no differences were found between the two MTBI subgroups as to the severity of affective, cognitive or physical postconcussional symptoms.

Association between current treatment status and outcome
Almost half of the patients with additional injuries were still in some form of treatment at time of the study, compared to 14% of patients with isolated MTBI and 0.5% of the control patients. To investigate the relation between treatment status and outcome, we divided each patient group in those that were in treatment and those that were not. As shown in Table 2b, current treatment was strongly associated with more physical and social impairments, greater negative health change and more severe postconcussional symptoms. Moreover, there was a significant interaction effect between group and treatment status for all postconcussional symptom clusters; whereas in all three groups patients in treatment reported more postconcussional-like symptoms, this difference was especially large in patients

with isolated MTBI. MTBI patients with and without additional injuries that were not in treatment, showed very similar functional outcome and equal levels of postconcussion-like symptoms. More specifically, they generally reported good global outcome and physical functioning scores comparable to population norms. Nevertheless, MTBI patients that were not in treatment still reported lower social functioning than the population norms, and more severe postconcussional-like symptoms than the minor-injury orthopedic controls.

Impact of location and severity of additional extracranial injury
Of the 89 MTBI patients that sustained additional injury, injuries to the extremities were most frequent (n = 53) followed by injuries to the face (n = 32), chest (n = 21), abdomen (n = 8) and external (n = 1). Twenty-two patients suffered significant injuries to two or more AIS areas besides the injury to the head and in 13 patients injuries were severe (ISS >15). Tentative analyses were conducted to explore the role of the location and severity of the additional injury on six month outcome. Six months after injury, 75% of the patients with facial injuries and 82% of those with axial injuries reported good recovery on the GOSE, compared to 57% of patients with extremities injury and 59% of patients with multiple injuries, these differences however did not reach significance (Chi2 = 5.7, p = .127). Significant effects of location of injury were found in physical functioning assessed with the SF-36 (F (3,85) = 5.1, p = .003). Post-hoc analysis showed that patients with facial injuries do not report physical impairments (90.5 ± 13.8), whereas patients with multiple injuries (61.8 ± 33.3), or injuries to either the extremities (65.5 ± 30.4) or chest/abdomen (76.6 ± 22.2) still report substantial impairments. In case of severe injury (ISS > 15) more limitations in physical functioning were reported (mean 58.4 ± 31.9 vs. 76.4 ± 23.9, F (3,85) = 8.8, p = .003), whereas no differences were found regarding the other outcome variables. There

Table 2b. Comparison between patients with and without current treatment on six-month outcomes for the MTBI patients with and without additional injuries and the minor-injury controls

Current treatment	MTBI Additional yes (n = 39)		no (n = 50)		MTBI Isolated yes (n = 29)		no (n = 181)		Controls yes (n = 12)		no (n = 249)		p-value[b,c]
Type of treatment													
Physical therapy	26	67%			12	41%			12	100%			
Psychological support	5	13%			4	14%			-				
Medical specialist	4	10%			5	17%			-				
Other	4	10%			8	28%			-				
Global outcome													
GOSE-E													.0001[c]
Moderate disability (5/6)	22	56%	7	14%	20	69%	5	3%	n.a.[e]		n.a.[e]		
Good recovery (7/8)	17	44%	43	86%	9	31%	176	97%	n.a.[e]		n.a.[e]		
Changes in occupation[a]	21	54%	9	18%	18	62%	11	6%	3	25%	2	1%	.0001[c]
Psychosocial outcome													
SF-36 Physical functioning[e]	53.2 (30.4)		87.8 (15.0)		64.2 (27.3)		87.9 (19.6)		62.3 (27.5)		90.1 (15.7)		.0001[b]
SF-36 Social functioning[e]	50.3 (32.8)		78.3 (27.0)		57.9 (31.9)		78.0 (25.6)		77.5 (26.4)		88.4 (19.6)		.0001[b]
SF-36 Health change[f]	21.8 (20.8)		40.8 (25.9)		25.8 (29.0)		44.1 (20.0)		46.7 (26.5)		50.6 (46.7)		.0001[b]
Rivermead symptom clusters													
Physical	28.2 (23.6)		19.8 (25.0)		50.9 (33.6)		18.2 (25.1)		15.2 (26.6)		4.4 (11.0)		.0001[b,d]
Affective	36.9 (33.9)		19.3 (29.4)		54.3 (36.1)		18.1 (25.7)		15.1 (27.6)		5.6 (15.2)		.0001[b,d]
Cognitive	39.1 (36.4)		25.2 (30.3)		56.0 (38.2)		22.7 (29.5)		10.4 (21.7)		4.4 (15.1)		.0001[b,d]

[a] Defined as loss of work or change of working status into partial employment or other lower-level occupation due to the accident

[b,c] P-values represent main effects of treatment status with (b)Univariate Analysis of Variance adjusted for age, gender and AIS-Head. Main effects between patient groups are displayed in Table 2a or (c) Chi² analysis.

[d] Post-hoc comparisons: significant interaction between patient group and treatment status (p > .01)

[e] n.a. = data were not available.

[f] SF-36 Physical/ Social functioning: higher scores indicate a higher state functioning. SF-36 Dutch population norms (mean ± SD): Physical functioning = 85.2 ± 23.1/ Social functioning = 85.1 ± 21.5

[g] SF-36 Health change: a score of 50 indicates no change, lower scores indicate a decrease in perceived health compared to one year ago. SF-36 Dutch population norm (mean ± SD) = 52.6 ± 18.3 MTBI = Mild Traumatic Brain Injury

were no significant differences between both location or severity of additional injuries on severity of postconcussional symptoms or social functioning. Impact of location and severity of additional extracranial injury

Of the 89 MTBI patients that sustained additional injury, injuries to the extremities were most frequent (n = 53) followed by injuries to the face (n = 32), chest (n = 21), abdomen (n = 8) and external (n = 1). Twenty-two patients suffered significant injuries to two or more AIS areas besides the injury to the head and in 13 patients injuries were severe (ISS >15). Tentative analyses were conducted to explore the role of the location and severity of the additional injury on six month outcome. Six months after injury, 75% of the patients with facial injuries and 82% of those with axial injuries reported good recovery on the GOSE, compared to 57% of patients with extremities injury and 59% of patients with multiple injuries, these differences however did not reach significance (Chi^2 = 5.7, p = .127). Significant effects of location of injury were found in physical functioning assessed with the SF-36 (F (3,85) = 5.1, p = .003). Post-hoc analysis showed that patients with facial injuries do not report physical impairments (90.5 ± 13.8), whereas patients with multiple injuries (61.8 ± 33.3), or injuries to either the extremities (65.5 ± 30.4) or chest/abdomen (76.6 ± 22.2) still report substantial impairments. In case of severe injury (ISS > 15) more limitations in physical functioning were reported (mean 58.4 ± 31.9 vs. 76.4 ± 23.9, F (3,85) = 8.8, p = .003), whereas no differences were found regarding the other outcome variables. There were no significant differences between both location or severity of additional injuries on severity of postconcussional symptoms or social functioning.

Discussion

One third of the MTBI patients in our sample had suffered additional injuries, with injuries to the extremities being the most frequent, followed by injuries to the face and chest. In line with previous research in MTBI patients, the presence of extracranial injuries was strongly associated with inferior levels of physical functioning, lower return-to-work rates and poorer global outcome six months after trauma.(Dikmen 1994, Naalt van der 1999, Stambrook 1990) Outcome was poorest in patients that had suffered from injuries to the extremities and in those with injuries to multiple body areas besides the head. Overall, no differences were found in the severity of cognitive, physical or emotional postconcussional symptoms between the patients with and those without additional injury, which is in accordance with findings from studies using injury severity scores in regression analyses.(Bohnen 1994, Paniak 2002b, Savola 2003)

However, the results of the present study suggest that differences in outcome between patients with and without additional injuries also depends on treatment status at time of the assessment. MTBI patients with and without additional injuries that were not in treatment six months after injury both showed good physical functioning and good global outcome. Despite good physical recovery, these patients nevertheless reported more limitations in social functioning and more severe postconcussional-like symptoms than the minor-injury orthopedic controls. Conversely, patients that were in treatment at time of the study reported poorer outcome on all outcome measures. In all three patients groups, those in treatment reported more postconcussional-like symptoms than those not in treatment. Interestingly, this difference was especially large in patients with isolated MTBI and not in the ones with additional injuries as would be expected if functional limitations would indeed lead to more severe postconcussional-like symptoms complaints. (Binder 1986, Iverson 1997, Kibby 1997, Satz 1999). Potentially, patients with additional injuries that are still in the process of recovering

from their extracranial injuries, are less likely to report the more subtle postconcussional-like symptoms. The follow-up period needs to be extended to determine whether the report of postconcussional symptoms in the MTBI patients with additional injuries increase or rather decreases once physical disabilities have been resolved.

Besides more severe extracranial injuries, patients with additional injuries also seemed to have suffered a somewhat more severe impact to the head. However, head injury severity did not have significant influence on any of the outcome measures, which supports previous findings suggesting that there is no linear relationship between injury severity and the subsequent development of postconcussional symptoms.(Middleboe 1992, Ponsford 2000) Since our study did not include non-TBI controls with severe physical injuries, no inferences about the cause of the postconcussion-like symptoms can be drawn (Satz 1999). To clarify the controversies surrounding the diagnosis of postconcussional syndrome, these assumptions deserve further scrutiny.

Based on the results of this study, we strike a cautionary note for studies that use symptoms reported on admission to the ED as outcome predictors. Previous studies suggested that acute symptoms like nausea may have important predictive value for delayed outcome (Kruijk de 2002a, Rutherford 1989, Savola 2003, Stalnacke 2004b). However, in our study, patients with additional injuries were less likely to report sensations of nausea and headache at the ED. This may be explained by the more frequent use of analgesic medication in this group, and potentially, given the prominence of their additional injuries, from underreporting of symptoms related to the relatively mild head trauma. Accordingly, we believe that acute injury characteristics cannot be reliably determined in MTBI patients with additional injuries who receive analgesic or sedative medication and should therefore not be used as predictors of outcome in this subgroup of patients.

Overall, MTBI patients reported more impairments in daily functioning and higher levels of postconcussional symptoms than the controls with mere ankle or wrist distortions. This finding corresponds with the results of other outcome studies in ED-admitted MTBI patients that showed that, although good recovery is common, some patients will still experience postconcussional symptoms months after injury.(Bohnen 1994, Dacey 1991, Kruijk de 2002a, Ponsford 2000) Moreover, the commonly held assumption that most MTBI patients have returned to their premorbid level of functioning after 3 - 6 months after trauma, does not hold true for many patients with additional injuries and a longer follow-up in necessary to investigate final outcome in these patients. As expected, most patients in the control group had recovered well.

As the response rate in our study only just exceeded 50%, one should be cautious with extrapolating the findings to the general population. Respondents differed from non-responders with respect to age and gender. However, considering the large sample size and the finding that none of these factors had substantially affected the outcomes, we do believe that the results are representative of a general MTBI population as seen in emergency departments. Since we relied on questionnaires to assess outcome and did not perform structured interviews or actual neuropsychological testing, no formal diagnosis of Post-Concussional Syndrome could be made. Furthermore, the interpretation of the scores on the GOS-E we used to evaluate the patients' overall outcome was fraught in the patients with additional injuries since the instrument does not allow a distinction between impairments due to brain injury and impairments resulting from extracranial injuries. However, we feel we have successfully circumvented this bias by including several other validated questionnaires assessing outcome.

In conclusion, we demonstrated that, patients

with MTBI and additional extracranial injuries report inferior functional outcomes six months after trauma relative to patients with an isolated MTBI, but, overall, equal levels of postconcussional symptoms. For many patients, especially those with additional injuries, six-months is too early to determine final outcome, and the follow-up needs to be expanded. These results implicate that for the prediction of recovery from mild traumatic brain injury, both for clinical as well as research purposes, it is imperative to take the presence of concurrent injuries into account.

Chapter 4

How mild traumatic brain injury affects declarative memory performance in the post-acute stage.

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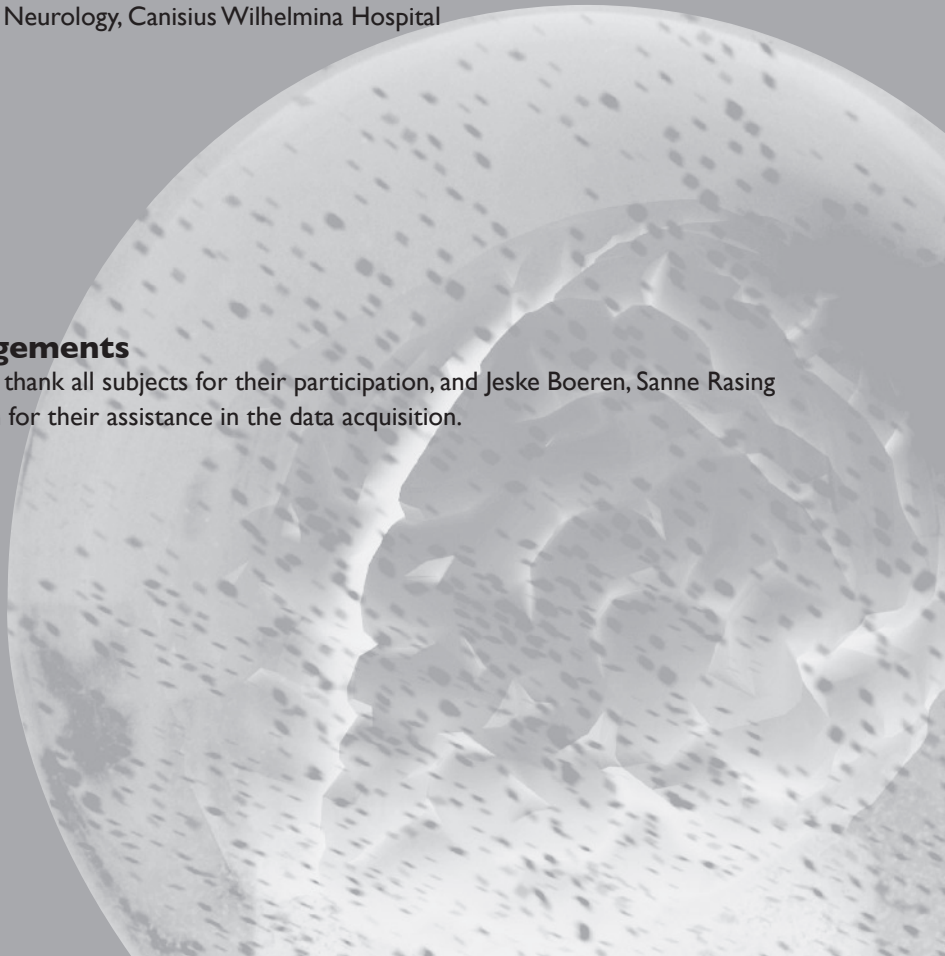
Abstract

Memory deficits are among the most frequently reported sequelae of Mild Traumatic Brain injury (MTBI), early after injury but in a minority also on the longer term. To date, these cognitive deficits remain poorly understood as in the majority of patients the core memory structures as the rest of the brain are macroscopically intact. To identify the mechanism by which MTBI causes declarative memory impairments, we have probed the functionality of the medial temporal lobe (MTL) and the prefrontal cortex (PFC) within six weeks after injury in 43 patients from a consecutive cohort and matched healthy controls. In addition to neuropsychological measures of declarative memory and other cognitive domains, all subjects underwent functional Magnetic Resonance Imaging (fMRI) probing prefrontal and medial temporal functionality. Behavioural results showed poorer declarative memory performance in patients than controls and decreasing performance with increasing injury severity (duration of post traumatic amnesia). Task performance in the scanner was, as intended by the task and design, similar in patients and controls, and did not relate to injury severity. Thus, differences in brain activity can not easily be attributed to simple differences in performance. The task used activated reliably the MTL and PFC. Although we did not find significant differences in brain activity when comparing patients and controls, we revealed, closely in line with our neuropsychological findings, a negative correlation between MTL activity and injury severity. In contrast, no difference in prefrontal activation was found between patients and controls nor a relation with injury severity. Thus, our findings suggest that reduced medial temporal functionality is causing poorer declarative memory performance in the post-acute stage of MTBI, especially in patients with longer duration of post traumatic amnesia.

Introduction

With an incidence of 100-300 /100.000, Mild Traumatic Brain Injury (MTBI) is one of the most prevalent neurological conditions world-wide (Cassidy 2004). It is well recognized that memory deficits are common early after injury, and disabling complaints like forgetfulness and learning problems persist for months to years after injury in a minority of patients (Bohnen 1994, Stulemeijer 2006b, Naalt van der 1999). These complaints are distressing, may contribute to a disabled lifestyle and prolong medical consumption. However, the mechanisms underlying these memory problems after MTBI remain poorly understood. Macroscopic abnormalities of brain tissue are often absent, and if present, do not consistently relate to cognitive impairments (Hofman 2001, Levin 1992, McCullagh 2001, Sadowski-Cron 2006). Rather, functional alterations in those brain structures that are involved in memory may underlie the deficits and complaints after MTBI, especially early after injury (McAllister 2001, Shaw 2002, Umile 2002). In the present study we will set out to reveal the mechanism by which MTBI causes cognitive symptoms related to declarative memory (i.e. consciously accessible events and facts). the present study is investigating functional MRI correlates of declarative memory impairments, or is seeking to identify possible anatomic substrates for such impairments Thus, we will probe the functionality of the medial temporal lobes (MTL) and the prefrontal cortex (PFC) by functional Magnetic Resonance Imaging (fMRI) in patients who recently suffered an MTBI. Both brain regions play a critical role in learning and memory (Fernandez 2001, Squire 1991), and are known to be vulnerable for traumatic impact due to their anatomical location (Belanger 2007, McAllister 2001). Hence, we hypothesize that dysfunctionality of these regions may cause the memory deficits experienced by many patients early after injury.

Although research on this topic is scarse, several studies in both animals and humans provide indirect support for this hypothesis. In rodents, for example, MTBI-like injuries can produce memory impairments and dysfunction of the hippocampus even without actual cell loss (Lyeth 1990, Lowenstein 1992, Slemmer 2002). Similarly, a study in humans found significant associations between abnormal activation in the temporal lobe and memory performance with magnetoencephalography (Lewine 2007). In addition, subtle changes in temporal lobe metabolism are detected with nuclear imaging techniques like positron emission tomography for up to six weeks after MTBI even in the absence of macroscopic tissue damage, and after the resolution of Post Traumatic Amnesia (e.g. Bergsneider 2001, Jacobs 1994, Umile 2002). However, the relation between perfusion abnormalities and cognitive performance is inconsistent (e.g. Ichise 1993, Kant 1997). Besides MTL dysfunction, impaired functionality of the PFC may negatively influence memory abilities. The critical role of the PFC in memory is well-established. Several processes attributed to the working memory system are in turn relevant for declarative long-term memory formation in the MTL. For example, cognitive operations like keeping information online, suppressing irrelevant information and binding of information across different modalities may support the formation of a unitary episode in declarative memory. (see Fernandez 2001 for a review). To date, fMRI studies on the involvement of the PFC in cognitive problems after MTBI have yielded conflicting results. Some studies showed increased activation in prefrontal areas during mental effort relative to controls, which may suggest that MTBI patients allocate additional cognitive resources in order to perform within normal limits (Hillary 2006, Jantzen 2004, McAllister 2001). Contrary, others have found less activation in the PFC during a working memory task (Chen 2007) and during a task requiring response inhibition (Easdon 2004). In all, there is reason to suggest that disturbances in both the MTL and PFC may underlie some of the cognitive problems observed early after MTBI. Still, current knowledge is limited as most of the few neuroimaging studies in this population had relatively small sample sizes, were often performed in selected samples (e.g. patients with persisting symptoms only) and have predominantly focused on frontal rather than temporal brain structures.

In the present study, we will apply behavioural measures of declarative memory and attention, and a neurophysiological measure of regional brain functionality in a large sample of MTBI patients (n= 43) in the post-acute stage (< 6 weeks) and 20 healthy, matched controls. In addition to simple comparisons between patients and control subjects, we will relate trauma severity to behavioural and neurophysiological data to establish a closer relationship between trauma and its effects on brain functionality. To activate the MTL and PFC, subjects perform the so-called n-back working memory task (Gevins 1993). The brain network subserving the n-back task, in which each new stimulus in a long series must be compared to the one presented n steps back in the series is known to involve primarily neocortical regions, particularly the dorsolateral PFC (Callicott 1999, Owen 2005). However, this task also produces a robust reduced activation or reduced engagement of the MTL including the hippocampus (Egan 2003, Meyer-Lindenberg 2001). As the n-back paradigm can equally well be executed by patients with impaired declarative memory performance as controls, thereby excluding the confounding effects of different levels of test performance on brain activation, it is suitable for use early after MTBI (McAllister 1999; Price 1999). We will test the following hypothesis: If an MTL dysfunction is present then we expect to observe reduced MTL activity without differences in n-back performance, but with reduced declarative memory performance. Dysfunction of the prefrontal cortex might

be reflected by reduced PFC activation and reduced performance on both the n-back and declarative memory task. Contrary, increased PFC activity and normal n-back performance would be expected in case the PFC exerts compensational effort to keep up with task demands.

Methods

Definition MTBI
In accordance with the criteria of the European Federation of Neurological Societies (EFNS), MTBI was defined as a history of impact to the head with or without loss of consciousness (LOC) ≤ 30 minutes, and with or without posttraumatic amnesia (PTA) and a hospital admission Glasgow Coma Score (GCS) of 13-15.(Vos *et al.*, 2002)

Subjects and procedure
All consecutive MTBI patients admitted to the emergency department (ED) of the Radboud University Nijmegen Medical Centre and the Canisius Wilhelmina Hospital Nijmegen between October 2004 and August 2006 were contacted early after injury with the request to complete a questionnaire on premorbid and current functioning. Patients were asked to participate in the MRI study when they were between 18 – 50 years of age, able to participate within six weeks after injury, had no contraindications to MRI scanning, and reported good pre-injury health (defined as no medication use and no previous neurological/ psychiatric condition). Each assessment started with the MRI scanning followed, after a 20 minute break, by a (neuro)psychological screening. A total of 50 MTBI patients participated in this study. Seven patients were omitted from the analyses for the following reasons: missing MR data due to claustrophobia (n = 2) or scanning session too demanding (n = 2), non adherence to task instructions (n = 2) and the incidental finding of non-traumatic brain abnormalities (n = 1). Thus, the final sample consisted of

43 MTBI patients (24 males/ 19 females, age range 18 – 49, mean = 31.1 years). In addition, 20 healthy subjects (11 males/ 19 females, age range 18 – 50, mean = 33.5 years), recruited via advertisements, participated in the study. No significant differences were found between the groups on age (F = .79, df (1,62), p = .375) and gender (Chi^2 = .004, df (1), p = 0.812). Also, no significant differences were found regarding educational level (scored on a 7-point scale ranging from 1: primary school to 7: college and university) between patients (mean = 5.4, SD = 1.5) and controls (mean = 4.9, SD = 1.7) (F = 1.14, df (1,62), p = .291). All subjects gave written, informed consent as approved by the local ethics committee.

Data acquisition

Clinical patient characteristics
Data on acute TBI variables such as LOC and PTA were collected by the consulting resident of Neurology on the ED as part of a standardized procedure (see Stulemeijer 2007a for a detailed description). In the present study, the duration of PTA is included as a measure of injury severity (Ahmed 2000). The assessment of the presence and resolution of PTA includes the testing of anterograde memory (using a three-word recall test) and orientation, and a behavioral screen of confusion and agitation. If PTA had already ended on admission, an estimate about the duration was made based on all information available (e.g. a patients' first memory after the accident, eyewitness reports). When PTA persisted on the ED, patients were admitted to the hospital for further monitoring. As most MTBI patients suffer only a brief period of PTA (in the range of minutes) and the first systematic assessment of PTA generally takes place at the ED, exact determination of PTA duration is often impossible. Therefore, for the present study we grouped the patients based on the estimation of PTA duration into three clinically meaningful categories that can be distinguished with a much higher degree of

certainty: (1) no PTA, (2) 1 to 30 minutes and (3) > 30 minutes. This subdivision is also used in previous studies and guidelines (Cantu 2001, Sweet 2000). General injury severity was scored with the Abbreviated Injury Score (AIS)/ Injury Severity Score (ISS) (Baker 1974). Post-acute functioning of the patients was assessed using the early questionnaire mentioned under 'Subjects and procedure'. The severity of experienced post concusional symptoms (PCS) was measured with the Rivermead Post-Concussion Questionnaire (RPQ). Subjects are asked to rate how problematic, if at all, each of 16 common PCS is experienced compared with the situation before they sustained their head injury (King 1995). Limitations in activities of daily living were assessed with the subscale 'Physical functioning' of the Short Form-36 (SF-36) (Aaronson et al., 1998), and levels of post-traumatic stress with the Impact of Events Scale (IES) (Sundin 2002).

Neuropsychological screening
A neuropsychological test battery was administered to all subjects, covering cognitive domains commonly affected early after MTBI. The screening included the Dutch version of the National Adult Reading Test (general intelligence) (Schmand 1991), the Digit-Symbol subtest of the Wechsler Adult Intelligence Scale-III (Wechsler 1997) (complex attention; visuo-motor speed), the Stroop Colour Word Interference Test (reading speed; nomination speed; inhibitory control) (Stroop 1935), the California Verbal Learning Test (verbal memory) (Delis 1987), and the subtest Faces from the Wechsler Memory Scale (visual memory) (Wechsler 1997). To assess emotional distress, all subjects completed the Beck Depression Inventory for Primary Care) (Beck 1997) and the Spielberger State-Trait Anxiety Inventory (Spielberger 1983). The items regarding state anxiety were completed at the start of the fMRI session.

fMRI n-back task
Subjects were presented with a pseudorandom series of single digits (1 – 9, white on a black background) viewed in central vision via a prismatic mirror fitted in the head coil. The task was a simple blocked design with two alternating conditions over the course of 10 cycles. During the 0-back condition (minimal working memory load), individuals were asked to decide whether the current digit was a '1'. During the 2-back condition (moderate working memory load), the task was to decide whether the digit currently presented matched the digit that had been presented two back in the sequence. On seeing a match, participants were asked to press a response-box button with their right index finger. Each block consisted of a series of 15 digits and was preceded by a sign indicating which condition was up next. As a reminder, this sign stayed on the screen below the digits throughout the block. Each digit was presented for 400 ms, followed by a 1500 ms interval. During each block there was a possibility of one, two, or three matches. Overall, each condition contained 17% targets. Participants rehearsed the tasks outside the scanner to ensure understanding of task demands.

MRI data acquisition
For fMRI we acquired $T2^*$-weighted images using an echo-planar imaging (EPI) sequence (Sonata 1.5 T, Siemens, 33 axial slices, ascending slice acquisition, volume repetition time (TR) = 2.27 sec, echo time (TE) = 30 ms, matrix size= 64 x 64, flip-angle = 90°, slice thickness = 3.0 mm, slice gap = 0.5 mm, field of view (FOV) = 224 mm). For structural MRI, we acquired T1-weighted images using a magnetization-prepared, rapid acquisition gradient echo (MPRAGE) sequence (176 sagittal slices, volume TR = 2.250 s, TE = 3.93 ms, slice-matrix size = 256 × 256, flip-angle = 15°, slice thickness = 1 mm, FOV = 256 mm).

Data analysis

Analysis of behavioral data
Statistical analyses were carried out using SPSS for Windows, 12.0 (SPSS Inc., Chicago, IL, USA). All effects were tested at the $p < 0.05$ level (two-tailed). Univariate analyses of variance were used to make group comparisons. Effect sizes (Cohen's d) were calculated using the procedure described by Zakzanis (Zakzanis 2001). By convention; effect sizes about 0.20 are considered 'small', around 0.50 as 'moderate', and from 0.80 as 'large'. Chi-square analyses were used in case of dichotomous variables. As described in the paragraph on Data acquisition, the impact of injury severity was assessed by comparing subgroups based on PTA duration. Considering the small numbers of subjects per subgroup, non-parametric Kruskall-Wallis tests were performed for these within-group analyses.

Analysis of functional MRI data
Single subject (1st level) analyses Image pre-processing and statistical analysis was performed using the SPM2 software (http://www.fil.ion.ucl.ac.uk). The functional EPI-BOLD (blood-oxygenation level-dependent) images were realigned and the subject-mean was co-registered with the corresponding structural MRI using mutual information optimization. The functional images were subsequently slice-time corrected, spatially normalized, and transformed into a common space, as defined by the SPM2 MNI T1 template, as well as spatially filtered by convolving the functional images with an isotropic 3D Gaussian kernel (10 mm full width at half maximum; FWHM). A general linear model analysis, modeling stimulus-related activation as a boxcar function convolved with the canonical hemodynamic response function, was used to create contrast images for each participant summarizing differences between block types (0-back minus 2-back/ 2-back minus 0-back),

and these images were used to create group average SPM (t) maps that were threshold at $p < .05$ family-wise error corrected (FWE). To regress out movement-related activations, the realignment parameters were added to the model as covariates. The data were high pass-filtered (128 s) to account for various low-frequency effects.
Between-group (2nd level) comparisons: The single-subject contrast images were then entered into second-level (random effects) analyses, consisting of ANOVAs comparing patients and controls. In addition, we performed a simple regression analysis examining the relation between the brain activation and PTA duration. Four categories ranging from no to long PTA duration were included as regressors (1 = controls, 2 = PTA no, 3 = PTA 1-30 minutes, 4 = PTA > 30 minutes). All analyses were first performed within region of interest (ROI). The ROI of the dorsolateral prefrontal cortex (PFC) covered Brodmann areas 9 and 46 and was made using the WFU Pick Atlas toolbox for SPM (Maldjian 2003), which provides a method for generating ROI masks based on the Talairach Daemon database. The second ROI covered the MTL, using the mask described by Amunts (Amunts 2005). In these ROI analyses, local maximum test statistics were employed and all reported p-values were FWE corrected. Secondly and exploratively, these analyses were repeated for the whole brain using a threshold of $p = .001$ (uncorrected). Coordinates are maxima in a given cluster according to the standard MNI-template implemented in SPM2.

Results

Clinical patient characteristics
Injury characteristics of the patients are shown in Table 1. Overall, the participating patients seem to represent a typical MTBI population; most patients suffered their injuries from traffic related accidents or falls, and experienced only a brief period of LOC with a varying duration of PTA. Macroscopic

abnormalities were detected in four patients (9%) and all four received a Trauma Coma Data Bank score of 2 which represents minor abnormalities that do not require neurosurgical interventions (Marshall 1991). At time of the MR assessment none of the patients was admitted to the hospital, however, all patients experienced postconcussional symptoms, and reported substantial limitations

significantly correlated with cognitive (shown in Figure 2), but not emotional or physical postconcussional symptoms. Furthermore, no association between PTA duration and age, gender, education level, the presence or location of CT abnormalities, or other early outcome variables was found (data can be provided on request).

Table 1. Injury characteristics of the 43 participating MTBI patients.

Injury characteristics	
Days since injury	mean = 24.6, SD = 10.5, range 6 – 42
Mechanism of injury	
traffic	n = 21 (49%)
falls	n = 10 (23%)
sports	n = 8 (19%)
other	n = 4 (9%)
Loss of Consciousness	n = 23 (54%), mean = 5 min, SD = 0.3
Post Traumatic Amnesia	
No	n = 13 (30%)
1-30 minutes	n = 17 (40%), mean = 11 min, SD = 0.6
> 30 minutes	n = 13 (30%), mean = 93 min, SD = 90
Brain CT abnormalities[*]	4 (9%)
# 1	bifrontal focal contusions
# 2	diffuse edema
# 3	focal edema at location of extracranial swelling
# 4	skull fracture left parietal with small focal subdural hematoma, diffuse edema left temporal and parietal
Extracranial injuries	n = 11 (26%), mean ISS = 6.5, SD = 3.9
Admission to hospital	n = 19 (44%), mean length of stay = 2.9 days, SD = 2.8
Early outcome	
RPQ Postconcussional symptoms [a]	mean = 19.4, SD = 12.2, range = 2 – 45
SF-36 Physical functioning score [b]	mean = 49.5, SD = 25.5, range =
IES Post traumatic stress [c]	mean = 7.7, SD = 7.8, range = 0 -29

[*] CTs were made according to published guidelines in 38 patients. [Vos *et al.*, 2002]
ISS = Injury Severity Score; RPQ = Rivermead Postconcussion Questionnaire; IES = Impact of Events Scale. a: scores above mean = 4.7, SD = 15.5 indicate high level of symptoms [Stulemeijer *et al.*, 2007], b: scores below 65 indicate severe limitation [Aaronson *et al*, 1998], c = scores above 26 indicate severe post traumatic stress [Sundin, 2002].

in daily functioning. On average, levels of post traumatic stress were in the low range, two patients had a score higher than 26 indicating severe stress (Sundin 2002). PTA duration was

Neuropsychological screening
A main effect of group was found for the tests in the memory domain, with patients scoring significantly poorer on both a visual

and verbal test of declarative memory. Effect sizes were moderate to large. For the performance on tests in the attentional domain, no effect of group was found for the Stroop test, measuring information processing speed (reading and naming) and executive control (color word interference). Patients did score significantly poorer on the WAIS symbol-digits test which measures complex attention and visuo-motor speed and which also has a memory component depending on the strategy used (Joy 2003). However, 39

Table 2. N-back performance, neuropsychological test scores and emotional distress scores for patients and controls.

	Patients (n = 43)			Controls (n = 20)		P-value	Effect size d
	Mean	SD		Mean	SD		
fMRI n-back performance							
0-back, % correct	99.6	2.8		99.8	1.0	.605	-0.09
0-back, mean rt (ms)	497.0	68.6		484.2	61.4	.517	0.19
2-back, % correct	89.9	18.2		87.2	20.8	.798	0.14
2-back, mean rt (ms)	620.1	118.2		594.8	92.8	.527	0.23
Neuropsychological screening							
IQ-estimation (NART)	95.8	13.6		98.1	15.3	.433	-0.16
Memory							
Verbal memory (CVLT)							
Immediate recall (List A)	-1.1	2.2		0.3	2.1	.011	-0.65
Speed of learning	-1.6	2.1		-0.3	3.0	.034	-0.55
Delayed-recall	-1.2	2.3		0.2	1.9	.030	-0.64
Recognition	0.2	1.5		-0.6	1.8	.080	-0.50
Visual memory (WMS Faces)	6.9	3.6		10.40	4.4	.002	-0.91
Attention							
WAIS substitution percentile	57.7	27.9		75.5	27.1	.012	-0.64
Stroop (t-score)							
Card 1: reading speed	49.9	8.5		50.6	13.5	.501	-0.07
Card 2: nomination speed	51.2	9.1		55.4	10.1	.130	-0.45
Card 3: response inhibition	53.4	8.0		57.1	10.6	.091	-0.42
Δ Card 3 – Card 2	53.7	7.4		55.1	9.9	.912	-0.17
Affective state							
Depressed mood (BDI-PC)	1.6	2.3		1.3	2.1	.520	0.13
State anxiety (STAI)[*]	42.2	4.3		44.7	4.6	.034	-0.57
Trait anxiety (STAI)[*]	46.7	4.5		47.5	3.9	.472	-0.19

NART= National Adult Reading Test; CVLT = California Verbal Learning Task; WMS = Wechsler Memory Scale; WAIS = Wechsler Adult Intelligence Scale, BDI-PC = Beck Depression Inventory-Primary Care; STAI = Spielberger State-Trait Anxiety Inventory.
[*] higher score is better (less anxiety)
Group differences are tested with Univariate Analysis of Variance.

patients (91%) still performed within normal limits (defined as a score within 2 standard deviations of the appropriate age and gender population stratum). No difference was found between patients and controls in the level of estimated general intelligence. Regarding emotional distress, patients were somewhat more anxious at time of the MRI assessment but did not report higher levels of depression in the past weeks or trait anxiety. Significant correlations between test performance and PTA duration were found for the delayed-recall of verbal information (shown in Figure 2) and complex attention but not for the other tests or questionnaires (data can be provided on request).

fMRI n-back performance
As shown in Table 2, no significant differences were found between the patients and the controls regarding their performance on the n-back task, and effects sizes were small. Response times were significantly slower during the 2-back condition (F(1,61) = 94.8, p < .001), but no effect of group was found (F(1,61) = 0.8, p = .374). Similarly, more errors were made in the 2-back condition than the 0-back condition (F(1,61) = 20.2, p < .001), but no differences were found between patients and controls (F(1,61) = 0.2, p = .675). No significant differences in working memory performance were found between the three PTA duration categories. For example, mean response times in the 2-back condition were as follows: controls = 594.8 (SD 92.8), PTA no = 587.6 (SD 119.7), PTA 1-30 = 633.5 (SD 100.7), PTA > 30 = 640.4 (SD 145.4) (Kruskal-Wallis chi-square (3,60) = 2.8 , p = .411). Addiotionaly, mean percentages correct in the 2-back condition were as follows: controls = 87.2 (SD 20.8), PTA no = 93.7 (SD 7.2), PTA 1-30 = 84.1 (SD 26.9), PTA > 30 = 87.3 (SD 22.8) (Kruskal-Wallis chi-square (3,60) = 0.8 , p = .842).

Functional imaging results
Main effects n-back task: The n-back task activated the expected network of brain areas (Owen 2005). Thus, the 0 minus 2-back contrast showed activation in bilateral hippocampi, bilateral middle/ inferior temporal gyri, bilateral superior medial gyri, bilateral rolandic operculum and bilateral middle cingulate cortex. Reversely, the 2 minus 0-back contrast showed activation in the bilateral dorsolateral prefrontal cortices, bilateral middle/inferior frontal gyri, superior frontal cortices, bilateral insula, supplementary
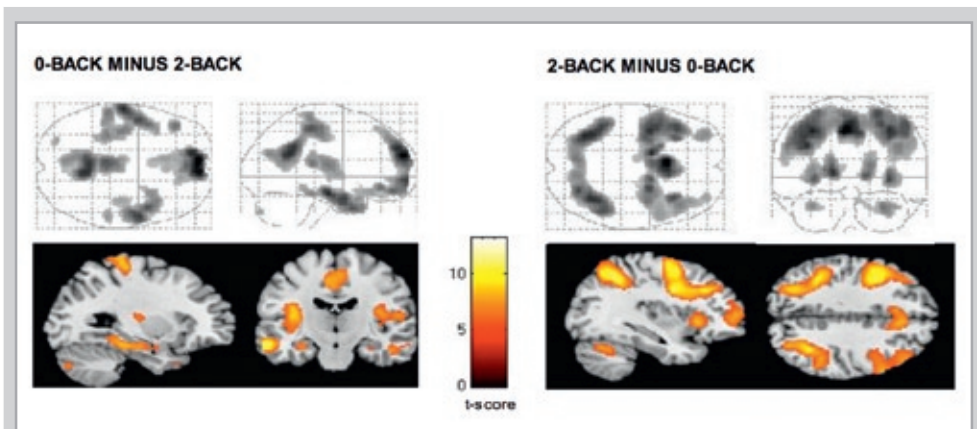

Figure 1. Maximum intensity projections of the statistical parametric maps *(upper panel)* of n-back task load comparisons in the patients and activation maps on selected sagittal, coronal and transversal slices *(lower panel)*. Left: areas of significant higher activation in the 0-back minus 2-back contrast. Right: areas of significant higher activation in the 2-back minus 0-back contrast. Displayed threshold p(FWE) < .001, extent > 25 voxels. See the results section for further details.

motor areas, bilateral inferior parietal areas and the cerebellum bilaterally. Shown in Figure 1 is the activation related to the two task conditions in patients. Comparable activations were found in controls (threshold p(FWE) < .01, extent > 25 voxels). Figures and detailed coordinates are available on request.

Between-group differences: No significant differences in brain activation were found between patients and controls in either the PFC (2-back minus 0-back contrast) nor the MTL region of interest (0-back minus 2-back contrast). Additionally, explorative whole brain analyses did not reveal significant activation differences between groups in response to both task conditions in other brain areas. To examine the potential confounding effect of higher state anxiety and poorer attentional performance in patients we exploratively repeated the 2nd level between-group analysis twice; once with the scores of the state anxiety questionnaire as a covariate, and once with the scores on the WAIS digit-symbol test of complex attention. These re-analyses did not change the results.

Association with injury severity

A significant negative correlation between PTA duration and MTL activation in 0-back minus 2-back contrast was found in the left hippocampus (local maximum x = -16, y = -30, z = -18, p(FWE) = .041, k = 52), and a
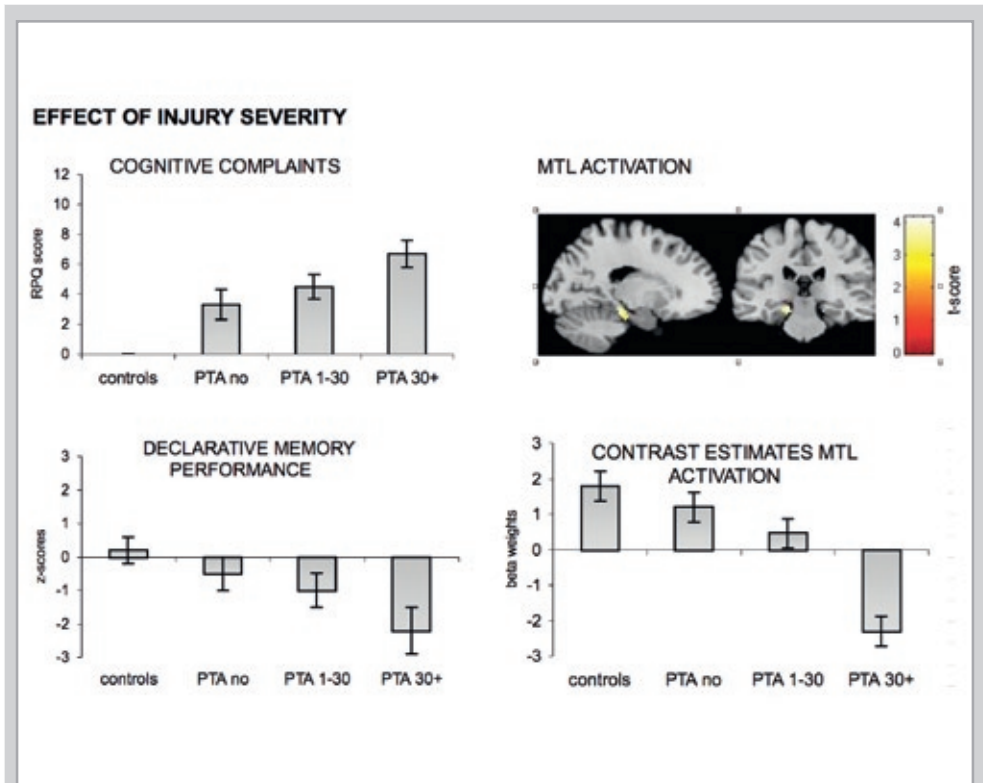

Figure 2. Left: severity of self-reported cognitive problems *(upper panel)* and performance on a declarative memory test (delayed-recall of the Californian Verbal Learning Test) *(lower panel)*. Values are displayed as means with standard error. Right: region in the MTL that correlated with PTA duration (global maximum x = -16, y = -30, z = -18, p(FWE) = .041, k = 52), derived from the 2nd level region of interest regression analysis, P = .001 correction for spatial extent *(upper panel)*. The beta weights were extracted from the between-groups ANOVA (most significant voxel in the MTL) *(lower panel)*.
RPQ = Rivermead Postconcussion Questionnaire, MTL = Medial Temporal Lobe, PTA = Post Traumatic Amnesia

trend was found in the right hippocampus (local maximum x = 18, y = -16, z = -26, p(FWE) = .075, k = 28). The fMRI and behavioral correlates of PTA duration are shown in Figure 2. In addition, explorative whole brain analyses showed a significant negative correlation between PTA duration and a cluster of activation in the brainstem, encompassing the left and right pons (local maximum x = 14, y = –16, z = –26, k = 807, p(FWE) < .001).

Discussion

In this study, we used behavioral assessment and fMRI to investigate memory performance in a large sample of patients who recently suffered MTBI, and healthy controls. The MTBI patients performed poorer on a test of declarative memory, and this performance was proportionally related to the severity of the injury. In addition, injury severity was related to more severe cognitive complaints. The fMRI results showed a correlation between injury severity and activation strength in the MTL, without performance differences between patients and controls. Together, these findings support our hypothesis that functional alterations of the MTL contribute to cognitive dysfunction early after MTBI.

To our knowledge, our study is the first to explore MTL functionality in MTBI patients using fMRI. The results suggest that MTBI disrupts the normal MTL disengagement pattern during performance of the n-back working memory task, as longer PTA duration related to less activation in the MTL in the 0-back minus 2-back contrast. As discussed by others in different patient populations, this pattern likely reflects an impaired ability to suppress MTL activity during the performance of the 2-back condition (Egan 2003, Meyer-Lindeberg 2001, Pochon 2002). Insufficient suppression may cause incidental learning of the digits thereby reducing the efficiency of working memory processes. Alternatively, due to the subtraction logic of our block design,

our findings might also reflect *more* activation during the 2-back condition in relation to longer PTA. Possibly, MTBI patients with more severe injuries may need additional MTL support in order to support the common working memory circuit. However, this latter explanation seems unlikely. Unlike previous studies which found hippocampal activation during a working memory task, our paradigm is very simple, does not require feature binding, and contains only a very brief maintenance period (Olson 2006, Piekema 2006). Hence, MTBI severity seems to go along with an MTL dysfunctionality which might explain effects of MTBI on declarative memory performance.

Although the 2-back condition strongly activated the expected regions associated with working memory (Owen 2005), including the PFC, no activation differences were found between patients and controls in the frontal lobes, and prefrontal activation did not relate to injury severity. In addition, patients did not show signs of impairments on the Stroop Colour-Word task which is considered sensitive for frontal dysfunction (Demakis 2004). Hence, in contrast to previous studies, our findings do not seem to support the hypothesis that MTBI patients have to allocate additional compensatory efforts in order to obtain the same behavioral results (Jantzen 2004, McAllister 1999, 2001), nor that frontal dysfunction is present (Chen 2007, Easdon 2004). However, we cannot rule out MTBI effects of PFC functionality as the n-back activation does not cover the entire PFC, and the design of our study does not allow exact replication of previous findings. For example, McAllister and coworkers found a disproportional increase of activation in the PFC under the 1-back versus 0-back condition in MTBI patients, but less incremental activation under the 2-back versus 1-back condition (McAllister 1999). As cerebral activation and increasing cognitive load may not be related in a linear manner, differences in activation between patients and controls might only become apparent

when a parametric modulation is introduced (Callicott 1999, McAllister 1999). As reviewed by Hillary, further characterization of the role of PFC in modulating working memory performance in clinical samples will require the use of longitudinal examinations, parametric manipulations with tight control over task load/performance relationships, and both verbal and nonverbal working memory paradigms (Hillary 2006).

The present study supports previous work suggesting that dysfunction of the MTL might underlie the memory deficits commonly observed early after MTBI. But currently many questions remain how MTBI induces these deficits, what magnitude of injury is required to trigger the dysfunction and why the MTL would be especially vulnerable for damage. It seems unlikely that direct structural injury to the hippocampus accounts for most of the memory deficits in MTBI patients, because circumscribed microscopic lesions on the basis of (in)direct trauma effects are rare. Rather, there is growing interest in the role of dysfunction of the cholinergic system in the development of acute as well as late cognitive deficits (McAllister 2006, Umile 2002). Animal studies have shown that a single concussive injury can induce selective disruptions of cholinergic neurons in the hippocampus, a structure in which they are particularly abundant, and might even lead to selective cholinergic cell loss (see McCarthy 2003 for a detailed description). In humans, patients with more severe TBI displayed atrophic changes of brain tissue which highly coincided with the distribution of the cholinergic system in the brain, including the bilateral hippocampus (Salmond 2005). In case of MTBI, disruption of the cholinergic system may be transient in most patients followed by recovery rather than cell loss. The presence of cholinergic dysfunction, its natural history and the relationship with memory performance after MTBI need to be further established. For a proper function the MTL depends on intact network connections with many other brain areas. Possibly, memory functionality may also be comprised by disturbances in the axonal connections within or between these networks (Arcienigas 2001). Diffusion tensor imaging in MTBI patients has shown promise for detecting abnormalities in structural connectivity between brain structures (Bazarian 2007, Kraus 2007). In addition, resting state fMRI is potentially useful for detecting MTBI related changes in the functional organization of memory networks (Salvador 2005).

An unexpected, yet intriguing finding was the strong negative correlation between the duration of PTA and the pons activation in the 0-back minus 2-back contrast. This brainstem structure is part of the ascending reticular activating system which governs overall basic arousal level, serves as a relay station for cerebellar afferents and is functionally related to corticopontine projections, parietal and prefrontal areas (Schmahmann 1997). The role of the pons in higher-order cognitive processes is not well-established, although pons activation during several effortful cognitive tasks (mental arithmetic (Critchley 2000), declarative memory (Weis 2004), (Chen 2005)) has been observed. As we did not have an a priori hypothesis regarding this relation, and the pons is not one of the structures known to be necessary to perform the n-back task, we may attach only limited significance to the results. Nevertheless, previous work relates the induction of PTA to a temporal disruption of the brainstem (Watson 1995). In addition, studies using single photon emission computed tomography have found relationships between the presence or duration of PTA and the degree of brainstem hypoperfusion (e.g. Gowda 2006, Lorberboym 2002) and brainstem auditory evoked potentials have been demonstrated to be abnormal in 10% to 40% of patients with acute MTBI (Rizzo 1983, Schoenhuber 1983, Soustiel 1995). Potentially, our results reflect that even after PTA has resolved, the brainstem is still somewhat functionally

impaired. As we did not include measures of brain stem integrity in our study this assumption remains speculative.

In the present study, only patients without significant emotional or physical problems before the injury were included, and most participants had suffered 'uncomplicated' MTBI (e.g. without evidence of CT abnormalities). This approach offers a much 'cleaner' view on the impact of MTBI on cognition, but may limit the generalisability of the findings to the entire MTBI population. However, the participating patients resembled the general ED-admitted population to a large degree regarding trauma and demographic characteristics and early functioning. At the time of MRI assessment all patients were still in the process of recovery, they experienced a range of postconcussional symptoms and reported limitations in daily life functioning due to the injury. In line with previous studies on early cognitive functioning, patients displayed poorer performance on tests of decralative memory and attention, and cognitive difficulties were among the most frequently reported problems. The patients did not report high levels of emotional distress, but nevertheless did experience significantly more anxiety at time of the MRI assessment. Explorative post-hoc analyses showed that including state anxiety as a covariate in the group analyses did not change the results. In all, the findings of our study do not seem to be greatly confounded by factors unrelated to the injury.

There is considerable debate about the impact of MTBI on cognitive abilities. Generally, it is assumed that neurological/ somatic factors explain the acute disturbances, whereas psychological factors account for most of the late cognitive problems (Iverson 2006). However, few studies measured brain activation during cognitive effort in the first weeks after injury and integrated neurophysiological and behavioural findings. The results presented in the current paper contribute to this discussion by revealing a system-level mechanism by which MTBI may cause a declarative memory deficit even in the post-acute stage. The MTL (and possibly also the pons) may be especially relevant for understanding MTBI induced changes in the brain, and could be selected as seed regions in future analyses. The clinical utility (e.g. guiding management) of our findings is yet unknown. It is known that cognitive deficits after MTBI resolve completely and spontaneously in most patients within three months, regardless of initial injury severity, whereas a minority will develop chronic cognitive sequelae. It is a challenge for future studies to demonstrate that early MTL dysfunction has the power to identify patients at risk for such long-term cognitive problems. There is preliminary evidence that fMRI is a sensitive tool for investigating changes in brain functionality related to recovery after MTBI (Jantzen 2004). Also, it would be of interest to examine the relation between emotional distress, personality traits and cognition in patients with persistent cognitive problems for it is well-known that such factors strongly relate to long-term cognitive problems but the neuronal underpinnings of these interactions remain poorly understood (Iverson 2005, Stulemeijer 2007b).

In conclusion, by using fMRI, we were able to detect alterations in functionality of the brain in patients with predominantly uncomplicated MTBI that would go unnoticed using standard imaging techniques. The findings suggest that reduced medial temporal lobe functionality may cause impaired declarative memory processing in the post-acute stage, especially in patients with more severe injury.

Chapter 5

Cognitive performance after Mild Traumatic Brain Injury: the impact of poor effort on test results and its relation to distress, personality and litigation.

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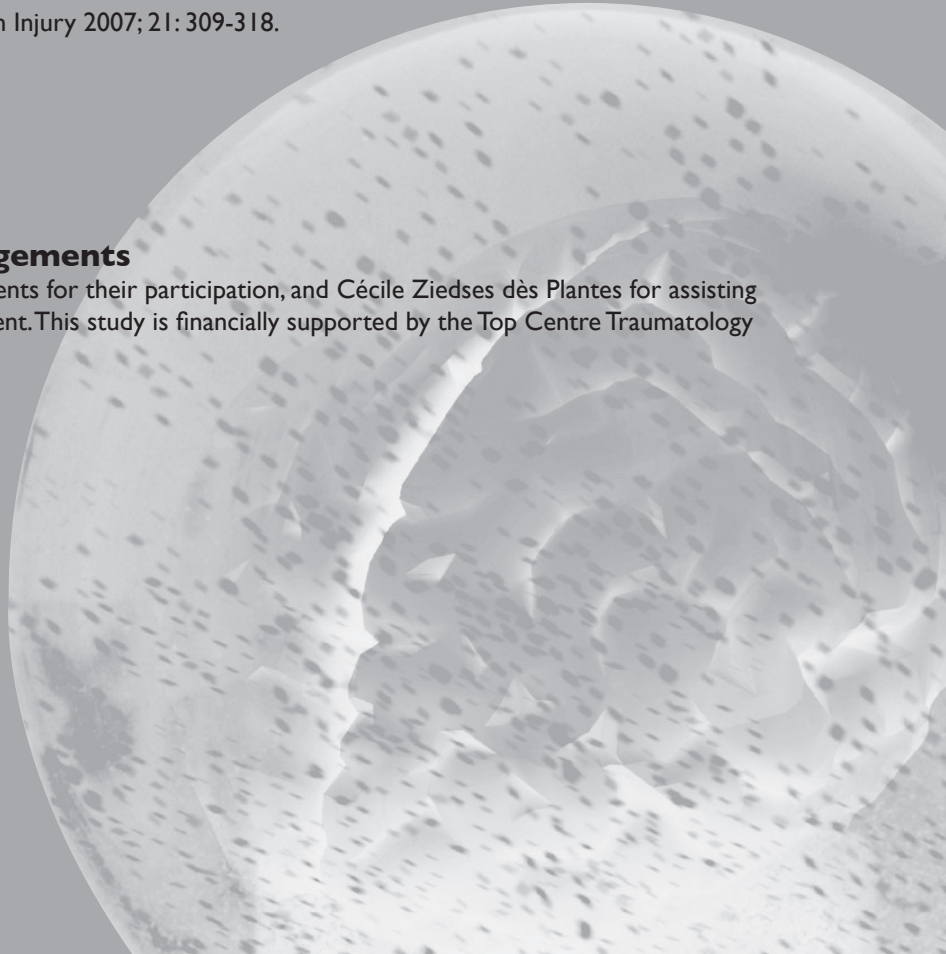
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Abstract

The primary objective of this study is to compare consecutive Mild Traumatic Brain Injury (MTBI) patients with and without adequate effort on cognitive performance, litigation status, fatigue, distress and personality. (Neuro)psychological assessment was done six months post-injury in 110 patients from a cohort of 618 consecutive MTBI patients aged 18 – 60, who attended the emergency department of our level I trauma centre. Effort was tested with the Amsterdam Short Term Memory test.

Our results show that thirty patients (27%) failed the effort test. Poor effort was associated with significantly poorer scores on seven out of eleven measures, covering all tested domains. Poor effort was associated with lower educational level and changes in work status, but not litigation. Furthermore, poor effort was related to high levels of distress, Type-D personality and fatigue. We conclude that even in a sample of non-referred MTBI patients, poor effort was common and was strongly associated with inferior test performance. These findings imply that effort testing should be part of all cognitive assessments, also outside mediolegal settings. Behavioural factors like distress and personality should be considered as potential threats to the validity of neuropsychological testing after MTBI.

Introduction

With an incidence of 100-300/100,000 hospital-treated patients, Mild Traumatic Brain Injury (MTBI) is one of the most prevalent neurological disorders (Cassidy 2004). Although many MTBI patients make a good functional recovery, persistent cognitive complaints are common (Alexander 1995). Several studies using neuropsychological tests found small but significant decrements in cognitive functioning (Barth 1983, Leininger 1990, Vanderploeg 2005), but the interpretation of these findings is complicated as injury characteristics have shown only very weak, if any, relation to test performance long after injury (Belanger 2005a, Binder 1997, Leininger 1990, Ponsford 2000). In contrast, there is growing evidence that behavioural factors may account for many of the impairments found (Binder 2003, Green 2001, Keller 2000, Ross 2006, Suhr 2002).

One such behavioural factor that may greatly influence neuropsychological test performance is the amount of effort that a patient exerts during testing. Used in this context, the term effort refers to the non-specific allocation of energy to mental activities associated with performing a test. (Kahneman 1973). Several studies suggest that in a considerable portion of MTBI patients, insufficient effort during testing is allocated, which greatly hampers interpretation of the results (Binder 2003, Green 2001, Moore 2004, Ross 2006). Measuring effort however, is no a straightforward task. Although many advances are made in the development of measures that enable discrimination between poor and adequate effort, a 'gold standard' is still lacking. Many of these tests, usually referred to as 'effort tests' or 'validity tests', are based on principles such as performing under chance level or performing under a norm-based criterion (Rogers 1993).

The amount of effort a subject exerts is dynamic not static, it can be increased or decreased by both involuntary processes (e.g. arousal level) and by intention (e.g. motivation) (Brehm 1983, Kahneman 1973). To date, effort testing in MTBI patients has generally been restricted to studies done in the mediolegal context. In these studies, poor effort is often regarded within the framework of 'malingering', a popular concept to describe patients that intentionally exert insufficient effort during testing or fake cognitive dysfunction in order to get some external incentive. Results of these studies

show that poor effort is a major contributor to poor neuropsychological test performance (Binder 1996, Constantinou 2005, Heinly 2005, Langeluddecke 2003). Outside the mediolegal context, effort tests are rarely used, implicitly assuming that effort level will be adequate if no external gain is expected. However, this view neglects the fact that there are many other factors that potentially affect the amount of effort a patient is able to exert during testing (Leininger 1990, Ross 2006, Suhr 1997. For example, state factors like anxiety, depression or fatigue, which are all common in MTBI patients, may decrease effort level (Gass 1997, Rapoport 2005, Stulemeijer 2006b). In addition, trait factors like individual personality structure or general intelligence may be associated with differences in performance style and as such may influence effort level (Cattelani 1996, Efklides 2006, Revelle 1993, Rose 2002).

Little is known about how much these factors which have little to do with intention, contribute to effort level during neuropsychological performance of MTBI patients. Furthermore, many questions remain about the necessity of including effort tests in assessments done outside the mediolegal context. Because results yielded in the absence of demonstrated good effort may be highly misleading, more knowledge is needed to advance the heated debate about the 'true' impact of MTBI on cognitive abilities, as well as to better understand the cognitive complaints reported by patients. Moreover, knowing which factors influence effort level may serve as a starting point for the design of effort enhancing interventions. The aim of this study was two-fold. Firstly, we used a validated effort test to explore the impact of poor effort on neuropsychological tests performance in non-referred MTBI patients, six months after injury. Secondly, to better understand the factors contributing to poor effort besides litigation, patients with and without adequate effort were compared on levels of distress, fatigue, and personality.

Methods

Definition MTBI
A history of impact to the head with or without loss of consciousness (LOC) ≤30 minutes and with or without PTA and a hospital admission Glasgow Coma Score (GCS) 13-15. Injury severity was classified according to the guidelines of the European Federation of Neurological Societies (Vos 2002).

Patients
All patients took part in a longitudinal prospective cohort study on outcome after MTBI. In this study 618 consecutive patients aged 18 – 60 who attended the emergency department (ED) of the of the Radboud University Nijmegen Medical Centre, a level I trauma centre, with a diagnosis of MTBI in the period November 2001 to October 2003 were sent a letter with information on the study and a questionnaire six months post injury. Of the 299 patients that returned the questionnaire, 113 patients were also willing to undergo (neuro)psychological evaluation. The final sample consisted of 110 patients, as three patients had missing data on more than one test and were excluded from the analysis. Compared to the patients that did not participate in the extensive study, participants more frequently reported posttraumatic amnesia (PTA) (76% vs. 64%, Chi^2 = 4.8, p = .029), no other significant differences were found in demographic variables or injury characteristics.

Procedure
The extensive study existed of a two-day (neuro-)psychological assessment in the outpatient clinic of the Radboud University Nijmegen Medical Centre. In the first session (1.5hrs) which was supervised by a research nurse (J.B.), patients completed computerized questionnaires. In the second session, two weeks later, patients completed a concise neuropsychological test battery. All tests were

done by a single neuropsychologist (M.S.). The study was approved by the ethics committee of the Radboud University Nijmegen Medical Centre and all patients participating in the study gave written informed consent.

Injury parameters

As part of a standardized registration procedure, a range of clinical injury indices were recorded on admission to the ED (e.g. GCS, risk factors for intracranial complications and mechanism of injury). The presence and duration of LOC was based on reports of witnesses or ambulance personnel, and the presence and resolution of PTA was assessed by a resident of Neurology by a series of questions regarding short-term memory and orientation. A CT of the head was performed according to international guidelines.[30] For the purpose of this study, CTs were classified as normal or abnormal. A CT was defined as abnormal if showing signs of contusion, oedema, subdural hematoma, epidural hematoma or subarachnoid haemorrhage, according to one rater blinded from all outcome measures (P.V.) If alcohol or drug intoxication was suspected, a blood draw was conducted on the ED to determine blood-alcohol levels.

Neuropsychological assessment

Effort testing: Effort was measured with the Amsterdam Short Term Memory Test (ASTM) (Bolan 2003, Hout van 2003, Schagen 1997), a test developed to detect negative response bias or insufficient effort. The test is presented to the subject as a test of short-term memory and concentration. The test consists of 30 items and 2 practice items. Each item consists of five printed words from the same semantic category, which the subject has to read aloud and try to remember. Subsequently, a distraction task is presented in which the subject has to mentally solve a simple written addition- or subtraction task. Finally, five words from the same semantic category as before are presented and the subject has to indicate the three words that were also presented in the

first series. The maximum score is 90 points (30 items×three words correct). Validation studies showed high average scores (> 89) for healthy subjects and severe closed head injury patients (Schagen 1997). In accordance with previous studies, scores below 86 points were considered to be indicative of poor performance (Schmand 1998).

General intelligence: the Dutch version of the National Adult Reading Test (NART) was used to estimate premorbid intelligence level (Schmand 1991). The NART consists of a series of words with an irregular pronunciation which the subject reads aloud.

Memory: was assessed with the Dutch version of the California Verbal Learning Test (CVLT) (Delis 1987, Mulder 1996). In the CVLT, subjects have to remember a shopping list of 16 items over five immediate recall trials. The list consists of four items from four semantically distinct categories. Following the five learning trials, a second, interference list is presented for one trial. Short-delay free recall and category-cued recall of List A are then tested. After a 20-min interval, long-delay free recall, category-cued and recognition memory recall of List A are assessed. In the present study, normative z-scores of the List A Total Recall, and long delayed free recall will be reported.

Attention: Two subtests of the computerized Test battery of Attention Performance (TAP) were applied (Zimmermann 1996). Firstly, Divided attention, in which visuo-spatial and auditory stimulation are presented simultaneously. The visual task was to detect squares made up by four crosses out of eight crosses that appear in 100 random configurations on the computer screen. The parallel acoustical task requires detecting irregularities in the alternating sequence of 200 high and low beeps. Secondly, Working memory, a visual 2-back task, in which participants were presented with a series of digits (1 – 9) and were to indicate whether the current stimulus matches the stimulus presented 2 stimuli back in the series. For both subtests, median reaction times

and number of correct responses will be reported

Information processing speed: Two subtests of the Complex Reaction Time Task (CRT) were used to measure speed of information processing and motor speed (Vercoulen 1998). In this test, five target buttons were situated on a response board at equal distance around a start button. Each target button contained a stimulus light. During the two tasks, the subject kept the start button pressed, until a stimulus lit up. In the first task only one stimulus button could light up. In the second task, three different target buttons could light up in random order. In both tasks subjects were asked to press the button that lit up as fast as possible. A distinction could be made between speed of information processing (time between light went on and start button was released) and motor speed (movement time between releasing start button and pressing the target button). Mean reaction times will be presented. Furthermore, the Digit-Symbol subtest of the Wechsler Adult Intelligence Scale-III was administered (Wechsler 1997). In this test, 93 numbers in a boxed, grid-like array are presented along with a "key" of nine numbers (1-9), each with an associated "symbol. Subjects must code as many number as possible within 90 seconds, in the empty square beneath it, with its proper symbol. Gender and age corrected normative t-score will be presented.

Definition of cognitive impairments

For all tests except the CRT, population based normative scores were available. Clinical impairments were defined a score below the fifth percentile of published population norms.

Psychological questionnaires

Distress: depressed mood was assessed using the Beck Depression Inventory for Primary Care (BDI-PC) (Beck 1997). The BDI-PC excluded the somatic and performance items of the original BDI, and only contains affective items like sadness, loss of pleasure and self dislike. The 7 items are rated on a 4 point scale (0–3), and patients were instructed to describe their symptoms for the "past 2 weeks including today".

Anxiety was measured with the SCL-90 Anxiety Subscale, a 10-item self-report scale, indicating the degree to which a person was distressed by a specific problem in the past week (Degoratis 1994). The measure uses a 5-point response scale, ranging from "not at all" to "extremely".

The Impact of Events Scale (IES) was administered to assess levels of post traumatic stress (Sundin 2002). The IES scale consists of 15 items, 7 of which measure intrusive symptoms (intrusive thoughts, nightmares, intrusive feelings and imagery), 8 tap avoidance symptoms (numbing of responsiveness, avoidance of feelings, situations, ideas), and combined, provide a total subjective stress score. Respondents are asked to rate the items on a 4-point scale according to how often each has occurred in the past 7 days.

Personality: The short version of the Eysenck Personality Questionnaire (EPQ-RSS) was used to measure degree of neuroticism and extraversion (Sanderman 1995). Both subscales comprises 12 yes/no questions that explore attitudes and tendencies.

In addition, a 14 item Type D personality scale (DS-14) was administered to measure the subjects' tendency to experience distress (Denollet 2005). The DS-14 comprises a 7-item subscale which measures negative affectivity (NA) (e.g. "I often feel unhappy"), and a 7-item subscale measuring social inhibition (SI) (e.g. "I'm a closed kind of person"). Ratings are done on a 5-point Likert scale ranging from 0= false to 4 = true. The subscales can be scored as continuous variables (range 0 – 28). Subjects that score high ($\geq$ 10) on both NA and SI are classified as having Type-D personality.

Fatigue severity and fatigue related dimensions were measured with the Checklist Individual Strength (CIS), a 20-item self-report questionnaire which measures four aspects of

Table 1. Patient characteristics and injury characteristics by effort level.

	Effort level				p-value
	Poor		**Adequate**		
	n = 30 (27%)		n = 80 (63%)		
Patient characteristics					
Male	22	73%	50	63%	.287
Age (mean) [a]	36.8 SD12.7		38.2 SD 10.4		.570
Higher education (>=12 years)	4	13%	41	51%	.001
History of psychiatric / emotional problems [b]	13	43%	19	24%	.044
Use of anti-epileptics, mood or sleep medication	5	17%	7	9%	.288
Changes in occupation [c]	13	43%	12	15%	.002
Currently involved in litigation [d]	8	27%	21	25%	.892
Mechanism of injury					.036
Traffic	11	37%	42	53%	
Fall	10	33%	21	26%	
Violence	7	23%	5	6%	
Other	2	7%	12	15%	
Head injury severity					
Hospital admission Glasgow Coma Score of 15	28	93%	68	85%	.243
Reported loss of Consciousness	14	64%	38	57%	.399
Post Traumatic Amnesia	18	62%	62	82%	.036
Retrograde amnesia	9	30%	26	33%	.544
Brain CT abnormalities [e]	4	17%	13	20%	.723
Other					
Time since injury in months (mean)	6.4 SD 0.7		6.2 SD 0.7		.293
Additional systemic injury	11	37%	27	34%	.774
Alcohol / drugs intoxication	5	17%	24	30%	.243
Admission to hospital	18	60%	43	54%	.557

Values are displayed as number/ percentage and group differences are tested with Chi² tests unless stated otherwise.
[a] Group differences are tested with Analysis of Variance.
[b] Based on self-reports of the patients.
[c] Defined as current sick leave or change of working status into partial or lower-level employment due to the accident.
[d] defined as current involvement in insurance claims or legal proceedings due to the accident
[e] CT imaging of the head was done in 89 patients, in all other patients this was not indicated.

fatigue during the previous two weeks: Fatigue severity (8 items), Concentration problems (5 items), Reduced motivation (4 items) and Reduced activity (3 items) (Dittner 2004, Stulemeijer 2006b). Each item was scored on a 7-point Likert scale. High scores indicate high level of fatigue, a high level of concentration problems, low motivation and low levels of physical activity.

Statistical analysis

Based on their scores on the ASTM two groups of patients were formed: those in whom poor effort was suspected (score < 86) and those patients that scored above this cut off which suggests adequate effort. Since responses on

some outcome measures were not-normally distributed, a natural log transformation was performed to correct for skewness. Analyses of variance were used for between-group comparisons. To minimize Type-I error, multivariate analyses of variance (MANOVAs) were used to make group comparisons across cognitive domains, and only when main effects were significant, univariate analysis were performed. Chi-square analyses were used in the case of dichotomous variables. Data analyses were performed using SPSS software version 12.0 (SPSS Inc., Chicago, IL, USA). All effects were tested at the $p < 0.05$ level (two-tailed).

Table 2. Cognitive test performance of MTBI patients by effort level.

	Effort level		
	Poor	**Adequate**	p-value
General intelligence			
NART IQ estimation [h]	84.3 (13.6)	97.1 (15.8)	.009 [a]
Verbal memory (CVLT)			**.001**
Immediate free recall List A [d]	-2.1 (0.3)	-0.4 (0.2)	.001 [a]
Long-delay free recall [d]	-1.5 (2.6)	-1.4 (2.3)	.361
Attention			**.004**
Divided Attention (TAP)			
Reaction time [f]	743.9 (15.7)	682.9 (9.1)	.124 [b]
No correct	27.9 (0.5)	29.1 (0.3)	.440 [a]
Working Memory (TAP)			
Reaction time [f]	714.3 (33.6)	655.2 (19.2)	.038
No correct	11.3 (0.4)	13.0 (0.3)	.001
Information processing			**.002**
Digit symbol No correct (WAIS) [e]	36.5 (2.1)	48.9 (1.2)	.001
Simple speed of information processing [g] (CRT)	395.6 (19.9)	301.8 (12.1)	.001
Processing of choice selection (CRT) [g]	427.2 (143.2)	335.7 (76.2)	.002
Motor speed			
Simple motor speed (CRT) [h]	263.7 (15.7)	214.0 (9.6)	.010

Group differences are tested with Multivariate (p-values in bold) and Univariate Analysis of Variance's, with education, premorbid emotional problems and changes in work status as covariates
[a] covariate education is significant/ [b] factor changes in work status significant
[d] z-score (SD); [e] t-score (SD); [f] median reaction time (SD); [g] mean reaction time (SD); [h] mean movement time (SD).
CVLT, California Verbal Learning Task; WAIS, Wechsler Adult Intelligence Scale; TAP, Test for Attentional Performance; CRT, Complex Reaction Time task; SE, Standard Error.

Results

Patient characteristics and the prevalence of poor effort

Thirty patients (27%) scored below the cut off value on the ASTM effort test, which was indicative for poor performance. As shown in Table 1, these patients had significantly lower educational levels and more often reported a history of psychiatric or emotional problems than patients who scored above the cut off. Furthermore, a significantly greater portion of all patients that showed poor effort had not returned to their premorbid occupation status. To control for potential influence of these variables on performance we included them as factors in all further analysis. In the tables unadjusted scores are presented. Regarding injury characteristics, a greater proportion of patients with poor effort was injured through violence, whereas PTA was less common.

Impact of effort on neuropsychological test performance.

As shown in Table 2, patients that failed the effort test performed significantly worse on seven out of eleven measures, covering all tested domains even after adjustment for potential confounders. On all four cognitive domains there was a significantly higher percentage of patients with clinically impaired scores within the poor effort group (Figure 1). Twenty-four patients (30%) of those that showed adequate effort scored within the clinically impaired range on one or more of the tests, of which 3 had impaired scores on 3 or more tests (4%). In comparison, 19 (63%) of the patients with poor effort scored within the clinically impaired range on one or more of the tests, of which 8 patients had impaired scores on 3 or more tests (27%) ($Chi^2 = 21.1$, $p < .001$).

Relation between effort status and distress, fatigue and personality

Main effects of effort status were found for measures of distress, personality and fatigue. As shown in Table 3, patients in the poor effort group reported more severe depressive symptoms and higher levels of post traumatic stress. Furthermore, these
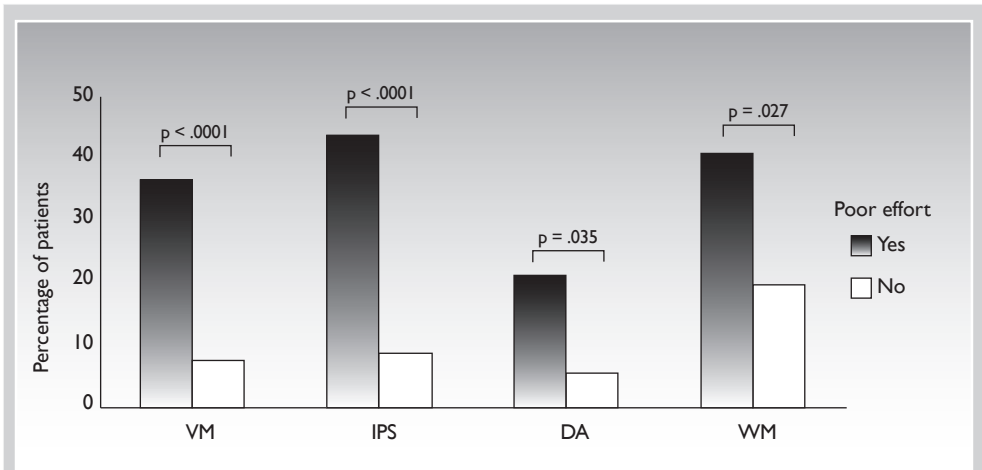

Figure 1. Proportion of patients with clinically impaired scores by effort level. [a]

[a] Clinical impairments are defined as scores below the 5th percentile of published population norms.
P-value represent differences for patients with and without suspected underperformance by Chi^2 analysis.
VM, verbal memory (immediate free recall of the California Verbal Learning Task); IPS, information processing speed (numbers correct, Digit symbol), DA, Divided Attention (median response time, Test for Attentional Performance), WM, working memory (median response time, Test for Attentional Performance).

Table 3. Scores of MTBI patients on psychological questionnaires by effort level.

	Effort level				p-value
	Poor		**Adequate**		
Distress					**.021**
Depressed mood (BDI; range: 0 - 21)	3.3 (2.7)		1.4 (2.0)		.004 [a]
Anxiety (SCL-90; range: 8 - 40)	16.7 (6.7)		13.4 (5.9)		.117 [a]
Post traumatic stress (IES; range: 0 - 75)	29.0 (12.3)		22.5 (8.3)		.045 [a]
Personality					**.008**
Neuroticism (EPQ; range: 0-12)	6.8 (2.1)		6.1 (2.4)		.172
Extraversion (EPQ; range: 0-12)	7.2 (2.5)		7.2 (2.2)		.911
Social inhibition (DS-14; range: 0 – 28)	11.8 (6.2)		8.4 (4.6)		.001
Negative affectivity (DS-14; range: 0 – 28)	12.8 (6.4)		9.2 (5.6)		.020
Type-D personality (N/ %)	16	53%	17	21%	.001 [b]
Fatigue and fatigue related dimensions (CIS)					**.011**
Fatigue severity (range: 8-56)	38.6 (12.3)		29.3 (14.2)		.039 [a]
Concentration problems (range: 5 – 35)	23.6 (9.1)		17.7 (9.1)		.089 [a]
Reduced motivation (range: 4 – 28)	17.6 (6.9)		11.6 (5.8)		.000
Reduced Activity (range: 3 – 21)	12.2 (5.7)		9.5 (6.1)		.247 [a]

Values are displayed as mean (SD). Group differences are tested with Analysis of Variance, with education, premorbid emotional problems and changes in work status as covariates unless stated urwise.
[a] covariate education is significant
[b] group differences are tested with Chi-square analysis
BDI-PC, Beck Depression Inventory – Primary Care; SCL-90, Symptom Checklist 90; IES, Impact of Events Scale; PTSD, Posttraumatic Stress Disorder; CIS, Checklist Individual Strengths; EPQ, Eysenck Personality Questionnaire; DS-14, Type D Scale-14 .

patients had higher scores on the personality constructs negative affectivity and social inhibition, but not on the constructs extraversion and neuroticism. Lastly, patients in the poor effort group showed higher fatigue severity and greater reductions in motivation.

Discussion

We performed neuropsychological testing in 110 MTBI patients from a consecutive cohort six-months after ED admission. Twenty-seven percent of the patients failed a validated effort test, which falls within the wide range of 15 – 60% reported in previous TBI studies (Binder 2003, Langeluddecke 2003,

Moore 2004). Direct comparison, however, is hampered as these studies employed different criteria for detecting poor effort and were performed in referred patients (e.g. claimants or symptomatic patients). In line with previous findings, poor performance on the effort task was strongly associated with poorer neuropsychological test performance and more clinical impairments on all tested cognitive domains. It affected both relatively simple (e.g. simple motor speed) as well as more effortful tests (e.g. verbal memory), and both self-paced and timed tests. Of all patients with one or more clinically impaired test scores (43/110), 44% patients failed the effort test.

To gain a better understanding of the factors

associated with poor effort we incorporated a range of questions regarding current as well as premorbid functioning. Regarding current functioning, our results showed that poor performance on the effort task was especially prevalent among patients who reported high levels of affective distress and more severe fatigue in the weeks before the assessment. In contrast to most studies done in mediolegal settings, involvement in litigation was not associated with poorer effort, although a larger proportion of patients with poor effort had not yet returned to former work status (Binder 1996, Paniak 2002a). Nine of these patients were still on sick leave and received wage-related disability state benefits without being in litigation. Of those 9 patients, 4 failed the effort task. Unfortunately, these numbers are too small to perform meaningful statistical analysis. The lack of association between litigation and effort may well be explained by the design of our study. We recruited patients from an ED admitted cohort and participants were explicitly informed that data were collected for research purposes only, and results would not be communicated to third parties. Other studies that separated compensation status from effort also found no effect of litigation (Leininger 1990, Suhr 1997).

Regarding premorbid functioning, poor effort was more common in patients with a history of psychiatric or emotional problems which is in line with previous findings (Moore 2004). In support of a relation between vulnerability for affective distress and poor effort, half of the patients that failed the effort task showed strong Type-D personality tendencies, compared to only 20% of the patients who produced adequate effort. This personality construct describes people who are inclined to experience increased negative emotions and tend to inhibit the expression of these emotions in social interactions (Denollet 2005). In cardiac patients, Type-D is increasingly being recognized as an important construct to understand individual differences in stress-related responses. It is associated with higher levels of distress but also relates to poor prognosis (Denollet 2006). The relation between Type-D personality and poor effort deserves further study, and prospective studies have yet to show whether this personality construct also has predictive value for outcome after head injury. Surprisingly, in contrast to several other studies on cognitive effort, poor effort was strongly related to lower educational level (Binder 2003, Hout van 2003, Langeluddecke 2003, Lindem 2003, Schmand 1998). Although no effects of education were found in the original ASTM validation study, this finding warrants further examination of the relation between effort and education in MTBI patients with lower educational level (Schagen 1997, Schmand 1999).

The findings of the present study may have important practical implications. First of all, the high frequency of poor performance in our sample of non-referred patients shows that assessment of performance validity is necessitated in all neuropsychological evaluations for both clinical and scientific purposes, and should not be limited to evaluations done in the context of incentive. Furthermore, the detrimental effects of poor effort on test performance emphasize that one should be very cautious when attributing abnormal neuropsychological test scores to possible brain dysfunction, and indicate that affective and behavioural factors should always be considered. In addition, our results suggest that poor effort poses a serious threat to the validity of the postconcussional disorder (PCD) diagnosis according to the DSM-IV criterion (Boake 2004). Besides self-reported complaints, this criterion requires cognitive deficits in attention and/or memory on formal testing. We believe that PCD should not be diagnosed in the absence of demonstrated good effort. Lastly, our findings may contribute to the design of therapeutic interventions to enhance

test performance. We showed that both state (e.g. fatigue and distress) and trait (Type-D personality) variables were related to poor effort. Additionally, others also suggest that behavioural factors like patients' expectancies or differences in goal-setting may influence test-performance (Keller 2000, Suhr 2002). In all, there is substantial evidence that, in order to optimize effort level and thereby the validity of cognitive test results, psychological strategies aimed at motivation enhancement or stress reduction may be effective.

The ASTM does not provide information about possible causes of poor effort (Millis 2001). Although deliberate faking of cognitive deficits cannot be ruled out, the diagnosis of malingering should never rely on a single test. Alternative explanations should also be considered as likely causes of poor effort. For example, poor effort may serve as a (unconscious) strategy to protect oneself against exhaustion, or may reflect the need to get recognition for complaints in the face of medical scepticism (Schmand 1998). Moreover, it may result from the poor physical and emotional state the patient is in at time of the assessment, although in this case detrimental effects would be expected to be most prominent on demanding cognitive tasks and not on a relatively easy task like the ASTM. In the present study, we considered only a few of many factors that may negatively influence effort level. Future studies could benefit from including other potentially important factors like pain or illness expectations.

As mentioned in the Introduction, there are many tests and techniques which can be used to detect poor effort, but a 'gold standard' is lacking. We used the ASTM, a forced-choice verbal memory test, based on the technique of symptom validity testing. The ASTM is specifically designed and validated to assess cognitive effort, and even patients with moderate to severe TBI and children from about 9 years old have shown mean scores above 89 (Schagen 1997). Ideally, the detection of poor effort should include converging evidence rather than being based on a single test score, and future studies are advised to also consider for example at atypical response patterns within the individual tests (Hout van 2003, Millis 2001). Nonetheless, we believe that the results of our study do show that inclusion of a validated effort test in non-referred MTBI patients offers important additional information for understanding the cognitive performances of these patients.

One should be cautious generalizing the results of our study, including the high frequency of poor effort, to the MTBI population as a whole, since only 18% of the whole cohort participated in the neuropsychological assessment. Although participating patients did not differ from non-participating patients on most injury characteristics, the sample was biased towards negative outcomes (75% of all patients still reported postconcussional complaints and 39% performed below the 5th percentile of population norms on one or more tests). Although it was explicitly stated in the study information that both patients with and without complaints were invited to take part, symptomatic patients showed to be more willing to participate in our extensive study.

In conclusion, we have found that poor effort is associated with poorer neuropsychological test performance in non-referred MTBI patients six months after injury. Although more research is needed to unravel the mechanisms underlying poor effort, our results suggest that non-neurological factors like lower education, distress and fatigue, negatively affect effort and should be systematically considered in all cognitive evaluations. To enhance the validity of cognitive evaluations in MTBI patients, effort testing is strongly advised as the interpretation of results yielded in the absence of demonstrated good effort, may be highly misleading or meaningless.

Chapter 6

Cognitive complaints after Mild Traumatic Brain Injury: things are not always what they seem.

M Stulemeijer[1], PE Vos[2], G Bleijenberg[3], SP van der Werf[1].

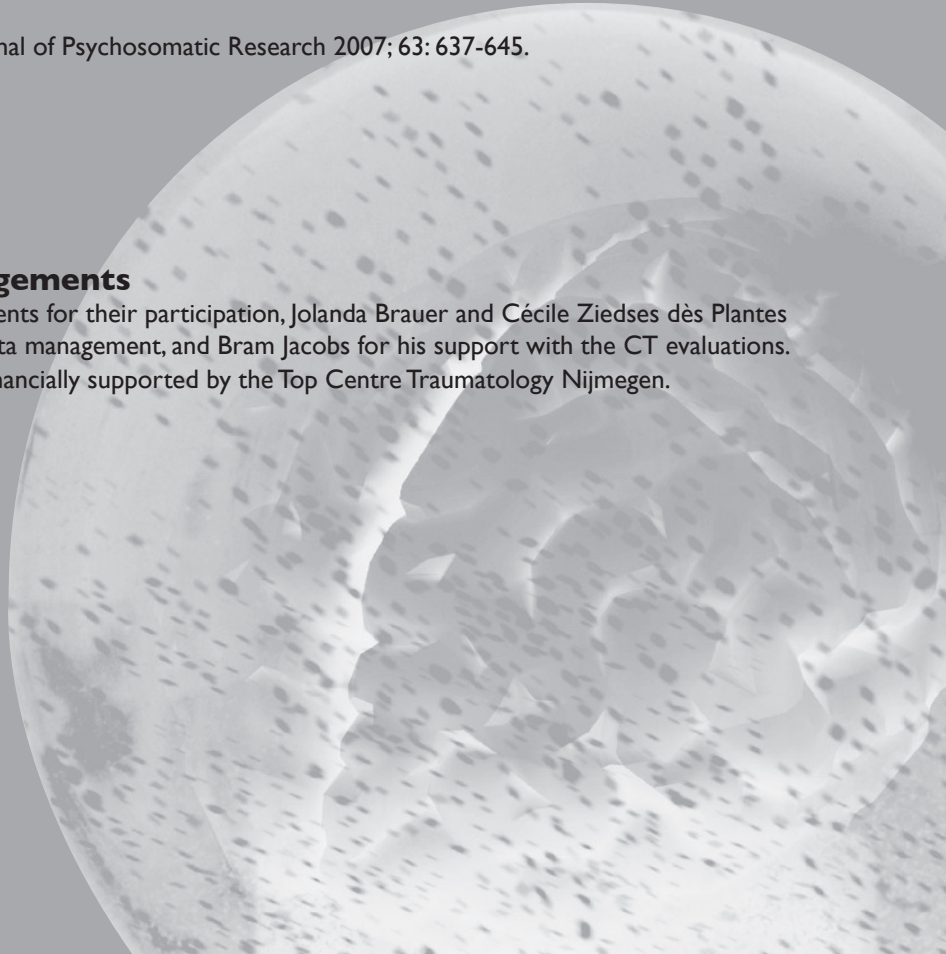1. Department of Medical Psychology, Radboud University Nijmegen Medical Centre
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Abstract

We sought to compare non-referred, ED-admitted Mild Traumatic Brain Injury (MTBI) patients with and without self reported cognitive complaints on (1) Demographic variables and injury characteristics, (2) Neuropsychological test performance, (3) Twelve-day self-monitoring of perceived cognitive problems, and (4) Emotional distress, physical functioning and personality. A (neuro) psychological assessment was carried out six months post-injury in 79 patients out of a cohort of 618 consecutive MTBI patients aged 18 – 60, who attended the emergency department of our level 1 trauma centre. Cognitive complaints were assessed with the Rivermead Postconcussional Symptoms Questionnaire (RPSQ). In addition, patients monitored concentration problems and forgetfulness during 12 consecutive days.

Our results show that self reported cognitive complaints were reported by 39% of the patients. These complaints were strongly related to lower educational levels, emotional distress, personality and poorer physical functioning (especially fatigue) but not to injury characteristics. Severity of self reported cognitive complaints was neither associated with the patients' daily observations of cognitive problems nor with outcome on a range of neuropsychological tests. We conclude that self-reported cognitive complaints were more strongly related to premorbid traits and physical and emotional state factors than to actual cognitive impairments. In line with previous work, this suggests that treatment of emotional distress and fatigue may also reduce cognitive complaints. Cognitive outcome assessment of symptomatic MTBI patients should not be restricted to checklist ratings only, but also include a (neuro)psychological screening. In addition, daily monitoring of complaints is a useful method to gather information about the frequency and pattern of cognitive problems in daily life.

Introduction

Over 80% of all traumatic brain injuries are classified as mild, and as such Mild Traumatic Brain Injury (MTBI) is one of the most prevalent neurological conditions world-wide (Cassidy 2004). Although most MTBI patients recover well, a minority reports cognitive difficulties for months to years after injury (Bohnen 1994, Chamelian 2006, Mickeviciene 2004, Naalt van der 1999). These complaints are distressing, may lead to a disabled lifestyle and prolong medical consumption (Drake 2000, Nolin 2006a). Clinicians are often puzzled by the apparent discrepancy between the severity of the cognitive complaints and the seemingly intact cognitive abilities based on neuropsychological test performance. The present study was designed to better understand the correlates of perceived cognitive insufficiency six months after MTBI. There is considerable evidence that cognitive complaints do not simply reflect diminished cognitive abilities caused by the head injury. Self-perceived cognitive problems are often only weakly related to injury severity, and cognitive complaints do not necessarily imply impairment of cognitive abilities (Barth 1983, Bazarian 1999, Bohnen 1992b, Chamelian 2006, Gfeller 1994, Leininger 1990, McCullagh 2001, Mooney 2005, Ross 2006). Generally, cognitive complaints are more prominent than the mainly subtle (if any) impairments found on neuropsychological tests, but the reverse pattern has also been found, and the strength of the association differs considerably between studies (Belanger 2005a, Binder 1997, Gfeller 1994, Hofman 2002, Leininger 1990, McHugh 2006). However, as many studies have been performed in small and/ or selected populations (e.g. litigants), without controlling for the validity of test performance, the interpretation of these findings is seriously hampered (Green 2001, Ross 2006, Stulemeijer 2007).

In line with findings in other neurological and non-neurological conditions (e.g.

(Carter 2003, Elixhauser 1999, Kliegel 2005, McCracken 2001)), a large proportion of the variance in cognitive symptom report seems to be accounted for by factors unrelated to the injury itself. For example, the presence of depressed mood and anxiety strongly relates to subjective cognitive complaints (Karzmark 1995, Rohling 2002, Trahan 2001). In addition, premorbid personality characteristics like neuroticism, seem to make some individuals more prone to experience cognitive problems than others (Cattelani 1996, Hanninen 1994, Kliegel 2005). In MTBI patients, more knowledge is needed about the influence of potentially relevant forms of emotional distress such as post traumatic stress, or traits like Type-D personality or the disposition to focus on internal bodily sensations (Bryant 1999, Denollet 2005, Werf van der 2002). Furthermore, although severe fatigue is increasingly being recognized as an important problem long after MTBI, the connection between fatigue, reduced capacity for mental effort and perceived cognitive problems has received little attention (Borgaro 2005, Stulemeijer 2006b).

Lastly, conclusions about a patients' cognitive state are often based on symptom checklists containing only a few items covering broad classes of cognitive functions. It has been argued that the use of these checklists results in over-reporting, as they are non-specific, sensitive for recall bias, and strongly influenced by emotional distress (Nolin 2006b, Prouteau 2004, Rabbitt 1990). Daily monitoring of cognitive problems might help to overcome some of these problems, but, to our knowledge, has not been performed in MTBI patients. The use of complaint diaries may provide important additional information about the frequency of cognitive problems encountered in daily life, as well as characterize meaningful fluctuations in cognitive functioning during the day (Servaes 2002, Thiele 2002, Vercoulen 1994). In addition, given the short interval between the actual occurrence of a problem and the subsequent registration, this diary approach is suggested to be less sensitive to bias.

To better understand the factors that relate to the experience of cognitive problems, we compared non-referred, ED-admitted MTBI patients with and without self reported cognitive complaints who passed a validated effort test on four domains: (1) Demographic variables and injury characteristics, (2) Neuropsychological test performance, (3) Daily self observed cognitive complaints during 12 days, and (4) Emotional distress, personality, physical functioning and fatigue.

Methods

Subjects and study design

All patients took part in a longitudinal cohort study on outcome after MTBI as previously described (Stulemeijer 2006b). In short, the sample consisted of consecutive patients aged 18 – 60 who attended the emergency department (ED) of the Radboud University Medical Centre Nijmegen, a level 1 trauma centre, with a diagnosis of MTBI in the period November 2001 to October 2003. MTBI was classified according to the guidelines of the European Federation of Neurological Societies (Vos 2002). Patients were approached six months after injury and invited to complete a postal questionnaire and take part in a two-session (neuro-) psychological assessment, six and twelve months after injury. In total 110 patients of a cohort of 618 patients underwent (neuro-) psychological assessment six months after injury. To enhance the validity of the data, we excluded the 30 patients who failed a validated effort test (defined as a score of < 86 on the Amsterdam Short Term Memory test) (Schagen 1997, Stulemeijer 2007a). In addition, one patient had missing data on more than one test and was excluded from the analysis. The sample in the present study thus consisted of 79 patients. Post Traumatic Amnesia (known in 564 of all 618 patients) was more frequent in this subset of patients (n = 60/79, 76%) than in the rest of the cohort

(n = 276/485, 59%) (Chi^2 = 15.7, p = .001). No other significant sample differences were found for age, gender, admission Glasgow Coma Score (GCS), loss of consciousness (LOC), the presence of CT abnormalities, Injury Severity Scores (ISS) and mechanism of injury.

Data collection
The Rivermead Post Concussion Questionnaire (RPCQ) was used to assess cognitive complaints (King 1995). The RPCQ consists of 16 commonly reported post concussional symptoms. We classified the symptoms into three domains (physical, cognitive, affective) and raw scores were transformed into a 1-100 scale. Serious cognitive complaints were defined as scores on the cognitive subscale of 2 standard deviations (SD) or more above mean of a control group of patients with an ankle or wrist distortion (mean = 4.7, SD = 15.5) (Stulemeijer 2006a). Patients with and without cognitive complaints were compared on the following four domains:

1. Demographic variables and injury characteristics
On admission to the ED clinical injury indices like GCS, risk factors for intracranial complications and mechanism of injury were collected as part of a standardized procedure. The presence and duration of LOC was based on reports of witnesses or ambulance personnel, and the presence and resolution of PTA was assessed by a resident of Neurology by a series of questions regarding short-term memory and orientation. A CT of the head was performed according to international guidelines (Vos 2002). Furthermore, the outcome questionnaire contained several questions on premorbid and current health, occupation, rehabilitation and litigation.

2. Neuropsychological test performance
Cognitive outcome was determined using a neuropsychological battery. Tests were selected to cover some of the domains most commonly found to be affected by MTBI (Belanger 2005a, Binder 1997). The assessment procedure took approximately 1 hour to complete, and was administered by a trained neuropsychologist (MS). The battery included the Dutch version of the National Adult Reading Test (general intelligence) (Schmand 1991), the Motor performance Tests (information processing speed) (Vercoulen 1998), the Digit-Symbol subtest of the Wechsler Adult Intelligence Scale-III (Wechsler 1997), the subtests divided attention and working memory of the Test Battery of Attentional Performance (attention) (Zimmermann 1996), and list A of the California Verbal Learning Test (verbal memory) (Delis 1987). For all tests except the CRT, population based age, and gender-corrected normative scores were available. Clinical impairments were defined a score below the fifth percentile of published population norms.

3. Daily observed cognitive complaints during 12 days
Daily observed cognitive problems were assessed with the Self-observation List (SOL) (Servaes 2002, Vercoulen 1996). Besides ratings of fatigue, pain and activity, the SOL covers 17 complaints of which two were cognitive (concentration and memory problems). Patients had to rate whether or not they had experienced these symptoms four times a day for twelve consecutive days. Patients were instructed to fill in the diary at waking up, at noon, at approximately six 'o clock in the afternoon and at bedtime. The daily frequency of complaints was expressed as a percentage of the total number of time points (4x12 time points) that the patient registered memory or concentration problems. In addition, similar percentages (of 12 time points) were calculated for the four distinct time periods (morning, midday afternoon, evening).

4. Emotional distress, personality, physical functioning and fatigue.
Emotional distress was measured with Beck Depression Inventory for Primary Care (depressed mood) (Beck 1997), SCL-90

Table 1. Demographic and injury characteristics for MTBI patients with and without cognitive complaints.

	Cognitive complaints			
	No (n = 48/ 61%)		Yes (n = 31/ 39%)	p-value
Demographics				
Age [a]	36.8 (12.3)		37.7 (13.5)	.759
Male	29	60%	20	65%	.714
Higher education (>=12 years)	30	63%	10	32%	.009
Premorbid health status				
History of psychiatric / emotional problems [b]	10	21%	9	29%	.405
Premorbid medication use				.859
sleep or mood medication	2	4%	2	7%	
other	5	11%	4	13%	
Injury characteristics [c]				
Mechanism of injury				.313
traffic	25	52%	17	55%	
falls	15	31%	5	16%	
violence	3	6%	2	7%	
other	5	10%	7	23%	
Alcohol/drug intoxication	13	27%	11	36%	.428
Admission to hospital	26	54%	16	52%	.824
Loss of Consciousness (n = 67)	21	53%	17	63%	.397
Post Traumatic Amnesia (n = 74)	37	82%	23	79%	.755
Retrograde Amnesia (n = 71)	15	38%	11	36%	.861
Glasgow Coma Score 15	38	79%	29	94%	.082
Brain CT abnormalities (n = 64) [d]	9	23%	3	12%	.268

Values are displayed as number/ percentage and group differences are tested with Chi^2 tests unless stated otherwise. [a] Group differences are tested with Analysis of Variance. [b] Based on self-reports.
[c] Because for some patients certain injury characteristics were unknown or missing, the number of patients in which these variables were complete is presented between brackets.
[d] According to international guidelines, brain CT scans were made in 64 of the 79 patients. Traumatic lesions were found in 12 patients (19%) and consisted of the following intracranial abnormalities (not mutually exclusive): focal intra parenchymal contusions (single n = 5, multiple n = 3), cortical edema (n = 3), small epidural hematoma (n = 3), small subdural hematoma (n = 1), petechial hemorrhage (n = 1), subarachnoidal hemorrhage (n = 1). Six of these patients also had a skull(base) fracture. One patient underwent neurosurgical intervention for a depressed frontal skull fracture.

Anxiety Subscale (anxiety) (Degoratis 1994), and the Impact of Events Scale (post traumatic stress) (Sundin 2002).

Personality was investigated with the short version of the Eysenck Personality Questionnaire (subscales Neuroticism and Extraversion) (Sanderman 1995), Type D personality scale (subscales Negative affect and Social inhibition) (Denollet 2005).

Symptom perception was measured with the Body Consciousness Scale (subscales Public and Private) (Werf van der 2002).

Physical functioning was assessed with the SF-36 (subscale Physical functioning) (Aaronson 1998) and the Checklist Individual Strength (subscale Fatigue) (Dittner 2004).

Questionnaires a and c were completed at the outpatient clinic on a computer, supervised by

an experienced research nurse. Questionnaires b and the RPCQ were included in a postal questionnaire that patients received together with the study information.

Statistics

Statistical analysis was carried out using a standard statistical package (SPSS for Windows, 12.0 SPSS Inc., Chicago, IL, USA). All effects were tested at the p < 0.05 level (two-tailed). In case of skewed data, appropriate transformations were performed Analyses of variance were used for between-group comparisons. In the tables unadjusted scores are presented. Chi-square analyses were used in the case of dichotomous variables. To minimize Type-I error, multivariate analyses of variance (MANOVAs) were used to make group comparisons across domains, and only when main effects were significant, univariate analysis were performed. Effect sizes (Cohen's *d*) together with the percentage overlap between groups, were calculated using the procedure described by Zakzanis (Zakzanis 2001).

Ethics

The study was approved by the ethics

Table 2. Performance of MTBI patients with and without cognitive complaints on selected neuropsychological measures.

	Cognitive complaints		p-value	effect size (Cohen's d)	% overlap (approx)
	no	yes			
General intelligence					
IQ estimation (NART)	100.3 (15.1)	93.3 (16.4)	.449[1]	.45	73%
Motor speed					
CRT: Simple Motor speed (ms)	203.9 (87.7)	222.1 (72.4)	.761	-.22	85%
Information processing speed			**.192**		
CRT 1: simple reaction time (ms)	291.3 (52.2)	313.2 (71.0)	.228	-.37	78%
CRT 2: response selection (ms)	326.7 (47.8)	356.2 (85.1)	.069	-.47	70%
CRT 3: inhibition (ms)	445.2 (74.6)	464.3 (108.9)	.443	-.22	85%
WAIS digit symbols (t-score)	51.4 (10.3)	46.1 (11.1)	.086	.50	67%
Attention			**.853**		
Divided attention (TAP)					
n correct	29.7 (2.5)	28.6 (2.6)	.3081	.43	73%
median rt (ms)	673.7 (71.1)	643.5 (175.6)	.891	.11	92%
Working memory (TAP)					
n correct	13.3 (2.3)	12.8 (1.8)	.422	.24	82%
median rt (ms)	643.5 (175.6)	678.0 (162.2)	.583	.32	78%
Verbal memory (CVLT)[a] (z-scores)			**.011**		
Immediate free recall List A	0.0 (1.5)	- 0.8 (1.8)	.1631	.49	67%
Speed of learning	-1.17 (1.9)	-1.13 (2.0)	.2301	-.02	99%
Short term free-recall	1.9 (1.8)	1.0 (1.6)	.490	.52	67%
Long term free-recall	0.4 (2.0)	-.3 (2.5)	.079	.32	78%

Values are displayed as mean (SD) unless stated otherwise. Group differences are tested with Multivariate (p-values in bold) and Univariate Analysis of Variance, with education as covariate. 1: Covariate education is significant.
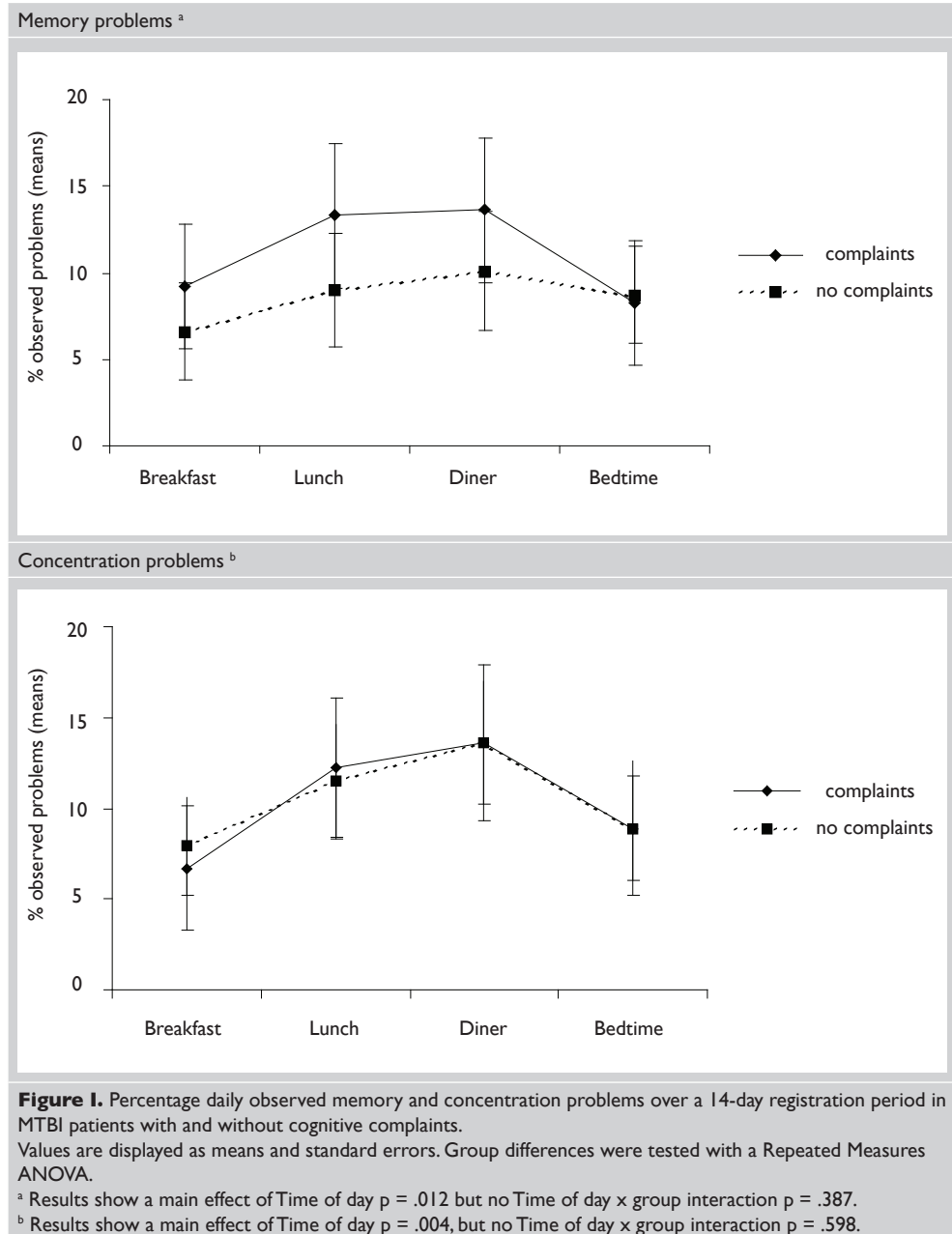CVLT, California Verbal Learning Task; WAIS, Wechsler Adult Intelligence Scale; TAP, Test for Attentional Performance; CRT, Complex Reaction Time task.

committee of the University Medical Centre Nijmegen and the Regional Committee on Research Involving Human Subjects. Informed, written consent was obtained from all patients prior to their voluntary participation in the study.

Results

1. Demographic variables and injury characteristics

Of all 79 patients, 31 (39%) reported high levels of cognitive complaints. As shown in Table 1, symptomatic patients generally had lower levels of education than patients

Figure 1. Percentage daily observed memory and concentration problems over a 14-day registration period in MTBI patients with and without cognitive complaints.
Values are displayed as means and standard errors. Group differences were tested with a Repeated Measures ANOVA.
[a] Results show a main effect of Time of day p = .012 but no Time of day x group interaction p = .387.
[b] Results show a main effect of Time of day p = .004, but no Time of day x group interaction p = .598.

without complaints. No other differences were found between the groups with respect to demographic variables, premorbid health and injury characteristics. In addition, current involvement in litigation was equally common in patients with complaints (n = 7, 23%) as in patients without complaints (n = 14, 29%) (Chi^2 = .319, p = .527).

2. Neuropsychological test performance

As shown in Table 2, there were no significant differences between the groups in performance on any of the tests. Thirty-nine percent (n=12) of the patients with cognitive complaints and 25% (n=12) of the patients without complaints had a score below the fifth percentile on at least one of the neuropsychological tests; a difference that did not reach statistical significance (Chi^2 = 1.67, p = .196). Effect sizes of the difference between patients with and without cognitive complaints fell in the small to medium range. The average effect size was .30. Thus, on average, the patients with cognitive complaints performed .30 of a standard deviation more poorly than patients without cognitive complaints.

3. Self monitoring of perceived cognitive complaints during 12 days

One patient did not fill in the diary, therefore

Table 3. Distress, personality, physical functioning and fatigue in MTBI patients with and without cognitive complaints.

	Cognitive complaints		p-value	effect size (Cohen's d)	% overlap (approx)
	no	yes			
Distress			**.001**		
Depressed mood (BDI-PC; range: 0 – 21)	0.9 (1.9)	2.3 (2.3)	.013	-.68	57%
Anxiety (SCL-90; range: 8 - 40)	11.6 (2.5)	16.5 (8.3)	.002	-1.03	45%
Post traumatic stress (IES; range: 0 - 75)	19.3 (7.1)	26.7 (8.4)	.008[1]	-.97	45%
Personality			**.015**		
Neuroticism (EPQ; range: 0-12)	5.7 (2.4)	7.0 (2.2)	.154	-.56	67%
Extraversion (EPQ; range: 0-12)	6.8 (2.0)	7.7 (2.7)	.223	-.40	73%
Type-D personality					
Social inhibition (DS-14; range: 0 – 28)	7.6 (5.0)	12.3 (5.6)	.001[1]	-.90	48%
Negative affectivity (DS-14; range: 0 – 28)	8.0 (4.7)	9.0 (4.5)	.153	-.22	85%
Body consciousness					
Private	10.3 (3.3)	12.8 (2.8)	.008	-.81	53%
Public	21.4 (4.0)	23.3 (5.4)	.171	-.42	73%
Physical functioning and fatigue			**.001**		
Physical functioning (SF-36, range: 100 – 0)	88.2 (19.5)	72.2 (23.3)	.0091	.76	55%
Fatigue (CIS, range 0 – 56)	23.0 (11.3)	39.3 (12.8)	.0011	-1.37	32%

Values are displayed as mean (SD). Group differences are tested with Multivariate (p-values in bold) and Univariate Analysis of Variance.
1: Covariate education is significant

these analysis contain 78 patients. Overall, patients with cognitive complaints (n=30) report to have experienced memory problems in 10% (SD 17.7) and concentration problems in 11% (SD 23.9) of time during the 12-day registration period, which was not different from patients without cognitive complaints, who reported memory problems 9% (F (2,77) = .75, p = .390) and concentration problems 6% of the time (F (2,77) = .03, p = .854). As shown in Figure 1, the frequency of cognitive complaints fluctuated significantly during the day, however, no significant differences were found between the groups and effect sizes were small ($d < 0.1$, data not shown). Overall, both memory and concentration problems increased from breakfast to lunch, remained constant until diner and then decreased again.

4. Emotional distress, personality, physical functioning and fatigue.

As shown in Table 3, patients with cognitive complaints reported significantly higher levels of post-traumatic stress, depressed mood and anxiety. Additional analyses show that 55% of patients with cognitive complaints report severe levels of post-traumatic stress (IES Total score > 26), compared to 15% of the patients without complaints (Chi^2 = 14.4 p < 0.001, odds ratio 7.1). Regarding personality traits, patients with cognitive complaints reported stronger tendencies for social inhibition, but not for neuroticism, extraversion and negative affectivity. Furthermore, patients with cognitive complaints reported higher awareness of internal bodily sensation, but not for public body consciousness. Lastly, symptomatic patients reported more physical limitations and higher levels of fatigue. The effect sizes of these differences were large (-.68 to −1.37). Additional analyses show that 60% of patients with cognitive complaints report severe levels of fatigue (defined as a score on the CIS fatigue > 40 (Stulemeijer 2006b, Vercoulen 1994)) to only 10% in those without (Chi^2 = 28.03, p < 0.001, odds ratio 18.1).

Discussion

The results of our study showed that six months after MTBI, cognitive complaints were common in non-referred, ED-admitted patients who passed a validated effort test. These complaints were unrelated to clinical injury severity indices, neuropsychological test performance and self-observed cognitive problems during a two-week period. Rather, premorbid characteristics (like proneness to focus on internal sensations and low educational level) and post injury emotional and physical status and fatigue were strongly associated with perceived cognitive insufficiency. In all, these findings provide additional support against the assumption that cognitive complaints merely reflect underlying cognitive impairments.

In line with previous studies, clinical severity indices did not relate to the severity of cognitive complaints six months after injury (Barth 1983, Bazarian 1999, Leininger 1990, McCullagh 2001, Ross 2006). Given the narrow range of scores inherent to the diagnosis of MTBI (e.g. GCS 13-15) and the low occurrence of CT abnormalities, this lack of association may not be surprising. Whether subtle trauma induced abnormalities in the brain contribute to the perceived cognitive problems remains to be seen. Results from fMRI and ERP studies suggest that MTBI patients have to allocate additional cognitive resources in order to perform within normal limits (McAllister 1999, Potter 2002, Solbakk 1999). Potentially, these compensational efforts may lead to the experience of non-specific cognitive complaints.

To increase the validity of our neuropsychological test data, we only included patients that passed a validated effort test. Using this approach, no significant performance differences were found between patients with and without cognitive complaints, and effect sizes were moderate at most. These findings confirm earlier work that assessment of cognitive complaints does not

replace actual testing (e.g. Chamelian 2006, Prouteau 2004). In a comparable MTBI study, Chamelian *et al.* (Chamelian 2006) found somewhat higher effect sizes (calculated from article; ranging from 0.6 for working memory to 0.9 for verbal memory recognition) than in our study, which might be explained by the fact that Chamelian *et al.* did not control for the moderating effect of effort and also included patients with moderate TBI.

In addition to the discrepancy between cognitive complaints and performance, symptomatic patients did not report more memory and concentration problems during the 12-day observation period, and the overall occurrence of problems was rather low. Furthermore, both groups showed a comparable course of cognitive problems during the day. As diary registration are considered to more accurately reflect the frequency of actual experienced problems than checklists, these findings seem to confirm the notion that checklists are sensitive for over-reporting (Nolin 2006b, Thiele 2002) Alternatively, patients with cognitive complaints may not report a higher frequency of daily problems as they might have successfully adjusted their activities such that cognitive 'stressors' are avoided. This hypothesis warrant further study.

Strong associations were found between cognitive complaints and both premorbid characteristics, and post-injury emotional and physical factors. Earlier MTBI studies have found mixed results regarding the influence of demographic variables on symptom report. In the present study, lower educational level but not gender or age, was associated with the report of cognitive complaints. Additionally, patients with cognitive complaints were characterized by differences in personality traits. Firstly, they showed stronger tendencies to inhibit the expression of emotions and behavior in order to avoid negative reactions from others. As reviewed by Denollet, such emotionally inhibited style may impede communication between patient and physician and result in the physician overlooking important psychosocial issues like depression (Denollet 2006). Secondly, cognitive symptom report was associated with higher awareness for experiencing internal bodily sensations in general which supports the assumption that a heightened self-focus may perpetuate post concussional sequealae (Gunstad 2004). Unlike other studies however, patient with and without cognitive complaints reported equal levels of neuroticism (Cattelani 1996, Hanninen 1994, Kliegel 2005).

In accordance with previous work, affective distress, physical limitations and fatigue were strongly associated with cognitive symptom report (Karzmark 1995, Rohling 2002, Trahan 2001). Importantly, over half of the patients with cognitive complaints reported severe levels of post-traumatic stress, and symptomatic patients were 18 times more likely to experience severe fatigue. Although the cross-sectional nature of the study does not allow to draw inferences about the direction of these relations, perceived cognitive difficulties and emotional distress are likely to be associated in a dynamic manner, so that each influences and maintains the other (Gallo 2005). In addition, fatigue can be both cause and consequence of perceived cognitive problems, and may be experienced as mental fatigue', 'bodily fatigue', or both. More detailed examination of the perceived nature of a patients fatigue, and the factors that trigger and perpetuate fatigue is needed. However, already, the results suggest that post traumatic stress and fatigue are important targets for intervention. Especially, since previous studies showed that cognitive complaints diminished when mood was elevated and physical impairments improved (Antikainen 2001, Mittenberg 2001).

The results of our study may have several clinical implications. Firstly, they show that conclusions about a patients' cognitive abilities cannot be drawn based on checklist ratings. Likewise, just as undisturbed performance does not make the patients' complaints

less 'real', poor test performance on itself is no prove for impaired cognitive abilities (especially if poor effort is not controlled for). Rather, cognitive complaints should always be considered within the framework of the patients' emotional and physical status, considering his/her intellectual ability and personality style. Additionally, to better characterize cognitive problems, clinicians may consider to let patients monitor the actual occurrence of problems for a longer period of time by means of a self-report diary.

Several methodological considerations are in order. Firstly, the generalizability of the results is limited due to the limited size and selective nature of our patient sample. Patients with PTA were overrepresented in our study sample. Whether this difference has affected the results is unknown; some studies do find poorer six months cognitive functioning in MTBI patients with longer PTA durations (e.g. King 1999), whereas others, including the present study (data not shown), do not (e.g. Bazarian 1999). Although participating patients did not differ from non-participating patients on other injury characteristics, the sample was biased towards negative outcomes. Our approach of excluding patients with demonstrated suboptimal effort meant further reducing our sample size with 30 patients, however, given the great detrimental impact of poor effort on performance, we believe that this has strengthened rather than weakened our data. Furthermore, the standard neuropsychological tests used in this study, have been criticized for being insensitive to capture the relatively mild impairments in this population, maybe a more demanding cognitive task would have differentiated between patient with cognitive complaints and those without (Thiele 2002). Additionally, as daily monitoring of complaints in MTBI patients has not been done before, its value in MTBI patients needs to be replicated. In order to further our understanding of the situational factors that trigger cognitive problems in daily life, future studies may consider to let patients report cognitive failures every time they occur, rather than at predefined intervals.

In conclusion, six months after MTBI self-reported cognitive complaints were more strongly related to premorbid traits and physical and emotional state factors than to actual cognitive impairments. Cognitive outcome assessment of symptomatic MTBI patients should not be restricted to checklist only, but also include a (neuro)psychological screening. Daily monitoring of complaints may give useful information about the frequency and pattern of cognitive problems in daily life.

Chapter 7

Leventhals' self-regulation model; an alternative approach for understanding the discrepancy between cognitive complaints and neuropsychological performance in patients with Mild Traumatic Brain Injury.

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Translated from Dutch (Original title: Onverklaarde klachten na licht traumatisch schedelhersenletsel: de discrepantie tussen cognitieve klachten en neuropsychologische testprestatie nader belicht.)
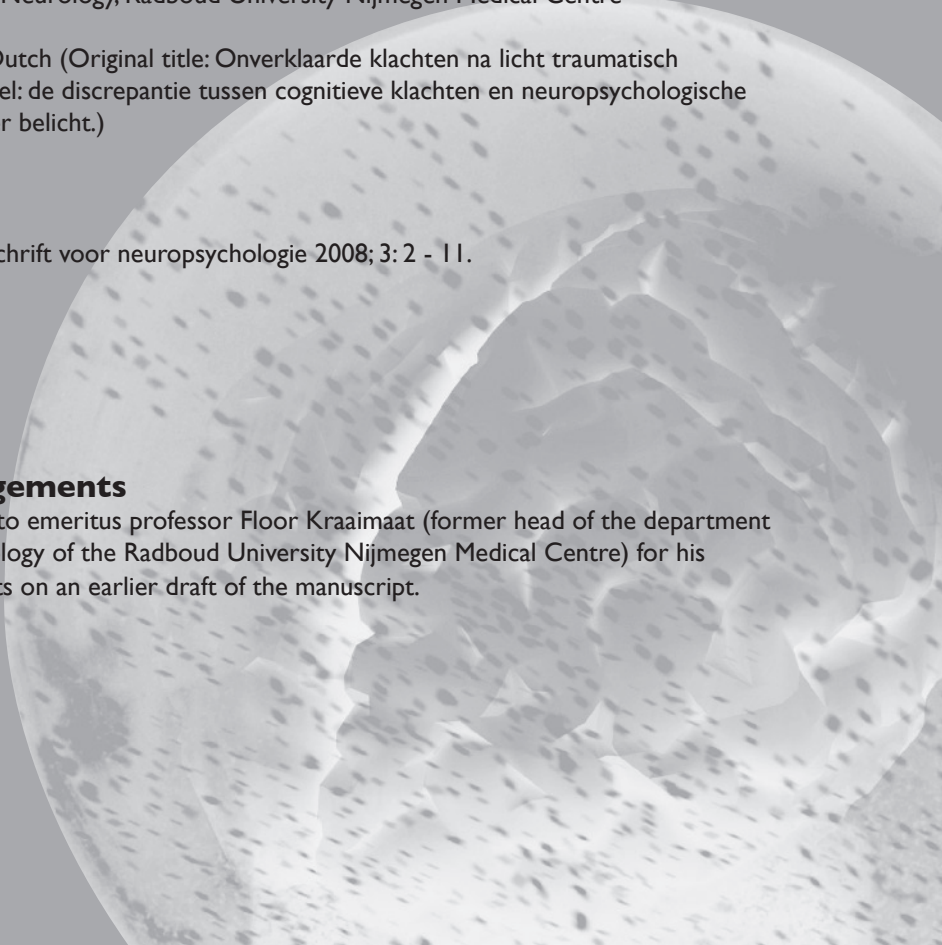
Abstract

Discrepancies between perceived cognitive deficits and the outcomes of neuro(psycho) logical assessments are quite common in neurological practice. Mild Traumatic Brain Injury in particular has stirred up the debate about possible explanations for these discrepancies. Despite a generally swift and full recovery, some patients keep reporting lasting and debilitating cognitive complaints that appear disproportionate to the severity of the sustained injury and also do not or only marginally correlate to their outcomes on neuropsychological tests. In the light of existing literature and own experimental findings, the current report proposes an explanatory model based on principles derived from health psychology that appears to offer new and better leads for an adequate diagnosis and treatment than a monodisciplinary, neurological model.

Introduction

Cognitive functioning after Mild Traumatic Brain Injury

Traumatic head injury results from a violent external impact to the skull causing a rapid acceleration, deceleration and rotation of the brain. The earlier distinction between commotio cerebri (cerebral concussion) and contusio cerebri (cerebral contusion) still prevalent in the Netherlands has been rejected as outmoded. Today, the severity of closed-head trauma is classified as 'mild', 'moderate' and 'severe'. Mild Traumatic Brain Injury (MTBI) is diagnosed if the impact induced unconsciousness for a maximum duration of 30 minutes and emergency attendants confirm a Glasgow Coma Score of 13 to 15 (Vos 2002). Most patients experience immediate complaints such as headache, dizziness and a raised sensitivity to light and sound, which usually disappear gradually in the course of several days or weeks. MTBI-related mortality is extremely low (< 0.5%),

neurosurgical interventions seldom required (≈ 1%) and the majority of patients recover spontaneously and fully within three months. Nevertheless, MTBI is considered a serious public (socioeconomic) health burden. With an estimated minimal incidence of 100-300/100,000 it is not only one of the most prevalent neurological syndromes, it also induces persistent complaints and impairments in approximately 5 to 10% of all patients (Cassidy 2004). Forgetfulness, difficulties concentrating and slowed thinking are among the most frequently reported MBTI-related complaints and commonly are part of a wider spectrum of self-reported emotional and physical problems. As these sustained complaints are also often associated with reduced quality of life and high medical consumption, they can seriously impede the recovery process (e.g. by delaying work resumption; Carr 2007).

The acute cognitive deficits like disorientation or posttraumatic amnesia generally fully recede in the hours following the incident but may persist several days. In the subsequent weeks MTBI patients tend to function more poorly than their healthy peers on tasks gauging speed of information processing, attention and episodic memory. After three months the greater majority will have regained normal cognitive functions (Belanger 2005a). Although the severity of the acute cognitive complaints and deficits depend on the severity of the injury, no consistent, longer-term (> 3 months post-trauma) associations have been reported between trauma severity, subjective complaints and test performance. Thus, severer injuries are not, by definition, associated with more serious complaints and vice versa. Moreover, despite the self-reported cognition problems, performance on neuropsychological tests usually does not deviate from norm scores. If observed, poor performance is generally attributable to interfering factors (for a description, see Stulemeijer 2007a and Stulemeijer 2007b). There is a strong relationship, however,

between persistent cognitive complaints and emotional problems (especially depressed mood, anxiety and posttraumatic stress), personality traits (e.g. neuroticism and heightened body focus), physical impediments (e.g. impairments due to pain) and fatigue (Carr 2007, Mooney 2005, Stulemeijer 2007a,b, Suhr 2005). Comparable results have also been documented for other patient populations (HIV, epilepsy and whiplash among other conditions; see e.g. Carter 2003, for more references, see Stulemeijer 2007b). The inferences health professionals make about the factors underlying the reported symptoms may have important implications for both diagnosis and treatment. Interpretational differences regarding the relevance of the observed discrepancies in performance levels such as between self-reported complaints and neuropsychological test outcomes, feature prominently in the ongoing debate about how persistent cognitive complaints are to be understood (Stulemeijer 2007b). This is also illustrated by the differences in the criteria the two most widely used classification systems, i.e. the International Statistical Classification of Diseases and Related Health Problems (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM), use to describe patients that remain impaired following an MTBI (In McCauley 2005). According to the ICD-10 criterion for 'Postcommotional/ Postcontusional Syndrome' cognitive complaints need to coincide with a preoccupation with the symptoms and the adoption of the sick role, but without manifest neuropsychological limitations. In contrast, the DSM-IV criterion for 'Postcontusional Disorder' mentions substandard performance on attention or memory tests as a key element. The ICD-10 thus seems to stress the possible negative influence of cognitive-behavioural processes while the complaints the DSM-IV specifies are implicitly attributed to 'objective deficits'. Neither diagnosis has as yet been adequately supported. In the present report we describe how cognitive complaints can be explained by a neurological model and how an explanatory model based on principles derived from health psychology can offer solutions where the neurological model falls short. With this model we bear out the increasingly expressed need for and evidence of the legitimacy of a more 'holistic' approach of MBTI.

Two explanatory models for persistent cognitive complaints after MTBI

Neurological model

The notion that subjective cognitive complaints in the chronic stage are also (partly) caused by the trauma-induced brain injury is still popular and has recently even gained ground due to the increased user-friendliness of advanced imaging techniques. According to the advocates of this neurological model, non-detection of brain damage is the result of the insensitivity, limited scope and invalidity of the measuring techniques employed to chart the effects of MTBI. It is standard procedure at A&E departments to order a CT scan to examine the brains of MTBI patients. Although an excellent procedure to visualise intracranial events like sub- or epidural haemorrhages and contusions, subtle focal irregularities or diffuse axonal damage tends to go undetected (Belanger 2007). And it is exactly this damage that is assumed to reduce the functionality of brain regions such as the frontal and temporal lobes (which, due to their anatomical location, are especially susceptible to traumatic impact), for instance by disturbing the neurotransmitter equilibrium. Even though it will not always become manifest at the behavioural level, the patient may still be aware of this diminished functionality. Using functional Magnetic Imaging (fMRI), McAllister and colleagues (McAllister 1999), for instance, demonstrated that, despite comparable performance outcomes on a working memory task, the prefrontal cortex of MTBI patients showed more activity during task performance than

it did in healthy controls. Although intuitively attractive, their theory that the non-specific MTBI-induced cognitive complaints result from such a 'compensatory activation' at the cerebral level has been quoted more than replicated. Neuropsychological evaluations of persistent cognitive complaints are also criticized. Many neuropsychological tests lack sensitivity to detect subtle cognitive declines and only partially capture cognitive effort in daily life. This also holds for most self-report instruments that try to assess cognitive functioning with only a handful of crude items.

It is important to appreciate that, in neuropsychology, correlations between 'objective' and 'subjective' data are generally low, explaining only about 10% of the shared variance, and that they seldom exceed the 0.30-level, not only in MTBI patients but also in other patient and normal populations (Deelman 1998). In itself this is not remarkable considering that 'brain processes', 'neuropsychological test performance' and 'assessments of own functioning' reflect different dimensions of increasing complexity.

related dimensions (Spaendonck van 2006). Relationships between cognitive complaints and neuropsychological performance outcomes will, therefore, mostly be deficient. And even though advances in imaging techniques will undoubtedly augment our understanding of how MTBI impacts the brain, they are unlikely to help bridge the gap between the various measuring dimensions.

Health psychology model

It is widely accepted that in the development and course of chronic complaints besides biological factors mental and social factors play a predisposing, eliciting and maintaining role (In Spaendonck van, 2006). In this 'biopsychosocial' approach the gamut of perceptions the patients entertains about the factors that cause or exacerbate his complaints is an essential psychological determinant. Leventhal's self-regulation model (Evers 2006, Ogden 1996) depicted in Figure 1 illustrates how these notions play a crucial role in the way patients cope with their self-perceived physical symptoms, providing a framework to interpret any individual differences between patients that are not
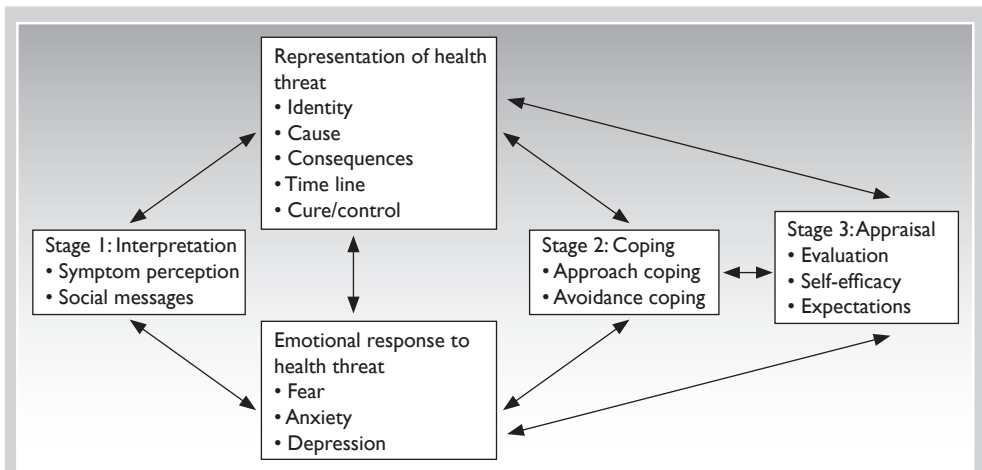

Figure 1. Leventhal's self-regulation model
From: J. Ogden (1996) *Health Psychology: a textbook.* Buckingham: Open University Press. p 41.

Each has its own descriptive associations, interactions and characteristics and can only be partially described by the other,

attributable to the severity of the (initial) medical condition. Experimental research often refers to this generic health theory to

explain determinants and maintaining factors in chronic complaints.

In this phased model the initial stage reflects the instance when an individual is confronted with a health threat, either in the form of a physical sensation that he perceives as alarming (feeling unwell after sustaining a blow to the head), or by external clues (physician diagnoses MTBI). The threat is accompanied by thoughts and opinions about the situation *(representations)* that give meaning to the complaint or diagnosis. In this cognitive process five representations are distinguished: identity (the diagnosis or label), cause, consequences (physical and psychosocial limitations in daily life), course (estimated duration of the disorder or complaint) and controllability or management of the complaint. Interpretations are founded on previous experiences and information originating from the patient's environment (e.g. from doctors, acquaintances, the media). The health threat also educes an array of emotions such as anxiety, frustration and even depression. The cognitive representations and emotional reactions hence influence each other and together 'determine' how a person deals with his complaints. This second stage of the model discerns two coping strategies: a problem-oriented and an emotion-oriented coping style. In the first, the individual actively tries to tackle the problem by minimising or reconceptualising the negative consequences, for instance by seeing their GP or by resting more. Rather than trying to solve the problem, in the emotion-oriented approach he focuses on ways to regulate his emotions, for example by prayer or by seeking distraction or support from others. In the third and last, the so-called evaluation stage of the model the patient assesses the effects (success or failure) of the strategies applied, judges his ability to cope with future health issues (self-efficacy) and forms expectations about the future. As it is a dynamic process, this cycle of interpreting, coping and evaluating will continuously be repeated.

MTBI signals an unexpected and acute change in the patient's life and can be sustained in various widely differing circumstances (e.g. in road or fall accidents, during violent attacks or playing sports). Many MTBI patients often also sustain additional injuries to other body parts and may moreover be confronted with repercussions in terms of court procedures or insurance disputes. This explains why many patients experience MTBI as a highly stressful event that places huge demands on their emotional and behavioural adaptability. With Leventhal's self-regulation model we can now illustrate how MTBI may lead to chronic cognitive complaints. A patient who ascribes cognitive symptoms like not being able to recollect a name or being distracted while reading a book to a possible brain injury will monitor his cognitive functioning more and more closely than a person who attributes the complaints to a temporary effect of the pain medication he is taking. Consequently, the threshold at which fluctuations in cognitive functioning are perceived is lowered, causing cognitive failures to be noticed more frequently, which, in turn, confirms the patient's conviction that something is wrong with his brain. The patient may hence start avoiding activities involving more cognitively loaded processes to evade having to use his brain. Although potentially effective in the short term, such avoidant behaviour may trigger a downward spiral. There is a risk that by further delaying a return to work or deferring from social activities (clubbing, sports) the 'tolerance threshold' for cognitive efforts is lowered even more. Once set in motion, this process may turn initial emotions of concern into feelings of frustration when the adopted coping strategies do not have the desired effect, eventually causing feelings of hopelessness (Kraaimaat 2006).

At present, few studies are available that have reported factual data corroborating that mentioned processes indeed help explain the persistent cognitive complaints after MTBI. Only one study explicitly used the self-

regulation model to predict posttraumatic complaints: Whittaker et al. (2007) showed that MBTI patients that expected the accident to have substantial negative consequences also tended to report (more) complaints in the longer term (Whittaker 2007). Indirect evidence has regularly been offered to underscore the likelihood that negative expectations about the consequences of MTBI and catastrophising interpretations of subjective symptoms will have adverse behavioural implications (Gunstad 2002, Mittenberg 1992). Ferrari et al. (Ferrari 2001) found Canadian MTBI patients to anticipate chronic complaints far more frequently than Lithuanian patients. The authors posited that the limited knowledge about MTBI in some countries and the fact that the patients consequently had no specific expectations about their recovery explained the higher incidence of chronic complaints in Canada. Additionally, various studies indicated that MTBI patients with higher scores on items relating to neuroticism or internal body awareness also reported more cognitive complaints (Stulemeijer 2007b). Such personality traits are assumed to relate to a heightened susceptibility to and a negative interpretation of bodily sensations, and more passive coping strategies (Kraaimaat 2006). Studies of patients with serious brain injuries demonstrated that avoidant coping styles and worrying, wishful thinking, self-blame and the use of (illicit) drugs and alcohol were strongly associated with emotional and psychosocial dysfunction and lower self-esteem levels (Anson 2006). There are indications that this also applies to MTBI patients (Bohnen 1992a). Which coping strategies in MTBI patients are associated with persistent (cognitive) complaints, and which cognitive and emotional representations underlie these styles is an important topic for future research.

Practical implications

Often, MTBI patients do not contact their GP or a neurologist until the perceived (cognitive) complaints have already led to considerable impairments in their daily functioning. Additional medical diagnostic examinations tend not to yield adequate explanations for the complaints and, given the limited availability of evidence-based treatment options, there is a risk that patients end up being driven from pillar to post. In this section we will outline several interventions aimed at the prevention or treatment of postcontusional complaints in general and offer various recommendations that we derived from the theories and findings on persistent cognitive complaints described above.

One of the key interventions in MTBI that has been proven to be effective in preventing long-term complaints and posttraumatic stress entails providing patients with timely information and reassurance about likely symptoms and possible coping strategies (either in the form of an information booklet or provided orally during outpatient visits; in Carr 2007). The routine referral to more comprehensive psychotherapeutic or rehabilitation intervention programmes, however, was found to be unsuccessful (Andersson 2007, Ghaffar 2006, Paniak 1998). Leventhal's self-regulation model implies that informing patients at an early stage will help reduce the threat posed by the complaints, thus reducing the patient's anxieties and eliciting more effective coping patterns. The effect early information has on the development of cognitive complaints has, however, not been investigated. We suggest supplementing the information about likely short-term cognitive symptoms with an explanation about the discrepancy between longer-term cognitive complaints and the absence of any observable defects.

An early assessment will additionally allow the health professionals treating MTBI patients (usually a GP or neurologist) to identify those patients that are likely to experience problems recovering spontaneously early in the process, facilitating timely referrals. If the cognitive complaints appear to be secondary

to a treatable physical condition or emotional problem (e.g. pain, insomnia, posttraumatic stress or depression), treatment of the primary symptoms may concurrently ameliorate the cognitive complaints. In a recent publication we show that the chance to be fully symptom-free after 6 months decreases sharply when patients already report numerous complaints or show high levels of posttraumatic stress shortly after the traumatic event or if they have enjoyed little formal training (Stulemeijer 2008).

When cognitive complaints persist and seriously affect the patient's day-to-day functioning or quality of life, additional treatment is indicated. Cognitive-behavioural therapy (CBT) targeting the patient's inadequate or counterproductive coping cognitions and behaviours has been shown to be one of the most effective interventions for medically unexplained complaints (Sumathipala 2007) and the first efficacy evidence for MTBI-specific CBT has recently become available (Tiersky 2005). Alternatively, patients may be referred for rehabilitation. Many rehabilitation centres offer programmes training patients to learn to cope with their limitations that are also suitable for MTBI patients with subjective persistent complaints and/or objectively demonstrated deficits. Programmes usually also comprise psychological treatment and supervision. However, as yet, no data are available demonstrating their effectiveness in reducing persistent cognitive complaints in MTBI patients.

Given the high level of spontaneous recovery, we advise against neuropsychological assessment within three to six months after the traumatic event. Only if complaints persist longer do neuropsychological tests offer a good framework to clarify the nature and severity of the reported problems. We recommend informing the patient prior to the tests that cognitive complaints and test performance reflect different dimensions that need not be related and that cognitive complaints often exist without tests revealing any deficits. Since underperformance is quite common in MTBI patients even when there are no external gains at stake (e.g. reparations or a court case), we advise to always also include a test battery assessing this phenomenon (Stulemeijer 2008). Apart from the diagnostic process, the neuropsychologist may also be involved in the actual treatment of the cognitive complaints; supplementary to informing the patient, delivering brief CBT also often lies within his competency. The (12-session) programme aimed at alleviation of persistent complaints following MTBI Ferguson and Mittenberg (1996) describe may serve as a starting point for tailored CBTs, although to date formal proof of its efficacy is lacking.

Conclusion

Mild Traumatic Brain Injury can justifiably be denoted as a 'neuropsychological' syndrome with neurological factors explaining the acute clinical picture and psychological and behavioural processes contributing to a substantial extent to the maintenance of subjective complaints. It requires knowledge of these various processes to understand why despite good neurological recovery and normal test performance outcomes some MTBI patients still perceive themselves to be cognitively impaired long after the incident. In this report we submit how seemingly contradictory findings (e.g. numerous and severe complaints versus normal test performance) can be explained from the perspective of principles derived from health psychology. As it takes the way patients interpret their complaints and the implications thereof into account, Leventhal's self-regulation model helps explain individual differences between patients that cannot be attributed to the severity of the initial head injury. We feel the proposed explanatory health-psychology-based model fosters adequate diagnoses and treatment more than a purely neurological model does.

Box 1: Quotes from MTBI patients*

"Before the accident I never used to forget a thing; now my head is like a sieve. And no matter what I try, nothing seems to work. The doctor tells me the scan doesn't show any defects, but I'm convinced something's wrong."

"I'm taking things easy because the lady next door told me that a neglected concussion can cause problems for years."

"According to the doctor I had sustained a sever concussion, but since I suffered no headaches, I thought that was a bit over the top. So, the next day I simply went to work, which I shouldn't have, for I felt as sick as a dog."

"Nobody knows exactly what happened, but the man driving behind me told me that I suddenly started swerving and then drove off the road. Personally, I think I may have suffered an epileptic fit or something in that nature. After all, things like that don't just happen, now do they?"

"I don't think my complaints were caused by the accident itself; I already happened to feel stressed out and the accident simply was the straw that broke the camel's back."

"An accident like that makes you realize all the more clearly how vulnerable you are as a human being. One instant you're on your bike and the next you wake up in the hospital. I can't concentrate as I used to before the accident, but hey, I'm lucky to have even survived being run over."

*Above observations were made by Dutch men and women that participated in a scientific study conducted within the framework of the Nijmegen-based Radboud University Brain Injury Cohort Study (RUBICS).

Chapter 8

Early prediction of favorable recovery six-months after Mild Traumatic Brain Injury.

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Abstract

Predicting outcome after Mild Traumatic Brain Injury (MTBI) is notoriously difficult. Although it is recognized that milder head injuries do not necessarily mean better outcomes, less is known about the factors that do enable early identification of patients who are likely to recover well. Our objective was to develop and internally validate two prediction rules for identifying patients who have a high chance for good six-month recovery. A prospective cohort study was conducted among ED-admitted MTBI patients. Besides MTBI severity indices, a range of pre-, peri- and early post injury variables were considered as potential predictors, including emotional and physical functioning. Logistic regression modeling was used to predict the absence of postconcussional symptoms (PCS) and full return to work (RTW).

Our results show that, at follow-up, 64% of the 201 participating patients reported full recovery. Based on our prediction rules, patients without pre-morbid physical problems, low levels of PCS and post traumatic stress early after injury, had 90% chance to remain free of PCS. Patients with over 11 years of education, without nausea or vomiting on admission, with no additional extracranial injuries, and only low levels of pain early after injury, had 90% chance on full RTW. The discriminative ability of the prediction models was satisfactory with an area under the curve > 0.70 after correction for optimism. We conclude that early identification of MTBI patients who are likely to have good six-month recovery showed feasible on the basis of relatively simple prognostic models. A score chart was derived from the models to facilitate clinical application.

Introduction

The incidence of traumatic brain injury is higher than any other neurologic diagnosis (Hirtz 2007). Over 80% of all traumatic brain injuries are considered mild (MTBI), because mortality is low and neurosurgical interventions are rarely needed (<1%). Nevertheless, MTBI is recognized as an important public health concern, as an estimated 5-15% of all patients suffer persistent symptoms and functional impairments for months to years after injury (Alexander 1995, Cassidy 2004, Iverson 2005). Given the high incidence of MTBI, and the good recovery in most patients, routine follow-up may not be feasible or needed. Unfortunately, the scientific foundations for reliable early identification of patients who are likely to recover well are weak.

In 2006, a review of prognostic models in TBI identified only few high quality studies concerning the prediction of MTBI outcome (Perel 2006). These studies were mainly directed at calculating the risk of post acute complications, rather than at long-term outcomes such as self-perceived symptoms or return to work. Although hundreds of studies report clinical risk factors for poor outcome, most of these are epidemiological or correlational in nature, using small or selected samples, considering only a limited set of predictors. Furthermore, very few studies address the validity of their models, or evaluate how to use these risk factors to guide clinical decision making, e.g. regarding the necessity of outpatient follow-up.

However, although such clinically usable prediction models are scarce, the existing literature does provide ingredients for a potentially powerful prediction model. For example, it is recognized that traditional head injury severity indices have limited power to predict outcomes such as persisting postconcussional symptoms or failure to return to work (Hanlon 1999, McCullagh 2001). Rather, other injury characteristics (e.g. early symptoms (Kruijk de 2002a, Savola 2003), presence of extracranial injuries (Dacey 1991, Stulemeijer 2006a,)), as well as pre- and post-injury physical functioning (e.g. pain, fatigue (Borgaro 2005, Lundin 2006)), and psychological status (e.g. emotional distress

(Levin 2005), personality (Mooney 2005)) are considered essential for understanding and predicting individual outcome patterns (Bryant 2001, Cattelani 1996).

In this prospective cohort study, we aim to develop and internally validate a prediction rule for favorable recovery six months after sustaining MTBI based on easily obtainable pre-, peri-, and post-injury variables. For this purpose, we will derive one rule to identify patients who report absence of postconcusional symptoms and a second for the prediction of full return to work. To facilitate clinical application, we will derive a score chart from the models.

Methods

Patients and procedure
The study was approved by the ethics committee of the Radboud University Nijmegen Medical Centre, and all patients gave written informed consent. All consecutive MTBI patients admitted to the emergency department (ED) of the Radboud University Nijmegen Medical Centre, a level 1 trauma centre, between October 2004 and August 2006, were eligible to participate in the study if they were between 18 and 60 of age, able to speak and write in Dutch and did not suffer from premorbid mental retardation or dementia. As soon as possible after ED admission, patients were informed about the study and asked to complete a questionnaire. Consenting patients were sent a follow-up questionnaire six months later.

Definition MTBI
In accordance with the criteria of the European Federation of Neurological Societies (EFNS), MTBI was defined as a history of impact to the head with or without loss of consciousness (LOC) ≤ 30 minutes and with or without posttraumatic amnesia (PTA) and a hospital admission Glasgow Coma Score (GCS) of 13-15 (Vos 20020.

Outcomes
1) Postconcusional symptoms (PCS). PCS were measured with the Rivermead Post-Concussion Questionnaire (RPCQ), a checklist assessing 16 common symptoms on a 5-point Likert scale. Patients were asked to rate how problematic, if at all, each symptom was experienced compared with the situation before they sustained their head injury (King 1995). Although the RPCQ is often used to measure PCS, a gold standard for classification of 'mild' versus 'severe' postconcusional symptoms is lacking. We defined favorable outcome as a score of 0 (no problem), 1 (not a problem anymore) or 2 (mild problem, but not interfering with daily activities) on at least 13 out of 16 symptoms. In a previous study, we reported on the severity of PCS in a cohort of non-brain injured patients with a wrist or ankle distortion (Stulemeijer 2006a). Ninety-four percent of all these patients would meet this criterion for favorable outcome.
2) Return to work (RTW). At follow-up, patients were asked to state their current employment status, and indicate whether they experienced negative changes in their work situation because of the trauma. Patients were classified as having full RTW when they were not on sick leave at time of follow-up, nor reported a change of working status into partial or lower-level employment due to the accident.

Prognostic factors
Clinical data were registered by the consulting resident of Neurology on the ED, and thereafter collected by a research nurse and registered on prespecified forms. All data were manually entered in the electronic Radboud University Brain Injury Cohort Study (RUBICS) databank.

Pre-injury
In addition to age and gender, the following prognostic factors were included:
Education: patients were categorized in three categories: low (about 10 years of formal

education or less), middle (about 11-14 years of formal education) and high level of education (about 14 years of formal education or more).

Premorbid emotional problems: a self-reported history of treatment by a psychologist, social worker or psychiatrist or current use of psychotropic medication, or both.

Physical co-morbidities: self-reported presence of one of the items listed in the questionnaire (asthma, chronic bronchitis, COPD; severe cardiac disease, cardiac arrest; epilepsy; diabetes; chronic back problems; spinal disk herniation; osteoarthritis; rheumatoid arthritis; malignancies, cancer) or in case of the presence of another health problem that can be expected to have great negative impact daily functioning.

Prior head injury: patients were asked if they ever suffered an injury to the head or brain before, and if so, what and when. As even very minor cases of head injury may result in chronic symptoms, any report of 'concussion' or 'contusion' was considered as relevant, as were non-traumatic causes of brain damage such as a brain tumor.

Peri-injury

GCS: admission CGS scores were assessed to indicate a patients' level of consciousness. In case of intubation or sedation, the GCS registered closest in time to admission was considered.

LOC: the presence and duration of LOC was based on reports of witnesses of the accident or ambulance personnel.

PTA duration: presence and resolution of PTA was assessed by the consulting resident of Neurology on the ED using a series of prespecified questions regarding short-term memory and orientation. The duration of PTA was classified in three clinically meaningful categories: (1) no PTA, (2) 1 to 30 minutes and (3) > 30 minutes.

CT characteristics: a brain CT was performed according to international guidelines, and scored using a predefined format.19 A CT was defined as abnormal if showing signs of contusion, edema, subdural hematoma, epidural hematoma or subarachnoid hemorrhage.

Early symptoms: based on previous reports we included dizziness, nausea/vomiting and headache reported on the ED as predictors in the model (Kruijk de 2002a, Savola 2003).

Additional extracranial injuries: extracranial injuries were considered present if, in addition to an MTBI, patients had a score of 2 or more in one of the body regions of the Abbreviated Injury Score/ Injury Severity Score (Baker 1974).

Early post-injury

Postconcussional symptoms: severity of PCS was measured with the above-mentioned RPCQ, and the same cut-off for 'severe PCS' was used (King 1999).

Post traumatic stress: the 15-item Impact of Events Scale (IES) measures intrusive symptoms (e.g. intrusive thoughts), and avoidance symptoms (e.g. numbing of responsiveness), and combined, provide a total subjective stress score. In accordance with the guidelines, scores above 26 were classified as severe (Sundin 2002).

Fatigue: self-perceived fatigue severity was measured with the 4-item Abbreviated Fatigue Questionnaire (AFQ). A cut-off value of 20 points was used to identify severe fatigue (Alberts 1997, Alberts 2007).

Pain: patients rated the severity of current pain on a four-point Likert scale (range from 0 (no pain) to 3 (severe pain)) on five body regions (head/skull, neck, arms/shoulders, chest/abdomen/back, pelvis/legs), a total pain score was calculated by adding the scores on the five items. High levels of pain were defined as a total score higher than 4. The questionnaire and scoring is provided in the Appendix.

Self-efficacy: the 10-item Generalized Self-Efficacy Scale was used to assess optimistic self-beliefs to cope with a variety of difficult demands in life. As suggested in the manual, a median spit was applied (Schwarzer 1995).

Most candidate variables were chosen from

previous research results. The predictors fatigue, pain and self-efficacy have, to our knowledge, not been examined prospectively, but are nevertheless included as they are repeatedly reported as potentially important in cross-sectional studies. e.g. (Borgaro 2005, Cattelani 1996, Gagnon 2005)Questions on pre- and post-morbid functioning were included in the early questionnaire.

Statistics

Comparisons of two groups were conducted with two-sample t-test analyses in case of continuous measures, and Chi-square tests in case of frequency data. A p-value < 0.05 was considered significant.As missing data were very scarce (<0.5% of all required values), missing values were not imputed. Logistic regression analyses were used to develop the prognostic models. To enhance clinical interpretability and reproducibility of the models, continuous measures were either dichotomized or split in categories mostly based on published cut-off scores. Variables that had a significant association with the outcome (p-value ≤ 0.10) were selected for the backward selection in the multivariable logistic regression. We used bootstrap sampling to estimate a shrinkage factor (Steyerberg 2003). The regression coefficients were thereafter multiplied with this shrinkage factor to correct the model for overoptimism. Sensitivity and specificity of the prognostic model and the area under the receiver-operating characteristic curve (ROC) were calculated, both with and without correction for optimism. Except for the bootstrap procedure, which was done with SAS 8.2, all statistical analyses were carried out using SPSS for Windows, 12.0 (SPSS Inc., Chicago, IL, USA).

Results

Study population and follow-up

Of 1003 patients who attended the ED with an MTBI during the study period, 539 met the inclusion criteria. Of those, 452 patients were sent the early questionnaire, whereas 87 were missed mostly for logistic reasons. Complete questionnaires were returned by 280 patients (62%). Only these patients received the six-months outcome questionnaire, which was returned by 201 patients (72%). Compared to the total cohort, the final sample contained less men (n = 127; 63%) than the sample in which no follow-up data were available (n = 252; 75%, p = .009), and patients were somewhat younger (final sample = 35.6 (SD 12.3) vs. rest of the cohort = 38.2 (SD 12.5), p = .001). No differences existed between the groups on admission GCS scores, MTBI category, type of injury, the presence of LOC and PTA, whether a CT of the brain was made and whether patients were admitted to the hospital. Table 1 lists the baseline characteristics. The early questionnaire was completed on average 9 days after injury (SD 7.1), and the follow-up questionnaire on average 6.5 months after injury (SD 1.0). No or mild postconcusional symptoms at six-months were reported by 152 patients (76%), and 153 (76%) patients reported full RTW. One hundred twenty-eight patients (64%) reported both the absence of PCS and full RTW (p < .001).

Prognostic model

The univariate associations of the determinants with the absence of PCS and full RTW at six months are presented in Table 1. Dizziness was not included in the model as only three patients reported this complaint. Table 2 presents the variables for the final prediction models after backward stepwise analysis.

Model 1: No or mild PCS. The absence of co-morbid physical problems, low levels of PCS and post traumatic stress early after injury, most strongly predicted good recovery. The odds of no or mild PCS at six months in patients without premorbid physical co-morbidities were 3.5 times the odds of when such co-morbidities were present. Similarly, there was a 5.5 fold greater odds of no residual PCS at follow-up in patients who did not

Table 1. Baseline characteristics of MTBI patients (n = 201), and univariate associations with no or mild postconcusional symptoms (PCS) and complete return to work (RTW) at six months following ED admission

Variable	N (%)	No/ mild PCS (n = 152)			Full return to work (n = 153)		
		OR	95% CI	p	OR	95% CI	p
Pre-injury							
Age (years): mean (SD)	37.7 (12.7)	1.0	1.0 to 1.0	.507	1.0	1.0 to 1.0	.756
Gender: woman	78 (39%)	1.0	0.5 to 1.9	.996	0.9	0.5 to 1.8	.831
Education				.0001**			.0001**
Low*	56 (28%)						
Middle	63 (31%)	2.3	0.9 to 5.4	.071	4.9	1.9 to 12.7	.0001
High	82 (41%)	5.4	2.3 to 12.6	.0001	6.4	2.5 to 16.5	.0001
Emotional problems: no	137 (68%)	1.9	1.0 to 3.7	.059	0.9	0.4 to 1.7	.649
Physical co-morbidity: no[a]	130 (65%)	5.5	2.7 to 10.9	.0001	1.8	0.9 to 3.5	.083
Prior head injury: no	129 (64%)	0.9	0.5 to 1.6	.850	0.8	0.4 to 1.5	.450
Peri-injury							
Admission GCS: 15	150 (75%)	1.6	0.8 to 33	.180	0.6	0.3 to 1.2	.149
LOC: no	73 (36%)	1.0	0.5 to 1.9	.944	0.6	0.3 to 1.3	.189
PTA duration (n = 7 missing)				.220**			
No PTA	77 (38%)	2.0	0.9 to 4.5	.092	1.7	0.8 to 3.7	.174
PTA 1-30 minutes	69 (34%)	1.6	0.7 to 3.5	.251	0.8	0.4 to 1.8	.629
PTA > 30 min*	55 (27%)						.186
CT characteristics				.300**			.010**
No CT made	28 (14%)	2.6	0.7 to 9.0	.141	7.8	1.6 to 37.7	.011
No traumatic abnormalities	133 (66%)	2.0	0.6 to 6.1	.236	4.0	0.9 to 17.6	.071
Traumatic abnormalities*	40 (20%)						
Mechanism of injury				.514**			.022**

Traffic*	110 (55%)	-			-		
Fall	40 (20%)	1.5	0.6 to 3.7	.364	2.2	0.9 to 5.0	.078
Sports	21 (10%)	1.0	0.4 to 3.1	.943	0.2	0.0 to 1.3	.082
Other	30 (15%)	0.7	0.3 to 1.6	.335	0.9	0.4 to 2.2	.884
Headache on admission: no	135 (67%)	1.1	0.6 to 2.2	.750	0.8	0.4 to 1.6	.535
Nausea or vomiting: no	170 (85%)	1.9	0.8 to 4.3	.122	2.4	1.0 to 5.3	.039
Additional extracranial injuries: no	125 (61%)	1.3	0.7 to 2.5	.403	3.9	2.0 to 7.6	.0001
Early post-injury[b]							
RPCQ severe complaints: no	109 (54%)	6.3	3.0 to 13.3	.0001	2.0	1.0 to 3.8	.047
IES Total score > 26: no	186 (92%)	16.1	4.3 to 60.0	.0001	2.3	0.8 to 6.8	.137
General self efficacy < 28: no	172 (86%)	4.4	1.9 to 9.9	.0001	1.3	0.5 to 3.1	.613
Pain				.268**			.007**
Low (0-2)	53 (26%)	1.9	0.8 to 4.3	.146	2.3	1.0 to 5.3	.046
Moderate (3-4)	65 (32%)	1.2	0.5 to 2.9	.720	0.7	0.2 to 1.9	.462
High (>4)*	83 (41%)						
AFQ Total ≥ 20: no	113 (56%)	4.8	2.2 to 10.6	.0001	2.0	1.0 to 4.0	.047

SD = standard deviation; GCS = Glasgow Coma Scale; PTA = Post Traumatic Amnesia; RPCQ = Rivermead Postconcusional Complaints Questionnaire; IES = Impact of Events Scale; AFQ = Abbreviated Fatigue Questionnaire.

* Reference category

** Overall P-value for the factor.

[a] = the following co-morbidities were reported: chronic back problems, spinal disk herniation (n = 21); asthma, chronic bronchitis or COPD (n = 12); osteoarthritis (n = 7); epilepsy (n = 4); diabetes (n = 3); severe cardiac disease, cardiac arrest (n = 2); rheumatoid arthritis (n = 2); malignancies, cancer (n = 2); other: chronic headache (n = 4); high blood pressure (n = 4); chronic kidney problems (n = 2); hypothyroidism (n = 2); Chrons disease (n = 1); Ménière's disease (n = 1); chronic skin problems (n = 1); unspecified (n = 3).

[b] = mean 9 days after injury (SD 7.1, range 1 – 37)

Table 2. Final multivariable model with predictors of no/mild postconcusional symptoms (n = 152) and complete return to work (n = 153) at six months following ED admission

Variable	No/ mild postconcusional symptoms	
	OR	95% CI
Premorbid physical co-morbidity: no	3.5	1.6 to 7.8
Early post-injury RPCQ PCS: no	5.5	2.3 to 13.2
Early post-injury IES Total score > 26: no	10.0	2.3 to 42.9
Variable	**Full return to work**	
	OR	95% CI
Premorbid education level		
Low*	-	
Middle	4.6	1.7 to 12.6
High	6.4	2.3 to 18.3
Peri-injury nausea or vomiting: no	5.1	1.8 to 14.3
Peri-injury additional extracranial injuries: no	3.4	1.6 to 7.3
Early post-injury severe pain (>4): no	2.3	0.9 to 5.9

RPCQ = Rivermead Postconcusional Complaints Questionnaire; PCS = Postconcusional Symptoms; IES = Impact of Events Scale; OR = odds ratio.
* Reference category

report severe PCS already early after injury, than in those who were symptomatic. Lastly, there was a ten fold greater odds of favorable outcome for patients without post traumatic stress compared to patients with severe post traumatic stress. The area under the ROC was 0.82. After shrinkage, the discriminatory ability of the model was decreased, but still fair (ROC .73).

Model 2: Full RTW. More than 11 years of education, the absence of nausea or vomiting on admission, the absence of additional extracranial injuries and no severe pain early after injury were associated with a higher chance of full RTW. The odds of full RTW at six months in patients with more than 11 years of formal education were 6.4 times the odds of favorable outcome in patients with less education. Similarly, in case patients reported no nausea and did not vomit on admission, the odds of full RTW were 5.1 the odds for favorable outcome then when this was the case. Thirdly, the odds for RTW were 3.4 times greater than in patients with no additional injuries than in those with. Lastly, the absence of pain shortly after injury,

was associated with a 2.3 greater odds of favorable outcome than when severe pain were reported. The area under the ROC was 0.79. Again, the discriminatory ability of the model decreased but was still fair (ROC .70) after correction for optimism based on the bootstrap samples.

Considering the loss of power associated with the use of binary or continuous independent variables in regression analyses, we also explored which models would result when the predictor variables without published cut-off scores (Pain, RPCQ, General Self-efficacy) were included as continuous variables. The resulting models were similar to those obtained in the original analysis. In Figure 1 and 2, a score chart with associated chances for recovery is provided for both models. For example; a patient without severe PCS and no post traumatic stress early after injury (76% of the whole current sample) has a 90% chance to be free of debilitating PCS at six months. To illustrate the impact of internal validation on the power of a regression model, the predicted probabilities both before and after

Model 1: No/ mild postconcusional symptoms					score
Premorbid physical comorbidities					-1
Severe postconcusional symptoms within weeks after injury					-1
Severe post-traumatic stress within weeks after injury					-2
				Total score	
Score	N				
			observed probabilities	predicted probabilities[a]	predicted probabilities after bootstrap[b]
0	78	39%	.96	.95	.90
-1	75	37%	.77	.80	.90
-2	34	17%	.47	.50	.60
≤ -3	14	7%	.21	.15	.35

Figure 1 Score chart for the early prediction of no or mild postconcusional symptoms six months after MTBI. If a predictor is scored positively, the given weight needs to be filled in. Subsequently the scores are added to calculate the 'Total score'. Using the score chart, the chance (%) of good recovery for an individual patient can be determined based on this total score. [a] = The predicted probabilities of severe PCS six months after injury based on the multivariate logistic regression analysis (AUC=0.82.), [b] = The predicted probabilities after shrinkage and correction for optimism (AUC = 0.73).

Model 2: Full return to work[a]					score
Less than 11 years of formal education					-1
Nausea or vomiting on ED admission					-1
Concurrently sustained extracranial injuries					-1
High levels of pain within weeks after injury					-1
				Total score	
Score	N				
			observed probabilities	predicted probabilities[a]	predicted probabilities after bootstrap[b]
0	52	26%	.97	.95	.90
-1	71	35%	.91	.90	.85
-2	62	31%	.71	.70	.70
≥ -3	16	8%	.38	.40	.55

Figure 2 Score chart for the early prediction of full return to work six months after MTBI. If a predictor is scored positively, the given weight needs to be filled in. Subsequently the scores are added to calculate the 'Total score'. Using the score chart, the chance (%) of good recovery for an individual patient can be determined based on this total score.
[a] = The predicted probabilities of incomplete return to work six months after injury based on the multivariate logistic regression analysis (AUC=0.79), [b] = The predicted probabilities after shrinkage and correction for optimism (AUC = 0.70).

bootstrap correction are reported.

Discussion

We have developed two models for the prediction of favorable six months recovery, in a prospective, unselected sample of MTBI patients consecutively admitted to the ED of a level 1 trauma hospital. To enhance the reproducibility of these models in future studies, we internally validated the models by bootstrapping. The models, based on easily obtainable pre- peri- and early post injury factors, identified a group of patients with

90% probability of absence of debilitating symptoms or full RTW at six months. The calculation of a score chart enabled easy identification of risk scores and associated probabilities for favorable outcome.

In line with most MTBI outcome studies, most patients in our study had recovered by six months after injury (Cassidy 2004, Naalt van der 2001). Still, one-third of the sample reported persisting PCS, incomplete return to work or both. Although these numbers correspond with previous studies in unselected samples (thus including patients with e.g. extracranial injuries or psychiatric co-morbidities) the prevalence of suboptimal outcome in the general MTBI population is expected to be lower, as the willingness to participate in research is thought to be lesser in those who fully recover (Bazarian 1999, Cassidy 2004, Hanlon 1999, Karzmark 1995, King 1999, Luis 2003, McCullagh 2003).

The results of our study illustrate that to enable prediction of outcome after MTBI, factors unrelated to the head injury are of major importance. Regarding pre-injury characteristics, the chances of good outcome significantly increased with higher levels of education, especially in relation to return to work which confirms earlier work (Boake 2005, Ruffolo 1999). Possibly, higher level jobs generally have better conditions for work resumption, like greater decision-making latitude and lower physical demands. Alternatively, higher educated patients may have more adaptive coping skills. In turn, the absence of physical co-morbidities predicted the absence of PCS, but not return to work. Possibly, people who are in suboptimal physical shape before the injury have less reserve to overcome the additional strain of an MTBI. Alternatively, symptoms that relate primarily to the comorbidity may falsely be attributed to the head injury (Mittenberg 1992). Factors that have incidentally found to be predicted to outcome (though at different times since injury) such as age, gender or history of emotional problems did not predict outcome

in the present study (Cattelani 2003, Edna 1987, Ponsford 2000, Savola 2003).

In accordance with many other studies, traditional injury characteristics like LOC and PTA duration could not predict long term PCS, and we could not replicate the finding of others that acute symptoms had strong predictive value for the development of PCS (Kruijk de 2002a, Savola 2003). Absence of additional systemic injuries predicted full return to work. This confirms our earlier findings that six months is too early to determine final outcome, because many patients with multi-system injuries are still in the process of rehabilitation (Stulemeijer 2006). Lastly, in the current study, the presence of nausea or vomiting at the ED was significantly related to incomplete RTW, rather than to PCS (Kruijk de 2002, Savola 2003). This finding is less easily interpretable, and the mechanisms remain poorly understood.

Regarding early post-injury factors, the absence of early PCS and low levels of post traumatic stress strongly predicted the absence of debilitating symptoms at six months (Lundin 2006, Nolin 2006a). These results support the importance of considering emotional well-being early after injury for long-term outcome (Harvey 2000, King 1999, Levin 2005). Post traumatic stress is closely related to other forms of emotional distress such as depression and anxiety that are known to negatively impact outcome (Bryant 2001). Our findings also add to the literature by suggesting that less perceived competence to deal with difficult and unforeseen circumstances, and early levels of severe fatigue are associated with greater likelihood of severe PCS at six months. As these factors were significant in the univariate, but not the multivariate analysis, they may not be of key-importance to MTBI outcome, but still worth considering.

Several limitations of the study should be noted. Firstly, our sample size was fairly small for prediction modeling and included only 37% of the whole cohort. The participants

do however, seem to represent a general ED-admitted MTBI population. No differences were found on any of the injury characteristics, compared to non-participating patients, and age and gender did not contribute to outcome. Although we performed internal validation of the models by using bootstrap resampling, external validation remains necessary to confirm the predictive value of our models in future patients and other settings. Furthermore, the prediction models could strongly predict good outcome, even after correction for optimism, but were less favorable for the prediction of poor outcome. These results are in line with most previous studies that did not succeed in finding strong and reliable predictors for suboptimal outcome (Naalt van der 2001, Perel 2006). In addition, the sensitivity and specificity of the models decreased substantially after internal validation, which may be due to the relatively small sample size, the many potential predictors, the low frequency of important predictors and the variance within the patient sample. Lastly, although we addressed many factors, there are other potentially relevant variables that we did not include, such as litigation or early cognitive testing (Bazarian 1999, Feinstein 2001).

Besides contributing to a greater understanding of factors influencing MTBI outcome, our findings may have important clinical implications. For example, models.

predictionThis knowledge may guide outcome assessment we showed that outcome could not be predicted based solely on pre- and peri-injury characteristics, but also required information regarding a patients emotional and physical functioning early after injury. As this information is relatively easy to obtain, an outpatient visit may not be necessary. Rather, consultation by phone or even through internet-based questionnaires may suffice. This would potentially represent a substantial overall saving in cost and time. In addition, we developed two score charts that may help to easily inform patients more accurately regarding their prospects for recovery.

In conclusion, the present study supports the feasibility of early identifying MTBI patients who are likely to have good six-month recovery, on the basis of only a few factors. Patients who will recover well do not seem to simply have suffered milder head injuries, rather, the results of our study illustrate that to enable prediction of outcome after MTBI, factors unrelated to the head injury are of major importance.

APPENDIX: Brief Pain Questionnaire
How much pain do you experience at this moment?
In case you used pain relief medication, please indicate how much pain you had before taking this medication.
(please circle one response per body region)

	No pain	Mild pain	Moderate pain	Severe pain
Head/ skull	0	1	2	3
Neck	0	1	2	3
Chest/abdomen/back	0	1	2	3
Arms/shoulders	0	1	2	3
Pelvis/legs	0	1	2	3

Scoring: A total score can be calculated by adding the values in each circled cell. Scores above 4 receive a score of −1 in the score chart for the prediction of full return to work (Figure 2).

Chapter 9

Summary of the main findings
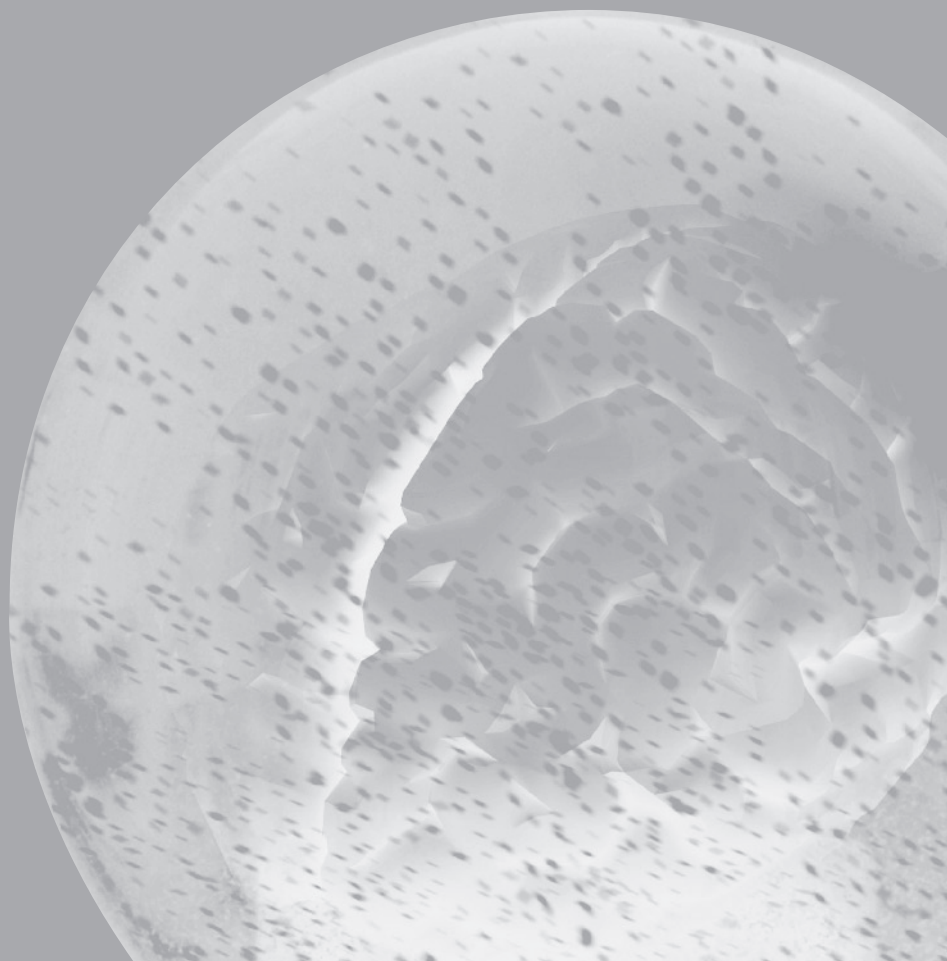
In 80-90% of the patients that suffer traumatic brain injury, the severity of the injury is relatively mild. Mortality in patients with such a Mild Traumatic Brain Injury (MTBI) is very low, neurosurgical interventions are rarely needed and most patients show a spontaneous, quick and full recovery. Nevertheless, MTBI is considered to be an important public-health concern as a minority of patients will develop debilitating symptoms that may persist for up to years after injury. Given the high incidence of MTBI, the number of patients that suffer from chronic symptoms is substantial. Typically, these so-called 'post-concussional symptoms' are present without evidence of gross cognitive impairments or other neurological abnormalities. This observation gave rise to a continuing debate about possible causes of persisting symptoms after MTBI. The studies in this thesis are performed as part of the Radboud University Brain Injury Cohort Study (RUBICS). RUBICS has developped a databank in which clinical records, radiological parameters and outcome scores of all patients with head injury admitted to the emergency department of the Radboud University Nijmegen Medical Centre are collected. The general aim of the presented studies was to gain more insight in determinants of post-concussional symptoms (especially fatigue and cognitive complaints), neuropsychological test performance and return to work six months after MTBI, by integrating neurological characteristics of the injury with a range of non-neurological factors such as a patients' physical and psychological functioning. This chapter summarizes the main findings.

In *Chapter 1* the outline of this thesis is presented.

Fatigue is one of the most frequently reported symptoms after MTBI. To date, systematic and comparative studies on fatigue after MTBI are scarce. *Chapter 2* describes a study aimed at determining the severity of fatigue six months after Mild Traumatic Brain Injury and its relation to outcome. Furthermore, it was tested whether acute injury indices had predictive value for late fatigue complaints. In contrast to previous studies, we used a validated and multidimensional questionnaire to assess fatigue. The results showed that significantly more MTBI patients (32%) reported severe fatigue than minor-injury orthopaedic control patients (12%). When patients reported severe fatigue; levels of fatigue-related problems in concentration, motivation and activity were also high. Moreover, in these patients, post-concussional symptoms as well as limitations in physical and social functioning were frequent and mean scores deviated from the normal range. Less-fatigued patients on the other hand, report hardly any problems on these variables. Regardless of fatigue-status, MTBI patients consistently reported more problems than the controls on all outcome domains, with the exception of physical functioning. In addition, the results suggest that fatigue may be especially associated with post-concussional symptoms and functional limitations in severely fatigued MTBI patients and less in those with a minor orthopedic injury. Traditional trauma severity indices did not relate to fatigue. However, nausea and headache experienced on the ED were significantly related to higher levels of fatigue at six months. The mechanism linking these acute symptoms to late fatigue however, needs further exploration.

In *Chapter 3*, we examined the impact of additional injuries on the severity of post-concussional symptoms and functional outcome six months post injury. Of all 299 subjects, 89 had suffered additional extracranial injuries. After six months, 44% of the patients with additional injuries were still in some form of treatment, compared to 14% of patients with isolated MTBI and 0.5% of the controls. Compared to patients with isolated injury, MTBI patients with additional injuries had resumed work less frequently and reported more limitations in physical

functioning. Other than expected, they did not report higher levels of post-concussional symptoms however, despite somewhat more severe head injury. This finding confirms prior studies that there is no proportional relationship between injury severity and subjective outcome in MTBI. Regardless of the presence of additional injuries, patients that still received some form of rehabilitation treatment (e.g. physiotherapy) reported significantly more severe PCS, with highest rates in patients with isolated MTBI.

Short-term, and in a minority of the cases also long-term cognitive deficits are frequently reported sequalae of MTBI. These cognitive deficits remain poorly understood as in the majority of patients the core memory structures, as the rest of the brain, are macroscopically intact. Neuroimaging techniques like functional Magnetic Resonance Imaging (fMRI) measure functional rather than structural characteristics of the brain. Therefore, these techniques may add important new knowledge to the understanding of cognitive complaints after MTBI. FMRI may be especially useful early after injury where the cognitive problems are thought to reflect disturbances in brain activity due to the impact. As described in *Chapter 4*, within six weeks after injury 43 patients underwent functional Magnetic Resonance Imaging while performing a task probing prefrontal and medial temporal functionality. In addition, out-of-scanner neuropsychological testing was done. Behavioural results showed poorer declarative memory performance and more severe cognitive complaints in patients than controls and both performance and complaints were linearly related to injury severity (duration of posttraumatic amnesia). Task performance in the scanner was, as intended by the task and design, similar in patients and controls, and did not relate to injury severity. Thus, differences in brain activity could not be attributed to simple differences in performance. The task used

activated reliably the medial temporal lobe and prefrontal cortex. Although we did not find significant differences in brain activity when comparing patients and controls, we revealed, closely in line with our neuropsychological findings, an inverse relationship between medial temporal lobe activity and duration of posttraumatic amnesia. In contrast, no support was found for the assumption that the non-specific cognitive complaints after MTBI result from a 'compensatory activation' at the cerebral level.

Subsequently, we looked at cognitive functioning six-months after MTBI. In contrast to the early cognitive problems, there is considerable evidence that poor test performance on the longer-term is associated with non-neurological factors. In *Chapter 5*, we explored the impact of poor effort on neuropsychological tests performance in non-referred MTBI patients. To better understand the factors contributing to poor effort besides litigation, patients with and without adequate effort were compared on levels of distress, fatigue, and personality. Effort was measured using a validated test, the Amsterdam Short-Term Memory Test. The results showed that 27% percent of the 110 participating patients failed the effort test. Poor performance on the effort task was strongly associated with poorer neuropsychological test performance and more clinical impairments on all tested cognitive domains. Effort affected both relatively simple as well as more effortful tests, and both self-paced and timed tests. Of all patients with one or more clinically impaired test scores (43/110), 44% patients failed the effort test. Poor effort was associated with lower educational level, a history of emotional problems and changes in work status, but not litigation. Furthermore, poor effort was related to high levels of distress, Type-D personality and fatigue.

The relations between cognitive complains and neuropsychological test performance and

possible factors that relate to the experience of cognitive problems are the focus of *Chapter 6*. We compared patients with and without self reported cognitive complaints on four domains: (1) Demographic variables and injury characteristics, (2) Neuropsychological test performance, (3) Daily self observed cognitive complaints during 12 days, and (4) Emotional distress, personality, physical functioning and fatigue. To increase the validity of the results, patients with demonstrated poor effort were excluded from the analysis. Self-reported cognitive complaints were reported by 39% of the 79 patients. These complaints were strongly related to lower educational levels, emotional distress, personality and poorer physical functioning but not to injury characteristics. Importantly, over half of the patients with cognitive complaints reported severe levels of posttraumatic stress, and symptomatic patients were 18 times more likely to experience severe fatigue. Interestingly, the severity of self reported cognitive complaints was neither associated with the patients' daily observations of cognitive problems nor with outcome on a range of neuropsychological tests.

Chapter 7 attempts to synthesize previous findings of our own studies and literature on persisting cognitive complaints. We argue that whilst neurological factors might explain the acute clinical picture, psychological and behavioural processes play an important role in the persistence of subjective symptoms. It requires knowledge of these various processes to understand why despite good neurological recovery and normal test performance outcomes, some MTBI patients still perceive themselves to be cognitively impaired long after the incident. As it takes into account the way patients interpret their complaints and the implications thereof, Leventhal's self-regulation model helps to explain individual differences between patients that cannot be attributed to the severity of the initial head injury. We feel the proposed explanatory

health-psychology-based model raises various interesting questions for future studies and offers clinical implications for diagnoses and treatment.

Predicting outcome after Mild Traumatic Brain Injury (MTBI) is notoriously difficult. In *Chapter 8*, we aimed to develop and internally validate two prediction rules for identifying patients who have a high chance for good six-month recovery. Besides MTBI severity indices, a range of pre-, peri- and early post injury variables was considered as potential predictors, including emotional and physical functioning. Logistic regression modelling was used to predict full recovery, defined as the absence of post-concussional symptoms (PCS) and full return to work (RTW). The results show that early identification of MTBI patients who are likely to have good six-month recovery was feasible on the basis of relatively simple prognostic models. At follow-up, 64% of the 201 participating patients reported full recovery. Based on our prediction rules, patients without pre-morbid physical problems, low levels of PCS and posttraumatic stress early after injury, had 90% chance to remain free of PCS. Patients with over 11 years of education, without nausea or vomiting on admission, with no additional extracranial injuries, and only low levels of pain early after injury, had 90% chance on full RTW. The discriminative ability of the prediction models was satisfactory with an area under the curve > 0.70 after correction for optimism. A score chart was derived from the models to facilitate clinical application. Extrapolation of our data to the general ED admitted MTBI population would suggest, with a high level of certainty, that about three quarter of all patients is expected to recover well.

Chapter 10

General Discussion
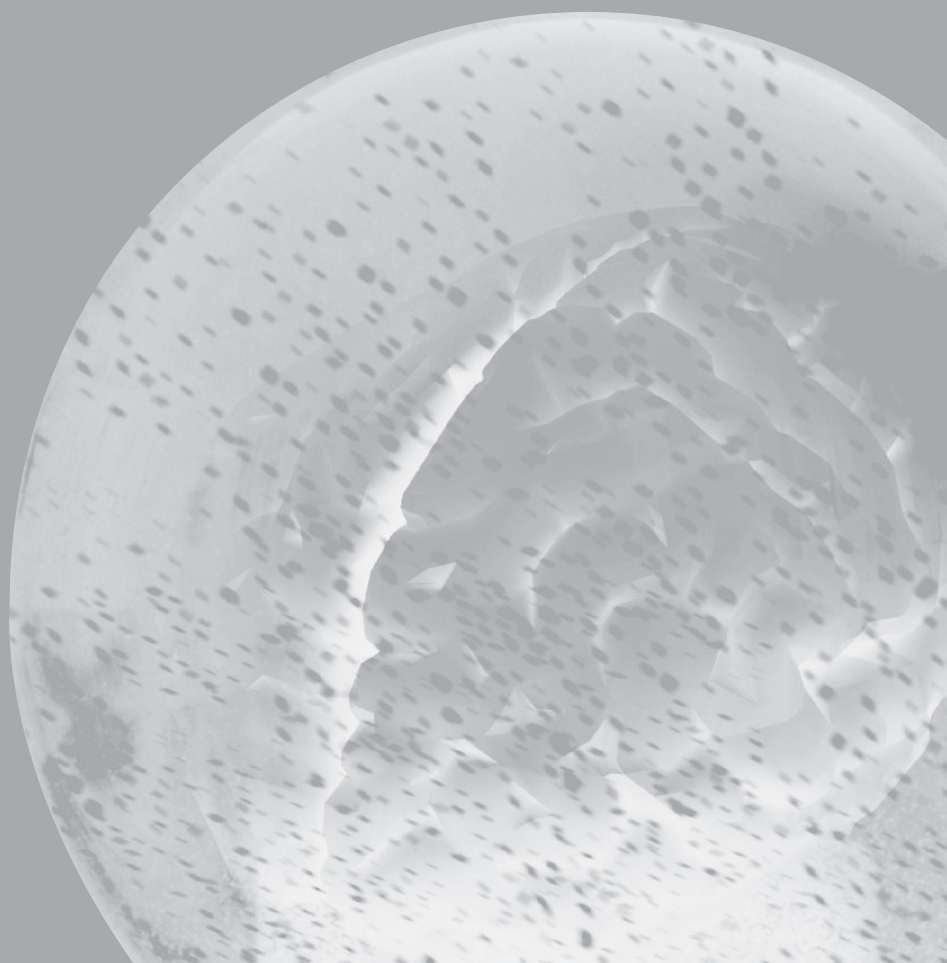
10.1 Introduction

Mild Traumatic Brain Injury (MTBI) is one of the most prevalent neurological conditions world-wide. There is general consensus that a minority of patients develop persistent debilitating symptoms. The studies presented in this thesis were aimed at gaining more insight in the determinants of these post-concussional symptoms, their relation to neuropsychological test performance and the prediction of return to work at six months in patients that visited the Emergency Department (ED) of a Level I trauma hospital. In contrast to many earlier MTBI outcome studies, we did not rely solely on symptom checklists. Rather, with a biopsychosocial model of health in mind, we assessed outcome along various dimensions (e.g. physical, cognitive, psychological and occupational functioning) and across several domains (brain activation, neurological examination, neuropsychological test performance, self-report questionnaires and daily self-observations). In addition, besides acute injury variables, a range of psychological and physical pre- and early post-injury indicators were included.

Overall, the findings described in this thesis underscore that MTBI is justifiably seen as an important public health concern. Whereas the injury to the head may be mild, the circumstances under which MTBI can be suffered and the consequences of the event are nothing but mild in a considerable portion of the patients. In the two patient cohorts that we studied, about one in five MTBI patients had not yet returned fully to their formal occupational status by six-months and about one in four patients reported persisting symptoms. To put this into perspective, this was the case in one in fifty (no full return to work) and one in twenty (persistent symptoms) of the control patients who suffered an ankle or wrist distortion. In this final chapter, these results will be integrated and discussed, together with clinical implications of the findings and suggestions for future research.

10.2 Determinants of post-concussional symptoms and return to work six months after MTBI

While one might naively consider that outcome after MTBI is mainly determined by the characteristics of the head injury, there was no relationship whatsoever between severity indices (like post-traumatic amnesia (PTA) and computed tomography abnormalities) and long-term outcome. The brain injury severity indices were of no influence in our predictive model for full recovery after MTBI (Chapter 8); they were not correlated to the amount, nor intensity, of self-reported complaints (Chapter 6) and, if any, only played a marginal role in the development of persistent fatigue (Chapter 2). These findings are in line with many earlier studies (for a review see McCrea 2008). Thus, it seems unlikely that the head injury in itself causes slower recovery in MTBI patients than in patients with minor orthopaedic injury. Rather, the studies in this thesis strongly suggest that it is the greater emotional and extracranial impact of the event that makes MTBI a more challenging event to overcome than, for instance, an ankle strain. Specifically, we showed that functional outcome after MTBI cannot be fully understood without considering the injuries suffered to other parts of the body than the head, a topic that has received surprisingly little attention in prior studies. About one third of all MTBI patients also sustained extracranial injuries (including its associated experience of pain), which significantly and consistently reduced the likelihood of full return to work at six months post-injury (Chapter 3 and 8).

Noteworthy, patients with additional injuries did not report higher levels of post-concussional symptoms, despite more functional limitations and somewhat more severe head injury (Chapter 3). Rather, such self-reported complaints were strongly associated with the emotional impact of the injury. Not only were post-concussional

symptoms strongly related to measures of emotional distress in cross-sectional analyses (Chapter 5 and 6), relatively high levels of post-traumatic stress experienced in the first days to weeks after trauma, strongly decreased the likelihood of favourable recovery at six-months (Chapter 8). Our findings thereby contribute to evidence that post-traumatic stress can, and in fact does, occur following MTBI, and is relevant to recovery (Bryant 1999, Hickling 1998). The relevance of post-traumatic stress disorder (PTSD) proofs to be a controversial issue as there are several authors who claim that MTBI and PTSD are mutually exclusive, since patients often have no recollection of the actual impact. However, we and others argue that such stress is caused by strong feelings of fear and helplessness shortly thereafter (Creamer 2005).

In addition to these peri and early-post injury factors, our studies identified several premorbid characteristics that might render some individuals more vulnerable to develop persisting problems after MTBI than others. We showed that these variables were especially relevant for the prediction of persisting symptoms, and less for return to work. First and foremost, we found, in line with several other studies (for instance Binder 1997, Boake 2005, Ruffalo 1999), a strong and consistent inverse relationship between level of education and both symptoms and occupational status. As reviewed by Adler, lower social economic status (to which lower educational level is closely related) might contribute to poorer health through interaction with both environmental factors, such as poorer availability of resources, and intra-personal factors, such as a low self-efficacy (Adler 1999). As shown in Chapter 8, higher self-efficacy was predictive for low levels of symptoms at six-months, and post-hoc analyses showed that education level was inversely related to self-efficacy (r = .56, p = .001. unpublished data). This finding is potentially important as feelings of self-efficacy can be enhanced through psychological interventions, e.g. by increasing a sense of control over the symptoms. Besides self-efficacy, our findings indicate the presence of Type-D personality is relevant to recovery after MTBI as well. This is a relatively new personality construct that refers to a combination of social inhibition and negative affectivity and has mainly been studied in patients with cardiac problems (e.g. DeNollet 2005, 2006). In our studies, patients with such personality traits reported more severe post-concussional symptoms at the longer term and more often had invalid performance on neuropsychological tests (Chapter 5 and 6). Interestingly, the social inhibition aspect of Type-D personality, more than negative affectivity, was consistently related to higher level of post-concussional symptoms. Social inhibition reflects the tendency to inhibit the expression of emotions and behaviour in order to avoid negative reactions from others. As summarized by Denollet in cardiac patient, such an emotionally inhibited style may impede communication between patient and physician and result in the physician overlooking important psychosocial issues like depression (DeNollet 2006). It would be an interesting topic for future research to see whether social inhibition (or other personality traits) affects the patient – doctor communication in MTBI patients as well.

Lastly, a general perceptual phenomenon was related to elevated post-concussional symptoms (Chapters 5 and 6). In line with findings in patients with Chronic Fatigue Syndrome, patients that have a higher tendency to focus on internal bodily-symptoms reported more post-concussional symptoms (Vercoulen 1998). As illustrated in section 10.4, this predisposition presumably relates to a heightened susceptibility to and a negative interpretation of bodily sensations (Miller 1981).

In conclusion, the studies presented in this thesis clearly show that whether or not a patient will recover cannot be determined on the basis of the characteristics of the head

injury. Instead, the physical and emotional impact of the trauma is of great importance and some patients are more vulnerable to develop persisting problems than others on the basis of premorbid personality characteristics.

10.3 Biological underpinnings of post-concussional complaints

In the above we have showed the importance of psychological processes in the development of persistent post-concussional symptoms. Without a doubt, these processes are tightly interwoven with changes in biological and physical processes including those at the level of the central nervous system. To complicate things even further, changes brought about by the impact to the head, might interact with pre-existing vulnerability factors. In recent years, advances in the fields of neuroimaging and genetics have greatly boosted the research on the biological underpinnings of post-concussional complaints. Also in this thesis (Chapter 4), we have shown the added value of advanced imaging techniques beyond standard measurement techniques such as neuropsychological tests. Using functional Magnetic Resonance Imaging, we detected a correlation between injury severity and brain activation without performance differences between patients and controls while performing a working memory task. Specifically, we found support for the hypothesis that functional alterations in the medial temporal lobe (MTL) might contribute to cognitive dysfunction early after MTBI. This finding raises interesting questions for future research. For instance, do subtle structural changes that go undetected by standard imaging techniques underlie these functional alterations (Meythaler 2001)? A relatively new MRI technique, Diffusion Tensor Imaging (DTI), enables in vivo measurements of axonal integrity. DTI quantifies white matter architecture through an extensive description of water diffusion in brain tissue (e.g.

Belanger 2007, Ulug 1999). Several studies have found evidence for reduced axonal integrity in normal appearing white matter in MTBI patients, hours to years after injury. Affected brain structures commonly, but not consistently, include the corpus callosum and the internal capsule (Arfanakis 2002, Bazarian 2007, Inglese 2005). Additionally, differences between MTBI patients and healthy controls have also occasionally been found in other brain structures such as the fornix (connecting the hippocampus to the hypothalamus) (Nakayama 2006) and cingulum (connecting components of the limbic system) (Rutgers 2007).

Even if abnormalities in brain functioning and structure are present, one should be cautious to attribute them to direct consequences of the head injury. Findings in other patient populations show that such alterations might also be a caused by emotional distress. For example, it is well known that acute and chronic stress may lead to changes in many brain structures including the medial prefrontal cortex, hippocampus, cingulate and amygdala. Patients with PTSD have repeatedly been found to have smaller hippocampi (reviewed by McNally 2006, Vermetten 2002). Findings in geriatric patients with depression showed reduced white matter integrity in the pathways that connect limbic structures with frontal regions (Taylor 2007). Whether such structural abnormalities represent the consequences of the disorder, or rather reflect a (genetic) pre-existing predisposition that renders the brain more vulnerable to the development of psychopathology is not yet known (e.g. discussed in McNally 2006). Nevertheless, these findings clearly illustrate that the brain structures subserving cognitive and emotional functioning are highly interconnected. This might explain why cognitive and emotional problems in many disorders, including MTBI, are overlapping and interacting (e.g. Salmond 2005). One shared pathway linking mood and cognition that might be of particular interest for TBI

and requires further study, is the cholinergic neurotransmitter system. Cholinergic pathways include many of the brain areas that are known to be sensitive to TBI (like the reticular formation, hippocampus, bifrontal lobes, and axonal connections between these structures) (Bigler 2007, Salmond 2005, Selden 1998). There is preliminary evidence for the hypothesis that disturbances of the cholinergic system might relate to cognitive and emotional consequences of (M)TBI (e.g. Arciniegas 2001, McAllister 2006, Salmond 2005).

Whether DTI and other 'new' neuroimaging techniques have additional clinical value in terms of the ability to explain and predict outcome in MTBI patients is not yet known. To date, some studies have found DTI parameters to be associated with self-reported complaints and/or cognitive performance (Bazarian 2007, Kraus 2007), others have not (Arfanakis 2002, Inglese 2005).

Though rapidly advancing, research on the biological underpinnings of post-concussional sequalea after MTBI is in its infancy. As discussed in Chapter 7 and the following section however, this does not mean that we are completely in the dark regarding our understanding of how MTBI patients develop persisting problems on a behavioural level.

10.4 A biopsychosocial perspective on poor outcome after MTBI

In accordance with a biopsychosocial perspective on health, it is assumed that biological, psychological and social factors are related in a dynamic, interactive manner in determining a patient's functioning. In MTBI, it is generally assumed that the impact to the brain accounts for most of the early symptoms, whereas emotional and behavioural factors contribute strongly to the exacerbation and persistence of these symptoms (King 2003, McCrea 2008). Our findings seem to be in accordance with this assumption. As described in Chapter 4, within the first six weeks after

trauma there was a positive relation between the severity of injury (expressed as the duration of PTA), cognitive complaints and poor cognitive performance. In turn, injury severity was related to activation strength in the MTL. In line with prior studies, the strength of the association between complaints and injury severity decreased over time. By six months after injury, the association between injury severity and different measures of cognitive functioning disappeared (Chapter 5 and 6). Patients with severe cognitive complaints did not suffer more severe injury to the head, nor did they perform poorer on a range of neuropsychological tests (at least if they passed a validity test, see 10.4) than patients without such complaints. Moreover, when these patients kept a diary of actual cognitive problems, they did not encounter more problems in their daily life than non-symptomatic patients. Psychological processes seem important in understanding why certain patients perceive their cognitive abilities to be abnormal even when their performance -on a test or in daily life- suggests otherwise. Based on our own findings and current literature, we will elaborate on how these processes might influence symptom report after MTBI and might lead to chronic (cognitive) symptoms.

It is common sense to assume that subjective symptoms are a direct and linear expression of some dysfunction in the body. One easily tends to forget that subjective health symptoms are by definition psychological events: bodily signals have to be perceived, interpreted, verbalised and expressed. Psychological processes related to each of these information processing steps can seriously influence and bias subjective health symptoms (Pennebaker 1982, in Van den Bergh 2002). MTBI is associated with a range of acute symptoms; some of which may be due to the impact to the head, others may be due to extracranial injuries or result from the emotional shock of the accident. It is likely that having suffered an accident results in a heightened attentional focus on one's bodily

sensations. In fact, as part of the guidelines on acute MTBI management, patients and their relatives are instructed to pay close attention to deterioration in functioning as this may signal the development of subacute complications (Twijnstra 2001). It is well known that such an attentional focus lowers the threshold for bodily symptoms to be noticed. As supported by our findings, this might especially be the case for patients that have already a disposition to focus on internal sensations (Chapter 6). The way the patients interpret these symptoms may greatly influence the subsequent process of recovery. How this process might work is conceptualized in Leventhal's self-regulatory model of illness behaviour. In Chapter 7, we apply this model to MTBI to illustrate how persisting cognitive complaints might develop. Several interpretation biases have been suggested to be relevant to MTBI patients. For example, many patients have shown to underestimate the prevalence of symptoms before the injury (the so-called 'good old days bias', Gunstad 2001). As found by others, the symptoms most commonly reported by MTBI patients (i.e. fatigue and cognitive complaints) are the same as those reported by healthy persons (Iverson 2003, Wang 2006). About 60% of healthy subjects for instance, reported the presence of concentration problems. After MTBI, these symptoms may be misattributed to the head injury. Possibly, this attribution bias underlies our finding that patients with pre-existing health problems were more likely to report persisting post-concussional complaints (Chapter 8). Existing literature also points towards a mediating role of expectations (Ferrari 2001, Gunstad 2002 2004, Mittenberg 1992, Whittaker 2007). Whittaker found that MTBI patients who early after injury expected to suffer substantial negative consequences also tended to report more complaints in the longer term. These cognitive-perceptual processes in turn affect physiological processes and behaviour. For example, as described in Chapter 7, patients who attribute bodily sensations to suspected brain injury may avoid physical or mental activity from fear of increasing the problems. This in turn may lead to physical deactivation and tension related complaints. On the other side of the spectrum, there are patients that do not take time to recover from the initial impact of the injury and persistently do more than they should. Both behavioural patterns may set in motion a downward spiral that may eventually lead to the exacerbation and persistence of complaints and functional problems. In patients with Chronic Fatigue Syndrome (CFS) similar subgroups based on activation patterns have been distinguished. Researchers from The Expert Centre Chronic Fatigue of the University Medical Centre Nijmegen showed that so-called "relatively active" CFS patients were characterised by nonaccepting and demanding cognitions leading to bursts of activity. For so-called "passive" CFS patients, fear that activity might worsen their symptoms (which results in an avoidance of activity) was the most important perpetuating factor. Based on these differences in perpetuating factors, separate cognitive behaviour therapy treatment manuals were developed for each subgroup (e.g. Bazelmans 2002, Van der Werf 2001). Possibly, a treatment tailored to these activation patterns might be useful in MTBI as well. However, before treatments can be generalised, studies on similarities and differences of the perpetuating factors in CFS and MTBI patients will have to be accomplished.

10.4 Post-concussional symptoms, test effort and cognitive performance: one thing leads to another?

The findings of our studies fully supported prior findings that fatigue (Chapter 2, 5 and 6) and cognitive complaints (Chapter 6) are among the commonest sequalae of MTBI. As mentioned in the General Introduction, it has been suggested that these complaints

might be caused by compensatory working memory efforts on the level of the prefrontal cortex in order to obtain normal behavioural performance (Jantzen 2004, McAllister 1999, 2001). As described in Chapter 4, fMRI findings of working memory activation in MTBI patients within six weeks after injury do not support this hypothesis. As we did not repeat fMRI at the follow-up assessment, we cannot rule out the possibility that compensational cognitive efforts do contribute to chronic rather than postacute complaints. Still, we consider this somewhat unlikely as other associations between injury severity and other measures of cognitive functioning disappeared within the six months interval between the assessments. In addition, post-hoc analyses show that neuropsychological test performance improves to a normal level in the majority of patients (unpublished data). Considering these improvements, it is remarkable that six months after injury almost one third of the participants from another resembling cohort fail a very low demanding memory test (the Amsterdam Short Term Memory Test, Chapter 5). Such tests, often referred to as 'symptom validity' or 'effort' tests are designed to appear effortful, whereas they actually require very little mental effort (Rogers 1993). Even children and severe closed head injury patients hardly ever fail these tests (Schagen 1997). When someone does make many errors this is strongly suggestive for a role of behavioural factors. As is discussed in more detail in de discussion of Chapter 5, the reasons for poor effort are not known, and many different factors (including fatigue, pain, anxiety and motivation) might play a role. In our study, patients with post-concussional complaints were more likely to fail the effort test. Possibly, these patients might expect symptoms to get worse when they concentrate too hard. Also, over half of the patients that exerted poor effort

had high scores on the Type-D personality questionnaire, thus tending to negative affect and socially inhibited communication style (DeNollet 2005). Hypothetically, exerting poor effort on a cognitive test serves as an indirect way of communicating to the healthcare professionals administering the tests that they are suffering from serious symptoms that require attention. This may be particularly important for MTBI patients who are often faced with scepticism. These assumptions require further study. Regardless of the reason for poor effort, we have shown that poor effort has substantial negative impact on neuropsychological test performance. There is no clear-cut way to overcome this problem, especially since patients that exert insufficient effort might not always be aware that they could have done better. There is some evidence that neutral framing of test instructions and external incentives for good performance significantly improves test effort (Green 2001, Suhr 2002). Green for example showed that in contrast to patients with severe TBI, MTBI patients were able to improve their performance to normal levels when they expected negative consequences of poor performance (in this case: being told that the results might impact on drivers license) (Green 2001).

10.5 Finally, recommendations regarding clinical management and outcome assessment

In the EFNS guidelines several recommendations are made regarding the follow-up of MTBI patients after being discharged from the ED. For example, it is recommended that all patients in MTBI category 3 who have been admitted to the hospital should be seen at least once in the outpatient clinic approximately 1–2 weeks after discharge. Based on current knowledge,

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[1] Note that the name 'effort' test is deceiving as these tests do not measure the amount of effort that someone exerts. Instead, they aim to examine whether the inserted mental energy suffices for drawing valid inferences about a patients' cognitive abilities on the basis of his test performance (see e.g. Rogers 1993).

including findings from the studies presented in this thesis, we advocate a more elaborate model of stepped care for the management of MTBI patients after their release from the ED.

(1) Provide information (< 1 week)

First, all patients should receive written information about MTBI, its possible consequences and adequate coping strategies. This could either be handed at the moment of discharge, or send to patients' homes within days after trauma. There is supportive evidence that educational interventions provided early following injury are effective in preventing long-term complaints (Snell 2009). An example of such information is provided by Mittenberg (Mittenberg 2003, accessible at http://www.southfloridapsychology.com/handbook.htm).

(2) Screen for patients at risk for suboptimal recovery (< 1 month)

Secondly, a brief early assessment of all patients regarding their emotional and physical functioning is required in order to identify those patients at risk for suboptimal recovery. As this information is relatively easy to obtain, consultation by phone by a research nurse within the first month after injury may suffice. Although this requires some investment considering the high prevalence of MTBI, it has several advantages. For example, early contact contributes to the prevention of chronic problems as patients' questions may be addressed and maladaptive attributions may be challenged. These interventions reduce the threat posed by the early complaints, thus reducing the patient's anxieties and promoting more effective coping patterns (Bell 2008, Mittenberg 2003). In addition, the number of patients that require further outpatients follow-up can be drastically reduced by identifying patients with a high chance of favourable recovery for whom further follow-up is likely to be unnecessary. Thus, outpatient monitoring by a neurologist can be reserved for the subgroup of patients who have a higher risk to develop long-term symptoms or occupational problems. The score charts we developed are highly suitable for patient screening (Chapter 8). However, before being implemented in clinical practice, the models require external validation, to determine whether its use in a level-1 trauma centre results in a benefit, such as reduced incidence of chronic post-concussional sequalea, better convenience or lower costs. Furthermore, as we included adult patients only, it should also be tested whether the models are valid for children and older adults. In our hospital, these subgroups constitute 45% of all patients submitted to the ED with MTBI.

(3) Outpatient appointment in patients at risk (1 month + 6 months)

Currently, the first outpatient visit is generally scheduled within weeks after injury. We advise to pay more attention to attributions and coping styles. Also, the presence of depressive or post-traumatic stress symptoms should be addressed in this first appointment. If severe symptoms are present, referral to a psychiatrist or clinical psychologist is warranted for further diagnoses and treatment. A brief trauma focused cognitive behavioural treatment (CBT) in patients with acute stress disorders has shown to be effective in reducing the development of PTSD at the longer term (Kornør 2008). After six-months a follow-up should be scheduled. In case of persisting problems at this time-point, a more elaborate assessment is necessary. As shown in Chapter 3 and 8, the six-month time-point might be too early for patients with extracranial injuries to reliably determine long-term outcome. For this group the follow-up period may have to be expanded.

(4) Refer patients with persisting post-concussional complaints to a neuropsychologist (> 6 months)

The EFNS guidelines suggest that in case of persisting cognitive complaints, neuropsychological examination may be useful (Vos 2002). On the basis of our findings, we advise that comprehensive
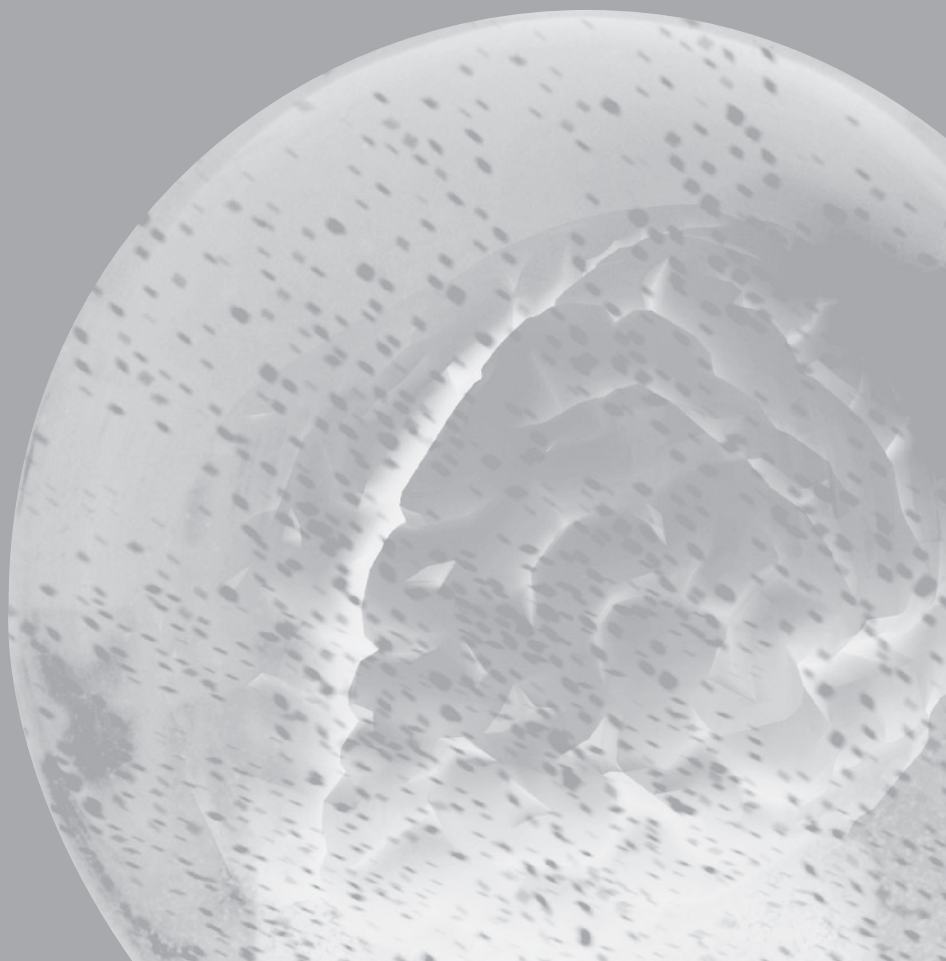
assessment of MTBI patients with long-term complaints should entail measuring along different dimensions (distinguishing at least physical, cognitive and psychological functioning), but also different types of methods (e.g. questionnaires, semi-structured interview, neuropsychological tests) should be employed. As poor effort was found to be common, cognitive outcome assessment of symptomatic MTBI patients should include a test of performance validity. In the guideline issued by the Neuropsychology section of the Dutch Institute for Psychology (Nederlands Instituut voor Psychologie), the Amsterdam Short-Term Memory Test (Schmand 1998) and Test of Memory Malingering (Tombaugh 1996) are suggested for this purpose (Saan 2004, concept version). To date, no biomedical interventions are available to reduce chronic post-concussional problems. Although methodological sound efficacy studies are scarce, there is some scientific evidence and wide clinical consensus that targeting psychological and behavioural factors by means of psychotherapeutic treatments like CBT can be beneficial (Snell 2009).

10.6 Concluding remarks

This thesis is the first to result from the Radboud University Brain Injury Cohort Studies (RUBICS). The RUBICS databank is ever growing and currently contains data of about 7600 TBI patients of all severities. The presented studies focused on patients with mild traumatic brain injury, which constitute over 80% of all patients. MTBI has been surrounded by controversies for decades, as a minority of patients will develop unspecific but debilitating symptoms that may persist for up to years after injury that seem disproportionate to the 'mildness' of the initial injury. Overall, the studies presented in this thesis underscore that poor outcome after MTBI can be well understood if only we look beyond the characteristics of the head injury. Especially, the emotional and extracranial

impact of the injury as well as premorbid vulnerability factors including demographic characteristics and personality are of major importance. A biopsychosocial perspective, which is increasingly adopted by researchers in the field of neurotrauma, offers an excellent framework to understand recovery after MTBI, for patients and clinicians alike. It is a challenge for future studies to translate this knowledge into clinical guidelines and tailored interventions.

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Samenvatting
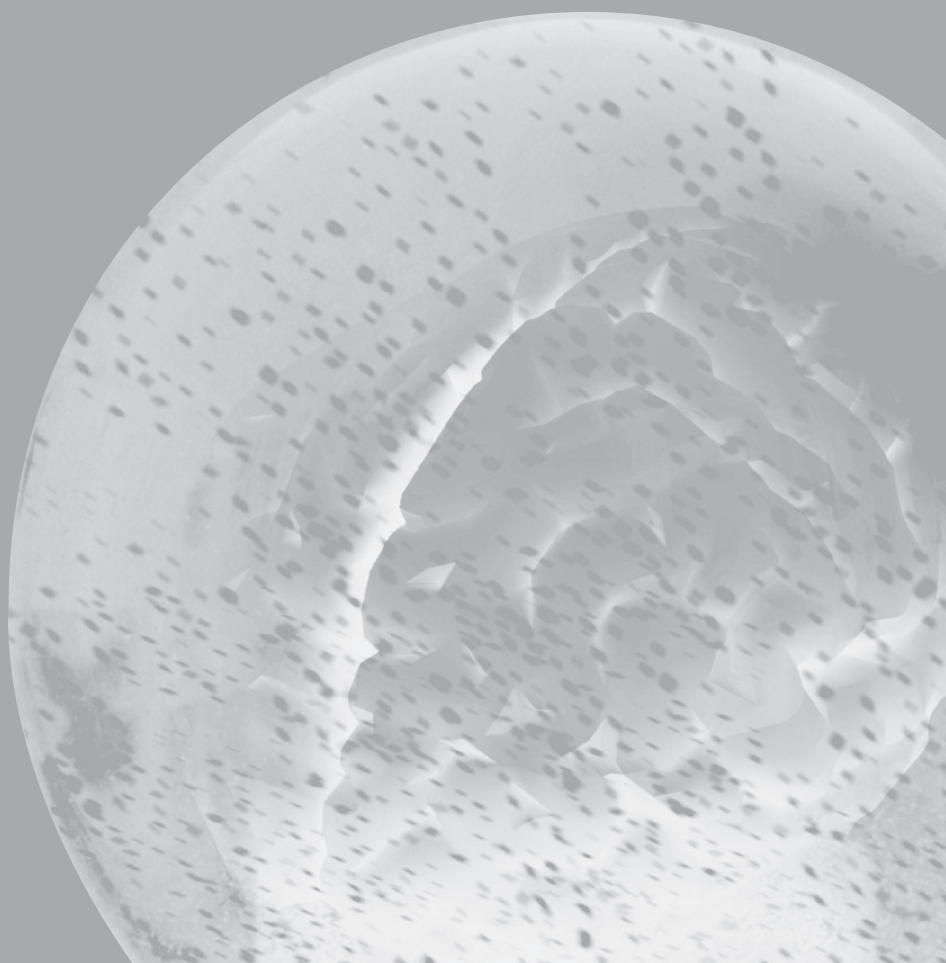
Samenvatting

In 80-90% van de patiënten die een traumatisch schedelhersenletsel oplopen is de ernst van het letsel relatief licht. De mortaliteit na Licht Traumatisch Schedelhersenletsel (LTSH) is laag, neurochirurgische interventies zijn zelden nodig en de meeste patiënten herstellen spontaan, vlot en volledig. Dat LTSH desondanks als een belangrijk maatschappelijk gezondheidsprobleem wordt beschouwd, komt doordat een minderheid van de patiënten niet goed herstelt en zelfs maanden tot jaren na het ongeval last blijft houden van invaliderende klachten. Door de hoge incidentie van LTSH is het aantal patiënten dat leeft met chronische klachten aanzienlijk. In het gros van de patiënten zijn deze zogenoemde postcommotionele klachten aanwezig zonder dat er aanwijzingen zijn voor ernstige cognitieve stoornissen of andere neurologische afwijkingen. Dit gegeven leidt al jaren tot veel discussie over de mogelijke oorzaak van de klachten.

De studies in dit proefschrift zijn uitgevoerd in het kader van de Radboud University Brain Injury Cohort Study (RUBICS). RUBICS heeft o.a. een database ontwikkeld waarin klinische, radiologische en uitkomstgegevens worden verzameld van alle patiënten die met traumatisch hersenletsel zijn opgenomen op de spoedeisende hulp van het UMC St. Radboud. Het algemene doel van de beschreven studies was om meer inzicht te krijgen in de determinanten van postcommotionele klachten (en dan vooral vermoeidheid en cognitieve klachten), neuropsychologisch testpresteren en terugkeer naar werk zes maanden na het oplopen van LTSH. Naast de invloed van neurologische karakteristieken van het hoofdletsel op deze domeinen, is gekeken naar de samenhang tussen demografische, psychologische en lichamelijke kenmerken en lange termijn uitkomst. Dit hoofdstuk geeft een samenvatting van de belangrijkste bevindingen.

Hoofdstuk 1 geeft een algemene introductie op de hoofdstukken die volgen. Allereerst worden enkele feitelijkheden genoemd over de definitie van LTSH, het vóórkomen ervan en de normale herstelcurve. Vervolgens wordt ingegaan op de huidige kennis ten aanzien van de patiënten die klachten blijven houden en passeren enkele open vragen de revue die de basis vormen van de in dit proefschrift beschreven onderzoeken. Tot slot wordt een beschrijving gegeven van de setting waarin het onderzoek is gedaan en volgt een kort overzicht van het doel en de inhoud van elk hoofdstuk.

Vermoeidheid is een van de meest gerapporteerde symptomen na LTSH. Er zijn echter maar weinig studies die vermoeidheid op een systematische en gecontroleerde wijze onderzocht hebben. *Hoofdstuk 2* beschrijft een studie die gericht was op het bepalen van de ernst van vermoeidheid zes maanden na LTSH en de samenhang tussen vermoeidheid en andere uitkomstmaten. Ook werd onderzocht of acute letselkenmerken een voorspellende waarde hebben voor vermoeidheidsklachten op de langere termijn. Anders dan in eerdere studies, gebruikten we een gevalideerde en multidimensionele vragenlijst om de ervaren vermoeidheid in kaart te brengen. Uit de resultaten bleek een derde van alle LTSH patiënten ernstige vermoeidheid te rapporteren. Dit was significant meer dan de 12% van de controle patiënten (die een enkel- of polsverzwikking hadden opgelopen). In het algemeen rapporteerden patiënten die ernstig vermoeid waren tevens meer aan vermoeidheid gerelateerde problemen, ernstigere postcommotionele klachten en meer beperkingen in lichamelijk en sociaal functioneren. Dit bleek in sterkere mate te gelden voor ernstig vermoeide LTSH-patiënten dan voor ernstig vermoeide controle patiënten. Traditionele letselkenmerken hingen niet samen met vermoeidheid na zes maanden. Daarentegen

was de aanwezigheid van misselijkheid en hoofdpijn op de spoedeisende hulp wèl in enige mate gerelateerd aan hogere vermoeidheidsscores op de lange termijn. Het is vooralsnog onduidelijk hoe deze bevinding te verklaren is.

Bij een ongeval waarbij het hoofd letsel oploopt, kan men uiteraard ook verwondingen aan andere lichaamsdelen oplopen. In veel LTSH uitkomststudies wordt hiermee weinig rekening gehouden. In *Hoofdstuk 3* hebben we de invloed van extracraniële letsels op postcommotionele klachten en functionele uitkomst zes maanden na het ongeval onderzocht. Ongeveer 1/3 van alle deelnemende LTSH patiënten bleek bij het ongeval tevens letsel aan andere lichaamsdelen dan het hoofd te hebben opgelopen. Gemiddeld had deze subgroep een wat ernstigere vorm van LTSH. Na zes maanden onderging 44% van de patiënten met additionele letsels nog een vorm van behandeling (zoals fysiotherapie), wat aanmerkelijk vaker was dan LTSH patiënten met een geïsoleerd hoofdletsel (14%) en de controles (0,5%). In vergelijking met patiënten met een geïsoleerd hoofdletsel, waren deze patiënten minder vaak volledig aan het werk en rapporteerden ze meer lichamelijke beperkingen. In tegenstelling tot onze verwachtingen, rapporteerden ze echter over het algemeen niet méér postcommotionele klachten. Los van de aanwezigheid van additionele letsels, hadden patiënten die na zes maanden nog een vorm van behandeling ondergingen ernstigere postcommotionele klachten, met de hoogste scores in patiënten met geïsoleerd LTSH. We concludeerden dat een meting zes maanden na het ongeval voor veel LTSH patiënten nog te vroeg is om de uiteindelijke uitkomst te bepalen, zeker indien er sprake is van extracraniële letsels. Gezien de grote invloed van extracraniële letsels op het functionele herstel na LTSH, dienen de bevindingen van LTSH studies die hier geen rekening mee

houden met voorzichtigheid te worden geïnterpreteerd.

Veel LTSH patiënten ervaren kort na het ongeval cognitieve problemen zoals vergeetachtigheid. Een minderheid rapporteert dergelijke klachten ook op de langere termijn. Er is nog veel onduidelijkheid over de oorzaak van deze klachten omdat de belangrijkste geheugenstructuren en de rest van de hersenen meestal macroscopisch intact zijn. Men denkt dat de vroege klachten na LTSH het resultaat zijn van een verstoring in de hersenactiviteit geïnduceerd door de impact tegen het hoofd, een hypothese die getoetst kan worden met behulp van functionele Magnetische Resonantie (fMRI). Deze beeldvormende techniek meet functionele in plaats van structurele kenmerken van de hersenen. Zoals beschreven in *Hoofdstuk 4*, hebben 43 LTSH patiënten binnen zes weken na het ongeval en 20 gezonde controles fMRI ondergaan terwijl ze een werkgeheugentaak uitvoerden. Tevens werden de deelnemers buiten de scanner neuropsychologisch gescreend. De resultaten van deze screening toonden aan dat de LTSH patiënten, zoals verwacht, meer cognitieve klachten rapporteerden en slechter presteerden op een declaratieve geheugentaak. Zowel klachten als slechter testpresteren bleken significant gecorreleerd met een langere duur van de post-traumatische amnesie (een maat voor de ernst van het hersenletsel). Zoals beoogd was er geen verschil in presteren tussen patiënten en controles op de werkgeheugentest in de fMRI scanner. Verschillen in hersenactiviteit kunnen dus niet worden toegeschreven aan verschillen in taakuitvoer. In lijn met de verwachting, activeerde de gebruikte taak de medio-temporale en prefrontale cortex. Hoewel er op groepsniveau geen verschillen werden gevonden in hersenactiviteit tussen controles en patiënten, werd een significante negatieve relatie gevonden tussen activiteit in mediale hersenstructuren en de duur van

de posttraumatische amnesie. We vonden echter geen relatie tussen ernst van het letsel en prefrontale activiteit. Geconcludeerd werd dat de bevindingen wijzen op een relatie tussen afgenomen functionaliteit van medio-temporale hersenstructuren en slechtere geheugenprestaties in de post-acute fase van LTSH, vooral in patiënten met een langere duur van de posttraumatische amnesie. We vonden geen steun voor de veel gebezigde aanname dat cognitieve klachten resulteren van een compensatoire activiteit in de prefrontale hersenschors.

Vervolgens hebben we gekeken naar cognitief functioneren zes maanden na LTSH. In tegenstelling tot in de acute fase, zijn er aanwijzingen dat slechte prestaties op neuropsychologische tests op de langere termijn vooral samenhangen met factoren die los staan van de ernst van het hoofdletsel. In *Hoofdstuk 5* hebben we de invloed van onderpresteren op neuropsychologisch testpresteren onderzocht. Om meer zicht te krijgen op de factoren die bijdragen aan onderpresteren hebben we patiënten met en zonder aanwijzingen voor onderpresteren vergeleken op factoren als de aanwezigheid van een letselschadeprocedure, emotioneel onwelbevinden, vermoeidheid en persoonlijkheidskenmerken. Voor het meten van onderpresteren hebben we een gevalideerde test gebruikt, de Amsterdamse Korte Termijn Geheugentest. Uit de resultaten bleek er in 27% van de 110 deelnemers sprake van onderpresteren. Onderpresteren was sterk geassocieerd met slechtere testsprestaties op alle cognitieve domeinen. Onderpresteren was voorts geassocieerd met lager opleidingsniveau, een voorgeschiedenis van emotionele problemen en veranderingen in werkstatus, maar niet het verwikkeld zijn in een letselschadeprocedure. Verder hing onderpresteren samen met ernstigere emotionele problemen, Type-D persoonlijkheid en vermoeidheid. We concludeerden dat toekomstige LTSH onderzoekers er goed aan doen om altijd een validiteitstest in de neuropsychologische testbatterij op te nemen, ook wanneer patiënten niet verwikkeld zijn in letselschadeprocedures. Onderpresteren bemoeilijkt het trekken van zinvolle conclusies over de cognitieve vermogens van een patiënt immers zeer. De resultaten onderschrijven eens te meer dat slechte testprestaties nooit zondermeer aan afwijkingen in de hersenen toegeschreven kunnen worden, maar altijd in de context van demografische, affectieve en gedragsmatige factoren beoordeeld dienen te worden.

Hoofdstuk 6 had tot doel meer inzicht te krijgen in de ernst en aard van cognitieve klachten zes maanden na LTSH. Patiënten met en zonder cognitieve klachten werden vergeleken op vier domeinen: (1) demografische variabelen en letselkenmerken, (2) neuropsychologisch testpresteren, (3) dagelijkse zelfrapportage van cognitieve klachten gedurende 12 dagen, en (4) emotioneel onwelbevinden, persoonlijkheid, lichamelijk functioneren en vermoeidheid. Om de validiteit van de neuropsychologische testgegevens te vergroten werden patiënten die mogelijk onderpresteerden niet in de analyses opgenomen. Ernstige cognitieve klachten werden door 39% van de 79 deelnemende patiënten gerapporteerd. Deze klachten hingen sterk samen met een lager opleidingsniveau, emotioneel onwelbevinden, persoonlijkheid en slechter lichamelijk functioneren, maar niet met letselkenmerken. Meer dan de helft van de patiënten met cognitieve klachten rapporteerden tevens een hoge mate van post-traumatische stress. Er werden geen significante verschillen gevonden tussen patiënten met en zonder cognitieve klachten wat betreft ervaren cognitieve problemen in het dagelijks leven, noch wat betreft neuropsychologisch testspresteren. Al met al suggereren de bevindingen sterk dat cognitieve klachten lang na LTSH minder over

cognitieve vermogens zeggen dan de klachten suggereren. Dit impliceert niet alleen dat een klachtenlijst nooit een neuropsychologisch onderzoek kan vervangen, maar ook dat een multidimensionele inventarisatie nodig is om de cognitieve klachten in perspectief te kunnen zien.
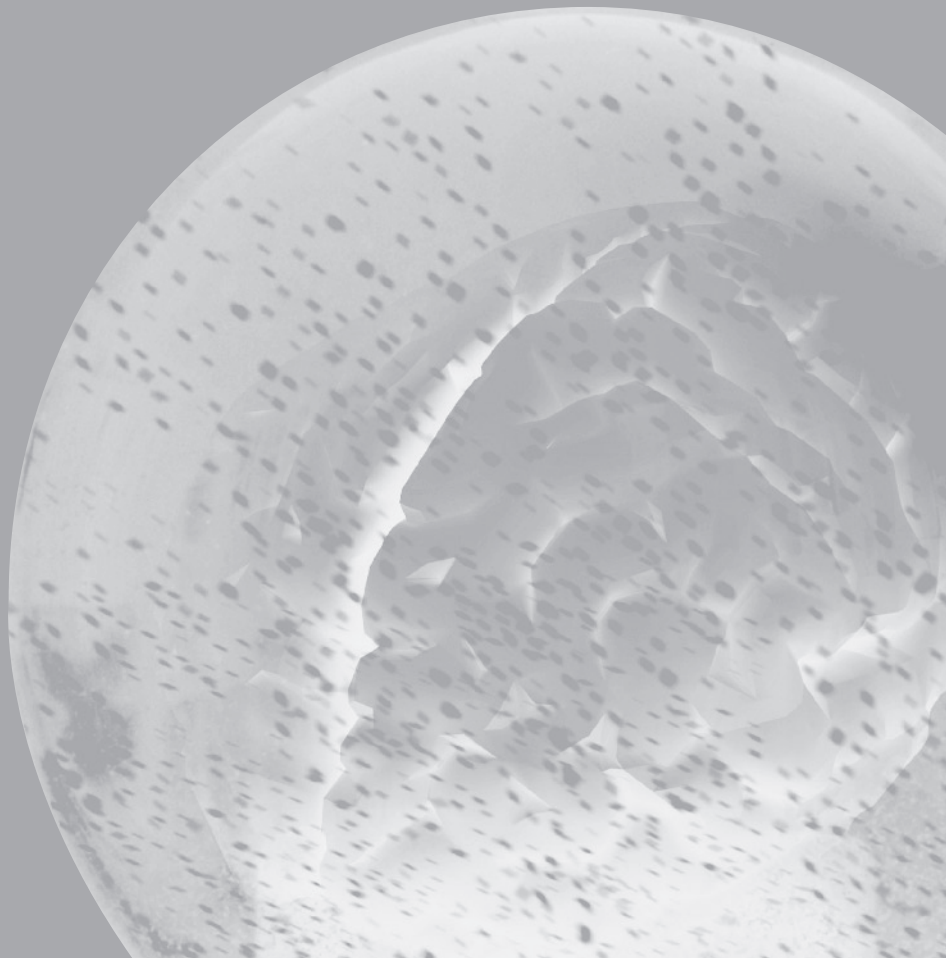
Wetenschappelijke literatuur en bevindingen uit eigen onderzoek suggereren dat psychologische en gedragsmatige processen een belangrijke rol spelen bij het in stand houden van cognitieve klachten na een LTSH. In *Hoofdstuk 7* wordt met behulp van een gezondheidspsychologisch model, het Zelfregulatiemodel van Leventhal, een tentatief antwoord gegeven op de vraag hoe het kan dat sommige LTSH patiënten ook lang na het ongeval het gevoel houden cognitief beperkt te zijn, ondanks goed neurologisch herstel en normaal neuropsychologisch testpresteren. Door aandacht te hebben voor de wijze waarop patiënten hun klachten interpreteren en welke gevolgen dit kan hebben, biedt het Zelfregulatiemodel een verklaring voor verschillen tussen patiënten die niet aan de ernst van het hoofdletsel kunnen worden toegeschreven. We bepleiten dat een gezondheidspsychologisch model in LTSH patiënten meer aanknopingspunten biedt voor diagnostiek en behandeling dan een neurologisch verklaringsmodel.

Uit vele onderzoeken is gebleken dat het voorspellen van uitkomst na LTSH een lastige zaak is. De studie beschreven in *Hoofdstuk 8* had tot doel om twee voorspellingsregels te ontwikkelen en intern te valideren om patiënten te kunnen identificeren die een hoge kans op goed herstel na zes maanden hebben. Naast letselkenmerken, werden verschillende variabelen van voor, tijdens en kort na het ongeval als voorspeller opgenomen, waaronder emotioneel en lichamelijk functioneren. Logistische regressie analyses werden gebruikt om volledig herstel te voorspellen (gedefinieerd als de afwezigheid van ernstige postcommotionele klachten en volledige werkhervatting). Na 6 maanden rapporteerde 64% van de 201 deelnemers volledig herstel. De predictieregels voorspelden dat patiënten zonder premorbide lichamelijke problemen, weinig postcommotionele klachten kort na het ongeval en lage mate van posttraumatische stress, 90% kans hadden om 6 maanden na het ongeval klachtenvrij te zijn. Patiënten die meer dan 11 jaar opleiding genoten hadden, niet misselijk waren of braakten op de spoedeisende hulp en kort na het ongeval geen ernstige pijnklachten ervoeren, hadden 90% kans om zes maanden later weer volledig aan het werk te zijn. De discriminatieve vermogens van de predictiemodellen waren voldoende. Om de klinische toepasbaarheid van de modellen te vergroten is een vereenvoudigde scoringslijst ontwikkeld. Wanneer we onze data extrapoleren naar de algemene LSTH populatie dan is de verwachting dat met een grote mate van zekerheid ten minste driekwart van de patiënten na zes maanden goed hersteld zal zijn. We concludeerden dat vroege identificatie van LTSH patiënten die goed zullen herstellen mogelijk is op basis van relatief eenvoudige prognostische modellen. Daarmee zouden deze modellen kunnen helpen om patiënten reeds kort na het ongeval over de prognose te informeren en tevens kunnen bijdragen aan de besluitvorming over de noodzaak van een poliklinische vervolgafspraak.

Een samenvatting van de belangrijkste bevindingen van de voorgaande hoofdstukken wordt gegeven in *Hoofdstuk 9*. Tot slot, worden deze resultaten in Hoofdstuk 10 bediscussieerd tegen de achtergrond van de ontwikkelingen in het vakgebied. Verder worden mogelijke implicaties van de bevindingen voor de klinische praktijk geschetst en worden suggesties gegeven voor toekomstig onderzoek.
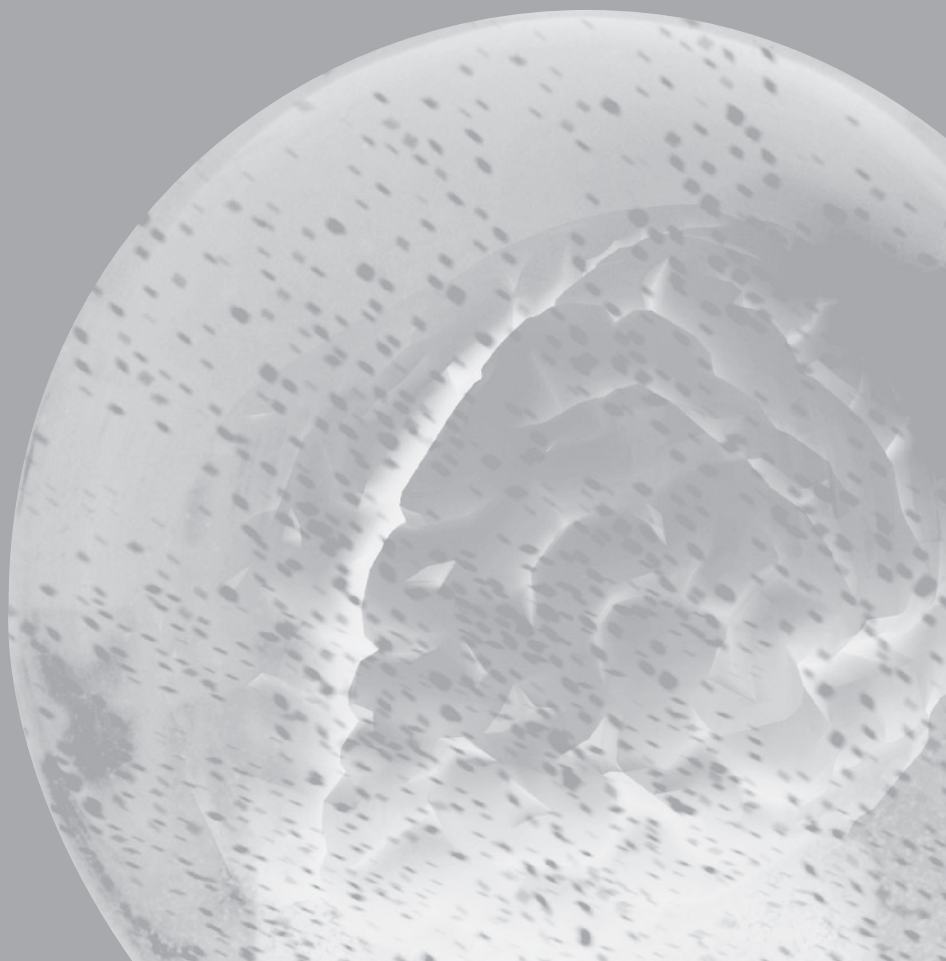
List of publications

List of publications

Andriessen TJMC, Stulemeijer M, Zwiers M, van Dijk G, van der Werf SP, Norris DG, Fernandez G, Vos PE. Postconcussive symptoms, depressed mood and white matter integrity in patients with mild traumatic brain injury: Results from a longitudinal Diffusion Tensor Imaging Study. In preparation.

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Dankwoord

Dankwoord

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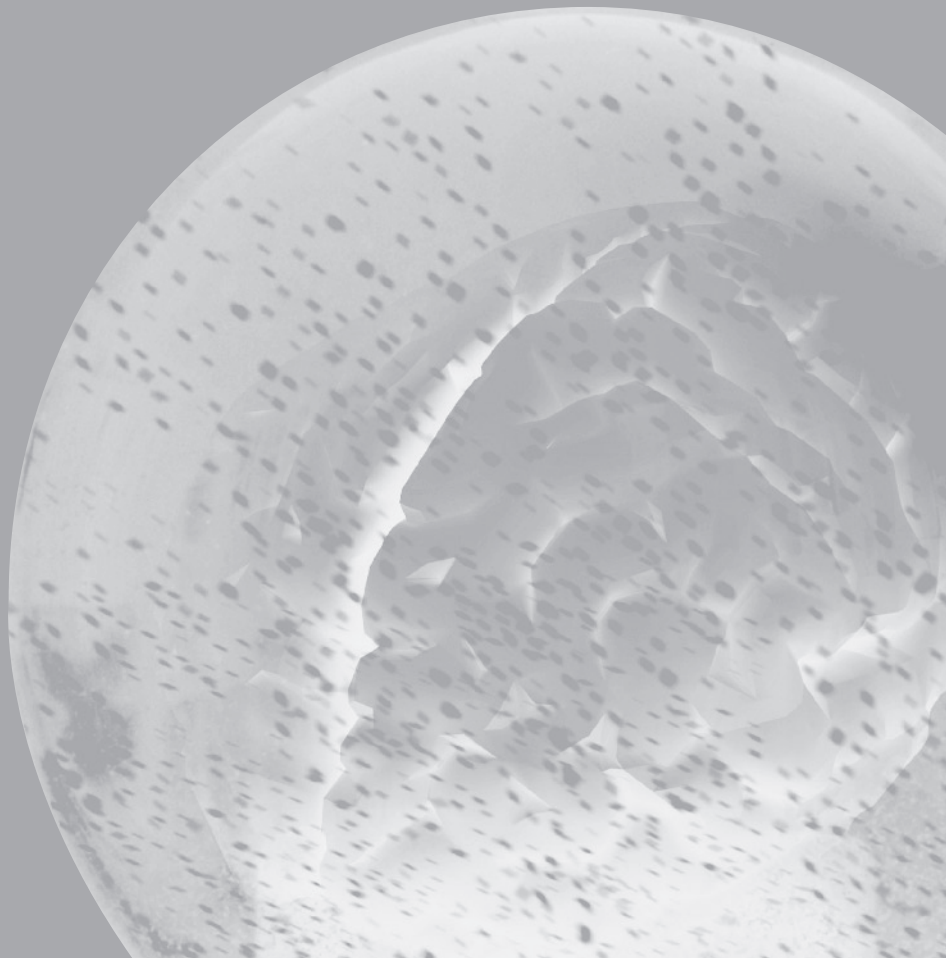
Florentia, Corrie, Rens, Meriam, Zusters Clarissen in Megen, jullie bijdrage aan mijn

persoonlijke groei zal ik nooit vergeten.

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Tot slot, Hugo. Zelfs ver weg, nog altijd dichtbij. Als geen ander was je er voor me. Wat hou ik van ons leven samen. Ten down, more to go! Pk, je M.

Curriculum Vitae

Curriculum Vitae

Maja Stulemeijer werd geboren op 13 oktober 1977 in Utrecht als dochter van Vera en Maarten en zus van Jiri. In 1995 behaalde zij haar HAVO diploma aan het Niftarlake College in Maarssenbroek en in 1996 volgde het VWO-diploma behaald aan het Regionaal Opleidingen Centrum te Utrecht. Na een jaar werken en reizen begon zij haar studie Psychologie aan de Radboud Universiteit Nijmegen (RU), destijds Katholieke Universiteit Nijmegen. In het kader van de afstudeerrichting Neuro- en Revalidatiepsychologie liep zij haar klinische stage in het Rivierenland ziekenhuis in Tiel. Vervolgens volbracht zij haar wetenschappelijke stage aan de RU bij het Nijmegen Institute for Cognition and Information onder begeleiding van dr. Paul Eling en dr. Gilles van Luijtelaar. Na haar afstuderen in 2002 startte zij als onderzoeker bij de afdeling Medische Psychologie van het Radboud Universiteit Nijmegen Medisch Centrum. In den beginne pendelde zij tussen de afdelingen Kinderpsychologie (alwaar zij de afronding van een studie naar het effect van cognitieve gedragstherapie bij jongeren met het chronisch vermoeidheid syndroom voor haar rekening nam) en de afdeling Neurologie (alwaar zij werkte aan het opstarten van de studies beschreven in dit proefschrift). Later werd deze laatste afdeling haar vaste standplaats. In 2005 was Maja de gelukkige winnares van de Spiegelberg Award voor de beste presentatie over een klinisch onderwerp door een junior onderzoeker en in 2006 ontving zij tijdens het International Neurotrauma Symposium een Young Investigator Award. Ook heeft zij enkele reisbeurzen voor congresbezoek ontvangen. Sinds januari 2008 volgt Maja de opleiding tot Gezondheidszorgpsycholoog bij het RINO-Zuid te Eindhoven. In dat kader is zij tot en met december 2009 werkzaam op de afdeling Medische Psychologie van het VieCuri Medisch Centrum van Noord-Limburg en binnen Pepas, praktijk voor eerstelijnspsychologie en psychotherapie. Maja leeft sinds een deccenium samen met Hugo van Ingen.

Cyclist hit tree when giving way to oncoming car

Hit on head by falling object in archive

Fell from stairs during epileptic seizure

Beaten-up during a game of field hockey

Bystander hit by golfball

Drunk hit head on pavement
after falling from bicycle

Car versus truck collision

Fell on head during sumo wrestling

Car hit tree

Hit by tractor that capsized

Cyclist collided with other cyclist
after being distracted

Jumped over fence and fell on face

Head injured after fall from
galloping horse

Cyclist hit by car

Tripped over toy and hit head
on radiator

Moped rider hit by car

Fell from wheelchair

Slipped on stairs

Car collided with car

Hit by car that slipped

Cyclist hit by car on roundabout

Fell from bicycle during a race

Soldier accidently hit by gun

Fell on back of head during
skiing

Woman hit head on fence after
tripping over shoelaces

Fell down from truck cabin

Slipped on snowy surface

Lump of ice fell on head during skiing

Car hit crash barrier with high speed

Head hit table

Drunk fell on head

Fell on chin after vasovagal faint

Head hit by soccer ball

Involved in a fight

Fell from tree

Cyclist hit by taxi

Super sexy cyclist slipped over cattle grating

Fell from roof

Woman fell down escalator and hit face

Suitcase fell on head whilst boarding the airplane

Car versus truck

Face hit pavement after front fork of bicycle broke

Head hit floor after being pushed in swimming pool

Tripped during game of tennis

Pushed down stairs by husband

Jumped from second floor balcony

Pedestrian hit by bus

Cyclist hit by moped

Cyclist fell after grocery bag got stuck
between wheels

Head collision during soccer game

Collapsed after vigorous attack of cough

Tripped and hit head on rim of the bed

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Hit on head with bottle