From Karolinska Institutet
Department of Clinical Sciences
Psychiatry Section
Danderyd University Hospital
Stockholm, Sweden

Mild traumatic brain injury – clinical course and prognostic factors for postconcussional disorder

Anders Lundin

Karolinska Institutet

Stockholm 2007

Cover image: Mohawk. Detail from a terracotta sculpture by Magnus Ringborg. Photo by Magnus Ringborg (www.magnusringborg.se)
Graphic design: Henrik Löfgren

All published papers reproduced with the kind permission of the publishers

Printed by Universitetsservice US-AB
Nanna Svartz väg 4, SE-171 77 Stockholm, Sweden

ISBN 91-7357-078-8

"The late effects of head injury can only be properly understood in the light of a full psychiatric study of the individual patient. It is not only the kind of injury that matters, but the kind of head that is injured that determines recovery of function"

Sir Charles Symonds (1937), British neurologist, in Mental disorder following head injury; Proceedings of the Royal Society of Medicine.

Abstract

Background

Mild traumatic brain injury (MTBI) is frequent and sometimes leads to persistent disability. It remains a matter of controversy as to what impact the different main determinants – brain injury factors and psychosocial factors – exert on the development of postconcussional disorder (PCD).

Aims, subjects and methods

The overall aim was to find predictors for PCD after MTBI. One hundred and twenty-two persons with MTBI were assessed with CT and MRI brain scans, S 100B, S 100A1B, and clinical variables. The first week after the trauma an extended assessment was performed, including previous history of psychiatric disorder, psychological function the year before the trauma, personality, coping ability, and concurrent psychosocial stressors. Three months post injury outcome was assessed by use of established self assessment questionnaires for MTBI related symptoms and disability. Cognitive impairment was assessed with a computerized Automated Psychology Test (APT) and neuropsychological testing. Thirtyfive healthy control persons were assessed for comparison.

Results

Is increased S 100 associated with cognitive impairment?

S 100B and S 100A1B were increased in 42 % and 64 % of the patients and in 60 % and 80 % of those with radiological signs of hemorrhage, respectively. Cognitive impairment was found in 8 % when assessed with APT and in 30 % when assessed with neuropsychological tests. No significant correlation was found between S 100B or S 100A1B and cognitive impairment, nor between subjectively reported cognitive dysfunction and test performance, regardless of the method used.

What is the clinical course after MTBI?

At least one persisting symptom was reported by 49 % of the patients at three months – most commonly poor memory, sleeping problems and fatigue. High symptom load at day one correlated with high symptom load and disability at three months, when 25 % also reported disability in at least one domain of everyday life.

How should PCD be defined?

The ICD-10 definition of PCD was considered too liberal as no disability was required. The results from neuropsychological testing had insufficient specificity to qualify, as proposed in the DSM-IV, as a defining property of PCD. A definition of PCD based on a minimum of three symtpoms and two domains of disability at three months post injury was proposed, which yielded 17 % PCD cases in the whole sample.

Which risk factors predict the development of PCD?

Preinjury psychological vulnerability (previous psychiatric disorder, trait anxiety, embitterment), lower preinjury psychological function (GAF) and concurrent psychosocial stressors were significant predictors of PCD. Posttraumatic stress (hyperarousal) one week after the MTBI had the highest impact on the outcome. Female gender and concurrent medical condition were also correlated to PCD, but no correlation was found between PCD and injury related factors.

In summary, signs of brain injury or brain dysfunction are present in the early phase after MTBI but show poor correlation to PCD as defined by at least three symtpoms in combination with disability at three months post injury. The results from neuropsychological testing had insufficient specificity to qualify as a defining property of PCD. Prognosis after MTBI is good in most cases, but a minority of patients develop PCD, which emerges as a result of the interaction between premorbid psychological vulnerability, brain dysfunction in the early phase, posttraumatic hyperarousal and concurrent psychosocial stressors.

Keywords: Mild traumatic brain injury, S 100, cognitive impairment, symptoms and disability, postconcussional disorder, prognostic factors

ISBN 91-7357-078-8

List of publications

I S 100 and cognitive impairment after mild traumatic brain injury.
Catharina de Boussard, Anders Lundin, Daniel Karlstedt, Gunnar Edman, Aniko Bartfai, Jörgen Borg.
Journal of Rehabilitation Medicine 2005; 37: 53–57

II Symptoms and disability until 3 months after mild TBI.
Anders Lundin, Catharina de Boussard, Gunnar Edman, Jörgen Borg.
Brain Injury, July 2006; 20(8): 799–806

III A comparison of three criteria sets for postconcussional disorder after mild traumatic brain injury.
Anders Lundin, Catharina de Boussard, Daniel Karlstedt, Aniko Bartfai, Gunnar Edman, Jörgen Borg.
(submitted)

IV Prognostic factors for postconcussional disorder after mild traumatic brain injury.
Anders Lundin, Catharina de Boussard, Gunnar Edman, Jörgen Borg.
(submitted)

List of abbreviations

APT	Automated Psychological Test system
AUDIT	Alcohol Use Disorders Identification Test
BBB	Blood Brain Barrier
CI	Confidence Interval
CT	Computerized Tomography (of the brain)
DSM-IIIR	Diagnostic and Statistical Manual of mental disorders, third edition, revised
DSM-IV	Diagnostic and Statistical Manual of mental disorders, fourth edition
ED	Emergency Department
ELISA	Enzyme Linked ImmunoSorbent Assay
GAF	Global Assessment of Function
GCS	Glasgow Coma Scale
HADS	Hospital Anxiety and Depression Scale
ICD-10	International Classification of Diseases, tenth revision
ICF	International Classification of Functioning, Disability and Health
IES-R	Impact of Event Scale – Revised
KSP	Karolinska Scales of Personality
LOC	Loss Of Consciousness
MRI	Magnetic Resonance Imaging (of the brain)
MTBI	Mild Traumatic Brain Injury
OR	Odds Ratio
PCD	PostConcussional Disorder*
PCS	PostConcussional Syndrome*
PTA	PostTraumatic Amnesia
PTSD	PostTraumatic Stress Disorder
RHFUQ	Rivermead Head injury Follow Up Questionnaire
RPQ	Rivermead Post Concussion Symptoms Questionnaire
S 100	Soluble in 100 % ammonium sulfate saturated solution
SOC	Sence Of Coherence scale
SSP	Swedish universities Scales of Personality
TBI	Traumatic Brain Injury

* In previous studies, the terms PCD and PCS are often used interchangeably. In Paper III the appropriateness of the two terms is discussed.

Contents

Background

Traumatic brain injury (TBI) is a common event in the population. Mild traumatic brain injury (MTBI) represents between 70 - 90 % of all TBI cases that present at hospitals, and the incidence of hospitalized adults with MTBI is about 200/100.000 in Sweden [1]. Falls are the most common cause and motor vehicle and bicycle injuries are the second and third most common causes of MTBI. Many individuals with MTBI do not seek medical help and the actual rate of MTBI, based on several population studies, is calculated to be over 600/100.00 per year [2]. The risk is greatest among young male adults – the male/female ratio is about 1.5/1.

There has been some controversy as how to define MTBI, and in previous research different definitions have been used, leading to some confusion. The American Congress of Rehabilitation Medicine in 1993 has therefore agreed on the following defintion:

A patient with MTBI is a person who has had a traumatically induced physiological disruption of brain function as manifested by at least one of the following:

- any period of loss of consciousness;
- any loss of memory for events immediately before or after the accident;
- any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and
- focal neurological deficit(s) that may or may not be transient but where the severity of the injury does not exceed the following:
  - loss of consciousness of approximately 30 minutes or less;
  - after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13-15;
  - post traumatic amnesia (PTA) not greater than 24 hours.

There are several ways – clinical, radiological and biochemical – of establishing the severity and immediate consequenses of the brain injury after a concussion. This is of importance for the acute management of the patients after presenting at the emergency ward. The acute indices of severity also constitute the basis for prognosis.

Assessments of brain injury

Clinical assessment

The duration of amnesia after MTBI, posttraumatic amnesia (PTA), is used as one of the defining criterias (< 24 hours), but there are few studies to support the reliability of this symptom. PTA is also referred to as anterograde amnesia, meaning inability to recall events immediately following the trauma. The PTA ceases when the individual is able to report coherent memories from the period after the trauma. PTA should ideally be established prospectively at the ED but crucial additional information can sometimes be obtained retrospectively through a thorough analysis of the patient´s history.

The duration of loss of consciousness (LOC) is another defining criterion (< 30 minutes) for MTBI. The clinically most elaborated and frequently used method to assess the level of consciousness is the Glasgow Coma Scale (GCS) score, see table 1.

Table 1. *Glasgow Coma Scale*

Score	Motor response	Eye opening	Verbal response
1	None	None	None
2	Extension to pain	Opens to pain	Incomprehensible
3	Flexion to pain	Opens to command	Inappropriate words
4	Withdrawal from pain	Opens spontaneously	Confused, disoriented
5	Localising pain	-	Normal
6	Obeys commands	-	-

Table 2. *GCS score and TBI severity*

GCS score	Severity of brain injury
3 – 8	Severe
9 – 12	Moderate
13 – 15	Mild

Assessment of GCS when the patient presents at the ED is the gold standard for grading of the severity of TBI, see table 2, and has been used as a guide for the acute management as well as for prognostic purposes.

A GCS score of 13 – 15 is thus consistent with "mild" traumatic brain injury. It has been proposed, though, that patients presenting with a GCS score of 13 should be classified as "moderate", as their prognosis in terms of acute complications and intracranial lesions are similar as for those patients who are moderately injured [3, 4]. Other symptoms and signs of clinical importance in the acute phase are vomiting, seizures and retrograde amnesia, i.e. inability to recall events that occurred before the trauma.

Brain imaging

Skull X-rays is sensitive for detecting skull fractures, which is a risk factor for intracranial complications, but the diagnostic accuracy with regard to these complications is poor [5]. The method has become of less importance since the introduction of the more sensitive computed tomography brain scan (CT) and magnetic resonance imaging of the brain (MRI). A Canadian study of 3121 patients with MTBI showed clinically important intracranial lesions in 4.8, 17.2 and 40.9 % of the patients with a GCS score of 15, 14 and 13 respectively [6]. MRI is more sensitive than CT to detect intracranial pathology [7].

With recent improvements, such as diffusion-weigthed MRI and diffusion tensor imaging, the MRI techniques have become even more sensitive than standard MRI [8] and have shown that diffuse axonal injury occurs more often than previously assumed [9]. Proton magnetic resonance spectroscopy studies have also indicated presence of cellular injury in frontal white matter that on conventional MRI appeared normal after MTBI [10]. Functional MRI, used in small studies to objectify brain injury after con-cussion, have shown different patterns of activation in concussed patients as compared to controls, even in the absence of observed deficits in behavioral performance [11]. Some studies indicate that flow deficits observed with SPECT better reflect the magnitude of the brain damage than CT [12], and PET has been used to visualize frontotemporal hypometabolism in MTBI patients with persistent cognitive impairment [13]. However, these techiques are not yet established tools for routine assessment of patients with concussion.

Biochemical markers

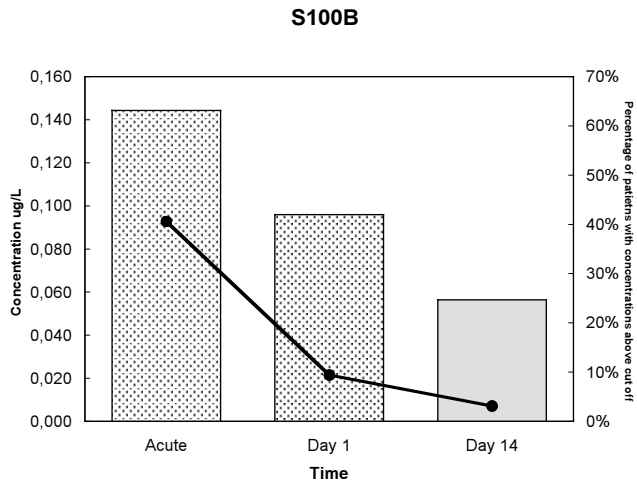
Damage to neurons and neuronal supporting cells causes release of proteins, some of which enter the cerebrospinal fluid, cross the blood-brain barrier (BBB) and leak into the peripheral circulation, where they can be measured by use of blood samples. Neuron-specific enolase and cleaved-tau are considered markers for neuronal damage [14, 15], whereas damage to supporting cells such as astrocytes and oligodendrocytes is reflected in increased serum levels of S 100B, creatine kinase BB isoenzyme and myelin basic protein [16-18]. Several factors, such as intrathecal concentration, metabolic consumption or reuptake, BBB disruption, molecular size, half-life, sensitivity and specificity of the assay and contamination of the marker from other sources in the body possibly affect the serum concentration of these markers and confound the interpretation of the measurements.

Most studies concerning biomedical markers have been performed on S 100B, a polypeptide belonging to a larger family of calciumbinding proteins, called S 100 due to its solubility in *100* % *S*aturated ammonium sulphate. S 100B has both intracellular and extracellular functions and exerts, depending on its concentration, neurotrophic as well as toxic effects [19]. S 100B is correlated to outcome in neurological disorders like stroke and global hypoxia. In severe brain injury a significant relation between outcome and initial S 100B concentration in blood has been shown [20]. However, short half-life (97 minutes), lack of specificity for neural tissue – S 100 is also found in fat and muscle cells outside the brain, and increased levels have been observed after bone fractures and contusions [21] – and uncertainty whether S 100B reflects parenchymal damage or BBB dysfunction are confounders that have resulted in conflicting evidence as to the clinical utility of this marker for diagnostic and prognostic purposes in MTBI patients [20].

In a previous paper from our cohort of patients with MTBI [22] it was demonstrated that serum concentrations of S 100B were significantly higher in MTBI patients ($z=3.94$, $p<0.001$) as well as in patients with mild orthopaedic injuries ($z=3.99$, $p<0.001$) as compared to non-injured persons. S 100B and S 100A1B concentrations in MTBI patients were initially increased, as well as the number of patients with values above cut off limits, and decreased rapidly over time, see figures I and II. Initial S 100B concentrations were higher in MTBI patients with CT and/or MRI abnormalities (60 % above cut off) than those without CT and/or MRI abnormalities (38 % above cut off). There was no correlation between concentrations of S 100

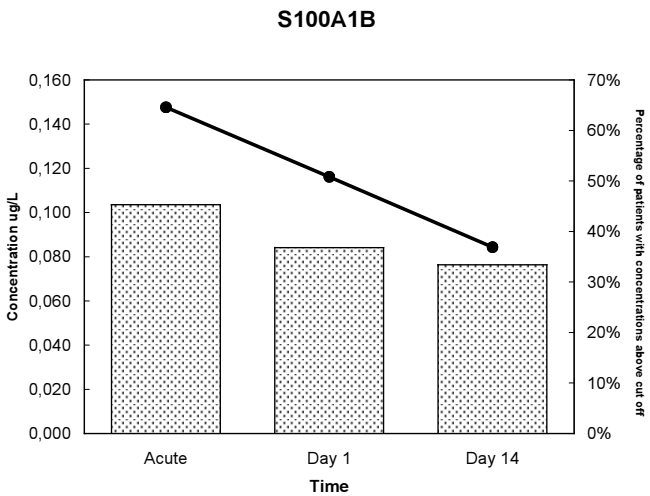
and symptom reports at three months. In summary, the diagnostic accuracy of S 100B and S 100A1B for MTBI was poor. Serum concentrations were not correlated to the severity of injury nor to symptom reports at three months post injury.

Figure 1. *Time course of S100B in patients with MTBI*



Bars: mean values of S100B
Line: percentage of patients with S100B concentrations above cut-off

Figure 2. *Time course of S100A1B in patients with MTBI*



Bars: mean values of S100A1B
Line: percentage of patients with S100A1B concentrations above cut- off

An association between the APOE epsilon4 allele and decreased cognitive performance after mild head injury has been found. In a population-based longitudinal study, within-person comparisons of probands exposed to mild head injury with the epsilon4 allele showed decreased cognitive performance, whereas injured probands without the allele were unchanged [23]. The prospective design of the study yields ideal conditions for comparing preinjury with postinjury performance at the individual level. Later prospective studies have not been able, though, to replicate the finding when comparing, at group level, neuropsychological outcome after MTBI in persons with and without the allele[24].

In summary, there is converging evidence that MTBI is associated with various signs of organic brain injury or dysfunction, although the long term prognostic significance of these findings for the development of persistant disability remains unclear.

Clinical course and outcome in previous studies

Heterogeneity in previous studies

Different observation periods, such as 6 weeks [25], 3 months [26-29] and one year [30, 31] have been used.
Case definitions range from at least one reported symptom [25, 26, 29, 30], significant ongoing problems [28] to at least three symptoms [32].
Control groups have included for example patients exposed to an orthopedic trauma [28], patients from different medical settings [33], uninjured subjects and their relatives [34], patients with traumatic back pain [35] and a matched control group [27]. Several authors have shown no or only minor significant differences in symptoms between exposed and non exposed individuals [34, 35], whereas others have reported some significant differences in endorsement of a limited number of symptoms (doing things slowly, fatigue and poor balance), especially when frequency as well as severity of symptoms have been measured [36].

Symptoms and disability

Most prominent symptoms at follow up have been headache, irritability and dizziness [25], headache, dizziness, fatigue and difficulty in concentration [26], headache and concentration difficulties [28], headache and dizziness [29], concentration problems and restlessness [34], headache, decreased

energy and dizziness [27]. Lack of consistency of the different symptoms have been pointed out by several authors [25, 26].

In a prospective study by Lidvall et al on 83 patients headache was the most commonly reported symptom (58 %), followed by dizziness, fatigue and difficulty in concentration [26]. Three months after the trauma 24 % of patients reported at least one symptom, attributed to the accident. In the early phase after the accident headache and dizziness dominated. Later the picture became more polymorphous. One out of three patients reported new symptoms, anxiety (anxiousness, nervousness, restlessness, mental tension) being the most common of these, followed by fatigue.

In a study by Ponsford et al of 84 MTBI patients, frequency and intensity of MTBI symptoms were measured one week and three months after injury and compared to controls, exposed to an orthopedic trauma [28]. One week after the trauma, MTBI patients showed significantly more symptoms than controls, specially headache, dizziness, irritability, fatigue and sleeping difficulty. Three months after injury, however, only the intensity of headache and concentration difficulties were greater in patients than in controls. Neuropsychological testing at three months showed no differences between patients and controls.

In a study by Bohnen et al of 71 MTBI patients, a principal component analysis of the post-concussive symptoms resulted in a two factor solution [37]. One factor (post-concussive-cognitive complaints) consisted of "typical post-concussional symptoms" such as headache, dizziness, intolerance to light, noise and other external stimuli together with items indicating problems with decreased work capacity and efficiency, tiredness, difficulty doing things simultaneously, and diminished concentration. The other factor (emotional-vegetative) included complaints of heart palpitations, wet hands, dyspnoe, flushing, problems with digestion, having a tense feeling in the chest as well as items of depression, emotional lability, restlessness and decreased libido. Patients with lasting symptoms had either a history of previous MTBI or preexisting emotional distress.

In a three-center study of neurobehavioural outcome in patients admitted to hospital after minor head injury, Levin et al assessed 57 patients within 1 week (baseline) after head injury and at 1 and 3 months postinjury [27]. A matched control group was used and patients with a history of previous

head trauma or neuropsychiatric disorder were excluded. Cognitive impairments demonstrated at baseline resolved during the first three months after the injury. Subacute postconcussion symptoms reported were headache in 71 %, decreased energy in 60 % and dizziness in 53 % of the cases. The incidence of symptoms at three months was: 47 % for headache, 22 % for decreased energy and 22 % for dizziness. Symptoms were grouped into three domains: somatic, cognitive and affective.

In a study by Middelboe et al, 28 patients admitted for neurological care were followed for one year after mild head injury [30]. Patients with previous neurologic or psychiatric disorder were excluded from follow up. At one year headache was reported by 32 %, dizzines, memory deficit and concentration deficit by 25 % and fatigue and irritability by 21 % of the patients. According to the definition of postconcussional syndrome (PCS) in this study – one or more symptoms attributed to MHI and/or occurence of significantly elevated score on GHQ-60 (General health questionnaire) and IES (Impact of event scale), two self-report measures of general wellbeing and level of posttraumatic stress, respectively – 50 % of the patients were cases at one year follow up.

Specificity of symptoms

In a small study by Gasquoine, symptom change reports in patients with concussion were compared with patients with traumatic back pain [35]. Even when only selected local head and cognitive dysfunction postconcussional symptoms were analyzed, there was no difference between the two groups, indicating a lack of specificity for the postconcussion symptoms.

In a study by Fox et al, base rates of postconcussive symptoms were determined in patients from different medical settings and controls and compared to patients with a recent history (within two years) of being knocked unconscious or bumping the head without losing consciousness [33]. Patients having been knocked unconscious or with a bump on the head reported more symptoms than those without head injury, but neurological, psychological and environmental variables – without any associated head injury – were also significantly related to PCS complaints. The knocked unconscious group reported a headache rate of 52 % and a fatigue rate of 60 % – symptoms normally considered core symptoms of PCS – which did not differ significantly from the unknocked group. The study points to the importance of disentangling the change in symptom perception post injury

as compared to symptoms at baseline. The study also indicated that the severity of symptoms, i e not only the frequence, in concussed patients compared to controls has to be assessed.

In summary, a variety of symptoms and behavioural changes are common in the acute stage after MTBI but a majority of patients recover within 3 – 12 months. Many methods have been used to evaluate outcome, but heterogeneity of study samples, study designs, follow-up periods and selection of outcome criteria have made comparisons between studies difficult and have complicated the interpretation of data [38]. The most commonly used outcome domains are cognitive function, persisting subjective symptoms and disability or need for surgical intervention and mortality. Unfavourable recovery after concussion is often referred to as Postconcussional syndrome (PCS) or Postconcussional Disorder (PCD). However, although discussed during more than a century, an unequivocal definition of the condition is still lacking (see below).

Cognitive impairment

Cognitive impairment is one of the domains of symptoms and disability. Subjective complaints of slowness of thought, memory problems and concentration difficulties are common after MTBI. Neuropsychological tests assess cognitive function, and several studies have been performed to evaluate the extent and type of cognitive impairment after MTBI with a variety of cognitive test batteries.

In a study by Levin et al cognitive impairment in the domains of memory, attention, and information-processing speed was present the first month after MTBI but was generally resolved after three months [27]. Subjective complaints tended to persist in cases even after recovery of cognitive function.

In a study by Hugenholtz, MTBI patients were significantly slower than the normal control group on the choice reaction time tests, which demanded an increased amount of attention and information processing during the 1st month after injury. The performance improved gradually, but minor differences were still present after three months [39].

In a study by Bohnen et al, MTBI patients with postconcussional symptoms six months post injury showed deficits in selective and divided attention as compared to patients without symptoms [40].

In a study by Killam et al, in which non-concussed, non-recent-concussed and recent-concussed athletes were compared, the findings indicated that recent head injury resulted in demonstrable memory problems, that resolved with time. There was an inverse correlation between the severity of the postconcussion score and scores for attention and delayed memory [41].

In summary, cognitive impairment is demonstrated for attention, memory and speed of processing after MTBI, but in most studies problems resolve with time and residual impairment are in most studies insignificant or difficult to demonstrate when MTBI patients are compared with control groups. Moreover, in some studies there is poor correlation between neuropsychological test results and the subjective reporting of symptoms.

Postconcussional syndrome / Postconcussional disorder

The concept of PCS, "postconcussional syndrome", has been criticised. The label of a "syndrome" would ideally require a more consistent association between the described symptoms and the supposed underlying pathophysiological mechanism. Moreover, the failure to identify any clear "point of rarity" for the condition, the lack of an association with a condition specific biological marker and the absence of effective, validated treatments do not support the existence of a discrete disease entity.

The multisymptomatic condition has phenomenological overlaps to multisymptomatic functional illnesses such as chronic pain and chronic fatigue [42], and the mix of somatic and psychological complaints is also found in several psychiatric disorders, such as depression, posttraumatic stress disorder (PTSD) and generalized anxiety disorder. The prevalence of depressive disorder after MTBI is about 20 - 25 % [43, 44], and 33 % after TBI [45]. PTSD have been found in 48 % of patients three months after having been knocked unconscious in a traffic accident and in 33 % after one year [46]. Thus, there is a basis for conflicting views as to whether PCS is in fact caused by the concussion or if it is just an alternative conceptualization of the emotional, cognitive and somatic symptoms that do also occur in functional somatic syndromes or depressive and anxiety disorders, or wheter the intensity of the symptoms of brain injury are just fueled by comorbid depression or PTSD. Although attribution of the symptoms to effects of the head injury seems logical and straightforward, the association is not uncomplicated. There are diverging opinions within the medical society about the nature of the illness as well as what determinants should be

considered crucial. For example, in a recent systematic review of MTBI the view was taken that the current labels in use for the condition – postconcussion syndrome and postconcussional disorder – were potentially misleading because of the implication that the symptoms de facto are a result of the concussion [38], a phenomenon elsewhere referred to as the "reification fallacy" [47].

The two existing formal definitions of PCS and PCD according to ICD-10 and DSM-IV are rarely used in MTBI studies. The DSM-IV diagnosis is just a proposed criteria set for further study and not an established new category. The ICD-10 formulation has been subject to substantial criticism. The presence of postconcussion-like symptoms are not unique to mild head injury. The symptoms are commonly found in healthy individuals and are highly correlated with depressive symptoms [48]. In one recent study, the ICD-10 PCS symptoms were unable to accurately classify the MTBI patients at three months post-injury [49]. Moreover, the ICD-10 and the DSM-IV definitions exhibit important differences [50-53], see table 3.

In addition to the head injury criterion, the DSM-IV definition requires disability and cognitive deficits verified by neuropsychological testing, wheras the two ICD-10 definitions only require presence of at least three symptoms for a diagnosis of PCS. Furthermore, the DSM-IV definition comprises changes in personality and apathy/lack of spontaneity as symptoms, thus bringing the definition of PCD closer to the concept of brain damage in the more severe end of the spectrum. The ICD-10 definition on the other hand includes "preoccupation with the symptoms and fear of permanent brain damage to the extent of hypochondriacal concern, overvalued ideas and adoption of sick role". The ICD-10 definition thus conceptualizes the illness in a more psychological way, whereas the DSM-IV definition puts the symptoms in a biomedical frame of reference, requiring "evidence from neuropsychological testing" of cognitive difficulties in addition to subjectively experienced and expressed symptoms. The differences are also seen in the DSM-IV definition of "significant concussion", which requires two of the following criteria: 1. a period of unconsciousness lasting more than 5 minutes, 2. a period of posttraumatic amnesia that lasts more than 12 hours after the closed head injury, or 3. a new onset of seizures that occurs within the first 6 months after the injury, whereas ICD-10 requires only the more unspecific "history of head trauma with loss of consciousness".

Table 3. *Criteria for post concussional syndrome/disorder according to the classifications in ICD-10 and DSM-IV. Trauma and exclusion criteria are not presented.*

	ICD10 (1992 clinical guidelines)	**ICD10** (1993 research criterias)	**DSM-IV** (1994 proposed criteria)
Symptoms (S-criterion) Following symptoms occur in all three definitions: - headache - dizziness - fatigue - irritability - emotional lability - insomnia Symptoms in the ICD10 definitions that do *not* occur in the DSM-IV: - subjective cognitive complaints Symptoms in the DSM-IV that do *not* occur in the ICD10 definitions: - changes in personality - apathy or lack of spontaneity	At least three of the following features 1. headache 2. dizziness 3. fatigue 4. irritability 5. difficulty in concentrating and performing mental tasks 6. impairment of memory 7. insomnia 8. reduced tolerance to stress, emotional excitement and alcohol 9. depression/anxiety 10. fear of permanent brain damage 11. hypochondriacal concerns 12. adoption of a sick role	At least three of the following features 1. *somatic symptoms* (headache, dizziness, malaise, fatigue, noise intolerance) 2. *affective symptoms* (irritability, emotional lability, depression and/or anxiety) 3. *cognitive symptoms* (subjective complaints of difficulty in concentration, in performing mental tasks and memory complaints, without clear objective evidence of marked impairment) 4. insomnia 5. reduced tolerance to alcohol 6. preoccupation with the above symptoms and fear of permanent brain damage to the extent of hypochondriacal concern, overvalued ideas and adoption of sick role.	At least three of the following features 1. becoming fatigued easily 2. disordered sleep 3. headache 4. vertigo or dizziness 5. irritability or aggression 6. anxiety, depression or affective lability 7. changes in personality 8. apathy or lack of spontaneity
Disability (D-criterion)	Not required	Not required	Significant impairment in social or occupational functioning
Objective signs of cognitive dysfunction (NP-criterion)	Not required	Not required	Evidence from neuropsychological testing of difficulty in attention (concentrating, shifting focus of attention, performing simultaneous cognitive tasks) or memory (learning or recalling information)

The controversy

The determinants of the clinical course after MTBI have been a matter of controversy for more than 100 years. The traditional biomedical model, emphasizes cerebral dysfunction factors, and presupposes that symptoms and disability result from and could be understood as consequences of the cerebral damage caused by the trauma. This way of understanding the suffering and the disability also seems to be the most common way to interpret the problems among lay people. However, several studies of the consequenses of MTBI have failed to show such a straightforward correlation between injury and outcome, as mild injuries with a similar acute impact can lead to grossly divergent outcomes. Instead, an increasing amount of studies have demonstrated impact from non-injury, contextual and personal factors, and the long term disabilities after an MTBI have in most cases remained unaccounted for by demonstrable anatomical and physiological changes.

The biopsychosocial model

The International Classification of Functioning, Disability and Health (ICF), was published in 2001 on behalf of World Health Organization (WHO) [54]. Body structure/body function, activity and participation are main components in this model, and these interact both with each other and with contextual and personal factors at different levels.

The ICF applies a biopsychosocial perspective to obtain a synthesis of the medical and the social model of understanding disability. A biopsychosocial model of understanding is often applied for the understanding of subjective health complaints that are not fully accounted for by demonstrable pathologic changes. In several common disorders no objective signs of physical pathology can be demonstrated. In primary care about one third of somatic symptoms lack medical explanation [55]. Medically unexplained symptoms are often chronic and strongly associated with depressive and anxiety disorders.

The biopsychosocial model was first formulated by psychiatrist George Engel [56]. Engel acknowledged the advances of biomedical research but problematized its omniscient claims. In the biopsychosocial model, illness is viewed as the result of interaction of a multitude of causal factors, operating at different levels in different phases of the illness process. Factors that do not easily fit into the biomedical model are, for example, psychological vulnerability, general distress, adaption of a sick role and the impact of the

Figure 3. *Etiological model.*

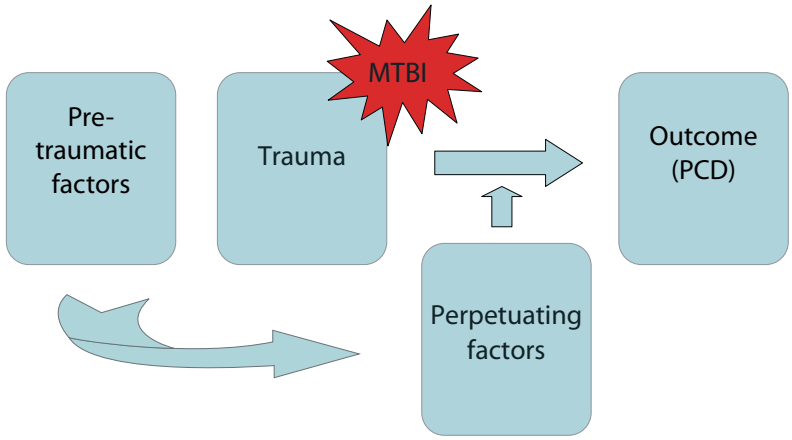


Table 4. *The biopsychosocial net, adapted to possible MTBI related issues.*

	Predisposing factors	**Precipitating factors**	**Perpetuating factors**
Biological	Genetic factors 5-HTT, short allele ApoE, epsilon 4 allele Medical condition Sex Age	Head injury GCS LOC PTA S 100	Inactivity Sleep disorder Drug or alcohol misuse
Psychological	Premorbid personality Negative affectivity Cognitive abilities Psychological vulnerability Prior psychiatric disorder Heredity for pscyh disorder Childhood experiences Illness experiences	Peritraumatic stress Hyperarousal Intrusions	Hyperarousal Anxiety/Depression Maladaptive coping style Catastrophizing Avoiding Victimization Sick role adaption
Social	Psychosocial stressors		Financial motifs Patient support group Psychosocial stressors Insufficient social support network Iatrogenic factors "Diagnosis threat"

Adapted from Gallagher, R.M. (2005). "Rational integration of pharmacologic, behavioural and rehabilitation strategies in the treatment of chronic pain" Am J Phys Med Rehabil 84 (3 Suppl): S64 – 76.

patient-clinicain relationship. In the biopsychosocial model it is customary to describe the determinants of the illness process in terms of predisposing (pretraumatic), precipitating (traumatic) and perpetuating factors, as described in figure 3.

The biopsychosocial model has been summarized by Gallagher [57]. Table 4 shows the model with some adaptions of the included variables according to the MTBI research agenda.

As present MTBI research has indicated that biological as well as behavioral, psychological, social and contextual factors affect the clinical course after MTBI, a biopsychosocial model was chosen for this study as the most appropriate conceptual framework for investigating the development of PCD.

Aims

The general aim was to contribute to the understanding of the development of PCD after MTBI.

The specific questions were:

Paper I: Is increased S 100 associated with cognitive impairment?

Paper II: What is the clinical course after MTBI?

Paper III: How should PCD be defined?

Paper IV: What are the risk factors for PCD after MTBI?

Subjects and methods

The study was approved by the ethics committee at the Karolinska Institutet.

Inclusion and exclusion criteria

Inclusion required a history of blunt head trauma, loss of consciousness (LOC) and/or posttraumatic amnesia (PTA), admission to hospital within 24 hours after the trauma, a Glasgow Coma Scale (GCS) score of 14 – 15 at first assessment in the ED and an age of 15 – 65 years. Exclusion criteria were any of the following: LOC > 30 minutes, PTA > 24 hours, other significant physical injury or other major neurological disorder, including previous significant head injury. No financial incentives were offered for participants and no specific intervention was attached to the study.

Study setting and study sample

Patients were recruited from three ED:s located in the central and north Stockholm, Sweden, between January 2000 and December 2001. The catchment area for the three ED:s has about 800.000 inhabitants in the age of 15 – 65 years. Mean age in the area is 38 years and about 51% are women. Stockholm is the capital of Sweden with a high percentage of employment in white collar professions. Thirty-eight % of the population between 15 and 65 years of age have an education exceeding twelve years; the corresponding figure for the total Swedish population is 26 %.

Recruitment was non-systematically interrupted and covered in total 20 months at Danderyd University Hospital and 3 - 6 months in the two other hospitals (Karolinska University Hospital and Stockholm Söder Hospital). During the recruitment periods all MTBI patients were consecutively considered for inclusion. In total one hundred and twenty-two patients with MTBI fulfilled inclusion criteria and gave informed consent. The majority (75 patients) were recruited from Danderyd University Hospital, where detailed data on numbers and reasons for non-participation were collected during a three months period (from February to April 2001). During this period 27 % of the eligible patients agreed to participate. Most common reasons given for non-participation were lack of time and lack of interest and motivation for the follow up program. Age and gender did not differ between non-participants and participants. For non-participants hospital-

ization rate was 53 % and CT scan was performed in 60 % of the cases, none of which was abnormal. Of the participants 80 % had been hospitalized, 93 % underwent CT scan, 7 % of which were abnormal.

Patients with high velocity traumas were managed in a tertiary trauma unit according to a regional trauma protocol and were not available for the study.

Patients

Seventy-one men (58 %) and 51 (42 %) women fulfilled the inclusion criteria and volunteered to participate in a follow up study, including six assessment sessions, a CT brain scan and an MRI brain scan. According to current routines most patients (80 %) were hospitalized after admission for observation over night.

Withdrawal during study

Twenty patients (16 %) dropped out from the study during the first three months. Dropouts were compared to non-dropouts with respect to age, gender, hospital, education, occupation, PTA, LOC, initial symptom severity, previous psychiatric history and alcohol intoxication at admission. Dropouts did not differ in any variable except for significantly fewer years of education (mean difference 2.3 years).

Controls

Thirty-five subjects without history of previous head injury and in good health according to self-report and working in different professions (25 % health care workers) or studying (14 %), were recruited by means of local advertisement for assessment of base rate symptoms and neuropsychological testing.

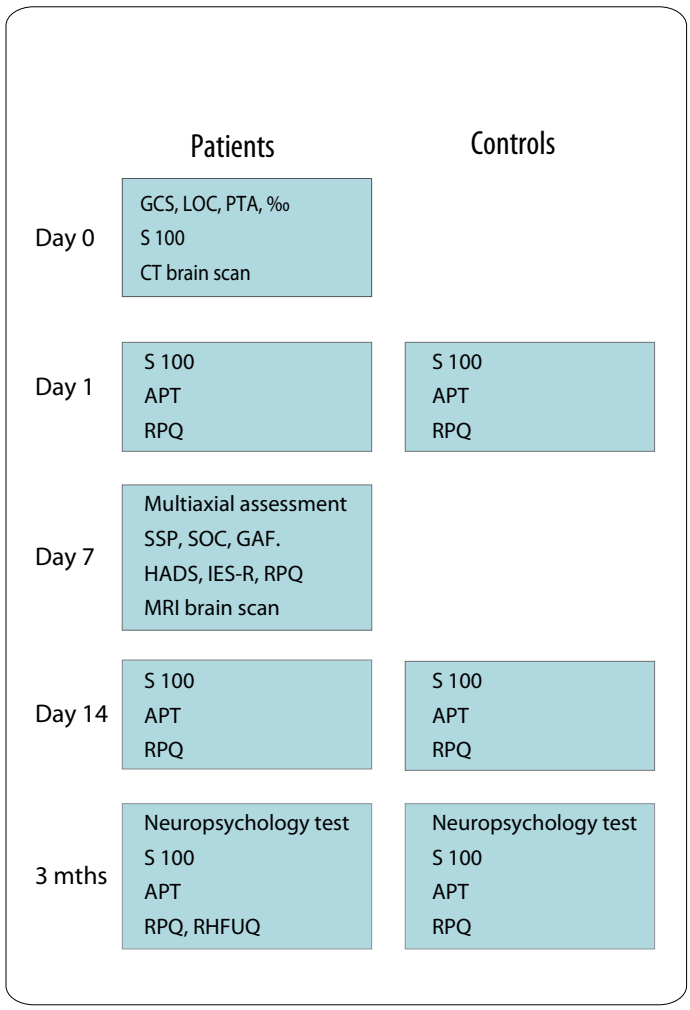
Procedure

After information about the study, informed consent was obtained from all participating patients before inclusion in the study. GCS score, duration of LOC, PTA and retrograde amnesia and results from breath alcohol test were recorded by the ED staff according to the study protocol. The ED:s were checked for new head injury patients by the research group staff every day of the week. Included patients were assessed after 1, 7 and 14 days and at three months post-injury. CT scan of the brain was performed within 24

hours after the trauma and an MRI scan of the brain was performed within one week (mean 7.4 days). Within one week after the injury, emergency data were reassessed with the patient and revised if additional or divergent information was reliably obtained by use of data not available at the initial assessment. At this occasion an extensive clinical investigation was also performed to assess pre-traumatic and post-traumatic status.

For overview and time schedule of the assessment procedures, see figure 4.

Figure 4. *Assessment procedures*



Assessments

Pre-traumatic variables

DSM-IV multiaxial assessment
A multiaxial assessment according to DSM-IV was performed by an experienced neuro-psychiatrist (AL). Previous and current psychiatric diagnosis on Axis I and Axis II according to DSM-IV criteria were established with a clinical interview. The assessment included a survey of general medical conditions (Axis III), and a neurological examination to detect sequelae from the recent injury and to exclude other concurrent neurological disorders. Psychosocial and environmental problems (Axis IV) were assessed by use of the Severity of Psychosocial Stressors scale, comprising 11 "yes" or "no" questions and the experienced level of distress was assessed on a six-graded scale (none, mild, moderate, severe, extreme, disastrous) as suggested in the DSM-III-R [58]. Comparisons between this scale and a more elaborate system for measuring life event stress (PERI), indicate that Axis IV ratings correlate significantly with PERI ratings of disruption associated with rated events [59]. Global Assessment of Function (GAF) was assessed by use of a self-report version of the Global Assessment of Functioning Scale according to Axis V and based on the original 0 – 100 scale [60], a valid and reliable unidimensional instrument measuring psychological, social and occupational functioning [61]. GAF was assessed for the last year ("GAF-1") and for the last two weeks ("GAF-2") before the trauma. Family history of psychiatric disorder was also noted.

The patients also completed a number of self-assessment inventories:

Swedish universities Scales of Personality (SSP)
Personality traits were assessed by use of a self-rating instrument, SSP, Swedish universities Scales of Personality [62]. SSP measures personality traits of possible importance for identifying individuals at risk for psychiatric disorders. SSP consists of 13 scales, listed and described in table 5. SSP is a revision of KSP, Karolinska Scales of Personality, a personality inventory widely used in psychiatric research [63]. KSP subscales related to anxiety proneness and hostility are associated with prevalence of physical symptoms [64] and with worse rehabilitation outcome after physical trauma [65].

Table 5. *The scales in Stockholm university Scales of Personality (SSP)*

SSP scales	Description
Somatic trait anxiety	Autonomic disturbances, restless, tense
Psychic trait anxiety	Worrying, anticipating, lacking self-confidence
Stress susceptibility	Easily fatigued
Lack of assertiveness	Lacks ability to be self-assertive in social situations
Impulsiveness	Acting on the spur of the moment
Adventure seeking	Avoiding routine; need for change and action
Detachment	Avoiding involvement in others; withdrawn
Social desirability	Socially conforming, friendly, helpful
Embitterment	Unsatisfied, blaming and envying others
Trait irritability	Irritable, lacking patience
Mistrust	Suspicious, distrusting people´s motives
Verbal trait aggression	Getting into arguments, berating people when annoyed
Physical trait aggression	Getting into fights, starts fights, hits back

Sense Of Coherence scale (SOC)

The sense of coherence (SOC) concept was developed to assess personality-related factors likely to protect people from falling ill. SOC consists of three main components: comprehensibility, manageability and meaningfulness [66]. Poor SOC has an association to major psychosocial risk factors and indicators of perceived mental health problems, use of mental health services and psychiatric diagnosis [67]. In patients with orthopedic injuries [68] a high SOC score predicted a better outcome after surgery after one year.

The Alcohol Use Disorders Identification Test (AUDIT)

Screening for hazardous alcohol use, dependecy symptoms and harmful alcohol use was made by use of Alcohol Use Disorders Identification Test (AUDIT) [69], an instrument with high sensitivity and specificity for detection of current alcohol problems [70].

Sociodemographic variables recorded were gender, age, marital status, years of education and sick-leave at the time of the injury.

Injury related variables

The immediate neurological impact and severity of the traumatic event was assessed by use of Glasgow coma scale (GCS), duration of loss of consciousness (LOC), duration of posttraumatic amnesia (PTA) and retrograde amnesia, and presence of injury related changes in brain imaging (CT or MRI brain scan). Alcohol breath test was performed and type of traumatic event was recorded. S 100 was measured at the ED and at day 1, day 14 and after 3 months.

S 100 proteins in serum
Collected blood samples were centrifuged and serum was separated and stored at -20˚ C until analyses were performed. Serum concentration of S 100B was measured using a comercially available immunoluminometric assay (LIA-mat Sangtec S 100 Sangtec Medical, Bromma, Sweden) [71]. An enzyme-labelled immunosorbent assay (ELISA) method S 100BB (by CanAg Diagnostics AB, Gothenburg, Sweden) was used for analysis of S 100A1B. The analyses were performed blindly. For all S 100 measurements cut-off limits were defined as above the 97.5 percentile of the average of the three S 100 concentrations in the non-injured persons.

Post-traumatic variables

The reaction to the trauma was measured within one week post injury by use of two different self assessment instruments:

Impact of Events Scale – Revised (IES-R)
The IES-R is a widely used, reliable and valid self-report measure for assessing stress reactions after traumatic events [72]. The 22 items in the revised scale contain three factors: Intrusion, Avoidance and Hyperarousal, that reflects the dimensions of psychopathology associated with PTSD [73].

Hospital Anxiety and Depression Scale (HADS)
Symptoms of anxiety and depression after the trauma were assessed with the Hospital Anxiety and Depression Scale (HADS) [74]. HADS has been widely used for medically ill populations, and excludes bodily symptoms overlapping with anxiety and depression. Its validity for assessing symptom severity and caseness of anxiety and depressive disorders has been confirmed [75]. HADS has been used in several studies to predict physical outcomes [76] and in patients with MTBI as a predictor for postconcussional symptoms [77].

RPQ (see below) assessed at one week post injury was also used as a predictor for the outcome.

Outcome measures

Cognitive function was assessed by use of two different methods, neuropsychological evaluation and The Automated Psychological Test system (APT):

Neuropsychological testing
The neuropsychological assessment included: Information, Digit Span and Digit Symbols from the WAIS-R [78], Block Span from the WAIS-R-NI [79], Buschke Selective Reminding Test (SRT) [80], The Stroop test [81], The Paced Auditory Serial Addition Test (PASAT) [82], and The Trail Making Test (TMT – parts A and B) [80]. Raw scores were transformed to standardized values according to the test manual. No measure of malingering was included. The neuropsychological assessment was performed after three months.

At the evaluation of cognitive function, the performance was considered "impaired" if two or more test results were below 1 SD from the mean or if there was a discrepancy of 2 SD or more in individual test results. Secondly, in patients with "impaired" results, premorbid factors that might contribute to low cognitive performance were considered. Available data were age, years and type of education achieved and occupational history. Furthermore, in some cases additional information on level of degrees and anamnestic data concerning possible developmental learning problems were available. Thirdly, when these factors did not explain the low level of results, concurrent potentially explanatory factors such as body pain and sleep disturbance were also considered. Patients were then classified into two groups:
1. patients with signs of cognitive impairment compatible with MTBI;
2. patients without such signs of cognitive impairment or with cognitive impairment more likely due to causes other than MTBI. Two neuropsychologists, with considerable experience from this group of patients, independently rated all data with an interrater reliability of .85, ($p<0.001$). In case of diverging assessments a third, senior neuropsychologist was asked for a decisive vote. The same evaluation was performed in the controls and the whole sample was assessed with blinding for whether the proband had been injured or not.

Automated Psychological Test system (APT)
The APT [83] is a computerized neuropsychological test battery with tests for a variety of cognitive functions, from which was chosen a batch of pertinent tests. The APT was performed at day 1, 14 and after three months in patients as well as controls by use of parallell versions of the test. The assessed domains were:

Motor speed (F-test) was assessed in five different subtests
Fingertapping with the right index finger.
Finger tapping with the left index finger.
Alternation between the right index and middle fingers.
Alternation between the left index and middle fingers.
Alternation between the right and left index fingers.
Selective attention (K-test)
The task is to decide, as fast as possible, whether "K" is present in a set of distractors presented in random positions on the screen. The test is adaptive in the early phase, i.e. there is process control of the level of test difficulty depending on subject performance.
Reaction Time (R-test) comprised four subtests
Simple auditory reaction time (RT), responding with the dominant index finger.
Simple visual RT, responding with the dominant index finger.
Two-choice visual RT; a visual signal to the right or left of a central fixation point, responding with the index finger of the corresponding side.
Two-choice visual RT with response inhibition if an auditory signal is co-presented with a visual signal (Go-NoGo test).
Longterm Associative Memory test (O-test)
First the proband responds to ten different alphabetical stimuli by pressing a numerical key that corresponds to the letter according to a translation list on the screen. Twenty minutes thereafter, the task is to respond to the letter stimuli without help from the translation list but according to what was remembered.

No reference data were available for repeated measurements. At the evaluation of cognitive function with the APT test a control group was used (see Control group). The same time intervalls were used for the control group, although no injury had occurred. For each APT session a separate composite score was derived based on ten variables, that were considered relevant

for the study. As reference values, mean and standard deviation for each of the ten test variables in the non-injured group at each session were used. If patients performed 1 SD worse than the mean for the non-injured persons in at least two of the four separate test domains on at least two occasions, they were coded as having signs of cognitive impairment. Secondly, premorbid and other concurrent factors were considered, as described above for the neuropsychological test evaluation, before a diagnosis of an MTBI related cognitive impairment was established.

Symptoms and disability

Swedish versions of the Rivermead Post Concussion Symptoms Questionnaire, RPQ [84], and the Rivermead Head Injury Follow Up Questionnaire, RHFUQ [85], were used. These two self-assessment instruments ask the patient to state *change* in symptom level and in social and occupational functioning respectively, and have been shown to reliably measure change in frequency and severity of postconcussional symptoms and disability after head injury of mild to moderate severity [84, 85]. In ICF, the term "disability" is used as an umbrella term for all components in the model, such as body functions, activity performance and participation. In this thesis "disability" is used in accordance with the previous WHO nomenclature (International Classification of Impairments, Disabilities and Handicaps, ICIHD), thus describing only activity limitation, in ICF terminology.

The RPQ score was calculated, as described by King et al, as the sum of all symptom scores excluding ratings of 1, as these indicated that symptoms had resolved. Mild symptoms were scored as 2, moderate as 3 and severe as 4. RPQ was administered at all occasions and RHFUQ at three months only.

Case definition of PCD

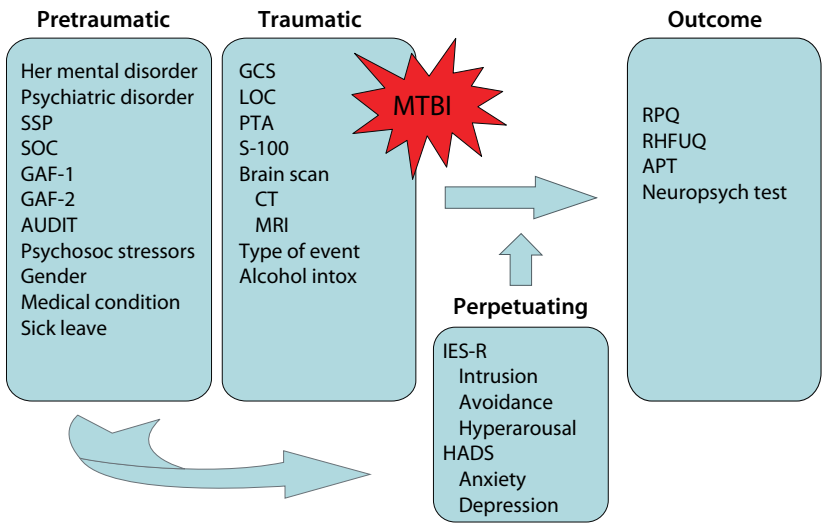
Three symtoms were required for caseness in the two currently used definitions. Symptoms listed in RPQ were used. There were some differences in the choice of eligible symptoms between RPQ, ICD-10 and DSM-IV, but these differences were not considered significant and were not taken into account. As three mild symptoms resulted in an RPQ score of 6, this score was chosen as the "symptom criterion" (S-criterion). As "disability criterion" (D-criterion) two reported changes of at least mild severity – corresponding to a RHFUQ score of at least 4 – was chosen as the cut off level. Signs of cognitive impairment compatible with MTBI, as defined in the previous section, was chosen as the "neuropsychological criterion" (NP-criterion).

An "intermediate definition of PCD", based on three symptoms in combination with two reported domains of disability, was chosen. The addition of a neuropsychological test criterion for a diagnosis of PCD, as proposed in DSM-IV, was not supported, as neuropsychological tests poorly differentiated the injured from the uninjured group, and did not correlate with reported symptoms, not even when restricted to symptoms within the cognitive domain. In paper IV, the intermediate definition of PCD was used as the outcome measure in the study of prognostic factors.

Summary of assessments

The performed assessments are summarized within the described etiological model, see figure 5.

Figure 5. *Measurements*



Statistical methods

All sociodemographic variables were summarized using standard descriptive statistics such as mean, range, and frequency. Differences in discrete variables (e.g. sex and education level) were analysed with the c^2-method (Fisher's exact test in case of expected cell frequencies less than 6). Differences in continuous variables were analysed with non-parametric Mann-Whitney (independent comparisons) or Wilcoxon matched pairs test (dependent comparisons), as many distributions were positively skewed.
In paper I, all S 100 variables were dichotomized into normal or pathological levels based on the reference data from the control group. The classifications were made using the acute measurement. If the acute value was missing a conservative, non-biased method was used in order to increase the power of the analysis. Thus, the classification was then based on the value at day 1. If this value was missing too, the patient was withdrawn from the analysis.

In paper II, the factor structure of the two rating scales, RPQ and RHFUQ, was investigated with a principal component analysis (Varimax rotation). The number of factors extracted was identical to the number of eigenvalues greater than or equal to 1.0. Analysis of the RPQ data was made for symptoms reported at day one. Analysis of the RHFUQ data was made for disability reported at three months. The factor analyses were only performed on the ratings of the patients. All comparisons were two-tailed with a significance level of 5 percent.

In paper III, the relationship between the criteria sets were expressed as a phi coefficient, which is a product-moment correlation coefficient for dichotomized variables. The significance levels was 5 percent (two-tailed).

In paper IV, the continuous variables were dichotomized according to *a priori* criteria (e.g. median, 1 SD from the mean, or pathological cut-offs for GAF). A logistic regression analysis was performed and the results are presented as odds ratios (OR). A significance level of 5 percent was used for enter in the logistic regression analysis. The same significance level was applied in the explorative correlational analysis.

Results

The results in all papers refer to the same study population. Differences in numbers and proportions between the papers are explained by missing data for some of the variables – especially S 100 blood samples in the acute phase and neuropsychological evaluation at three months.

Sociodemographic and clinical characteristics

There were no statistically significant differences between patients and controls with regard to age, sex, years of education or occupational status. The most common cause for MTBI was fall (59 %). Of traffic accidents (19%), bicycle accidents were most common. Alcohol intoxication was present in 25 %. In 7 % of the patients signs of traumatic, intracranial lesion on CT or MRI scan were found. Complete data are presented in table 6.

Paper I

Forty-one percent of the patients had S 100B and 64 % had S 100A1B serum concentrations above cut off. Eight percent of the patients had signs of cognitive impairment according to APT and 30 % had cognitive impairment according to neuropsychological testing at 3 months post injury. The relationship between the results of the two classifications of cognitive impairment was weak but significant (phi=0.45, $p<0.001$). Forty-four percent of the patients reported one or more cognitive symptoms from the RPQ the first day, 45 % on day 7, 27 % on day 14 and 26 % at 3 months.

There were no significant correlation between the dichotomized APT data and S 100B ($\chi^2=0.14$, $p>0.05$) or S 100A1B ($\chi^2=0.30$, $p>0.05$). Nor were there any significant relationship between signs of cognitive impairment according to the neuropsychological test at three months and levels of S 100B ($\chi^2=1.61$, $p>0.05$) or S 100A1B ($\chi^2=0.30$, $p>0.05$), see figures 6 and 7.

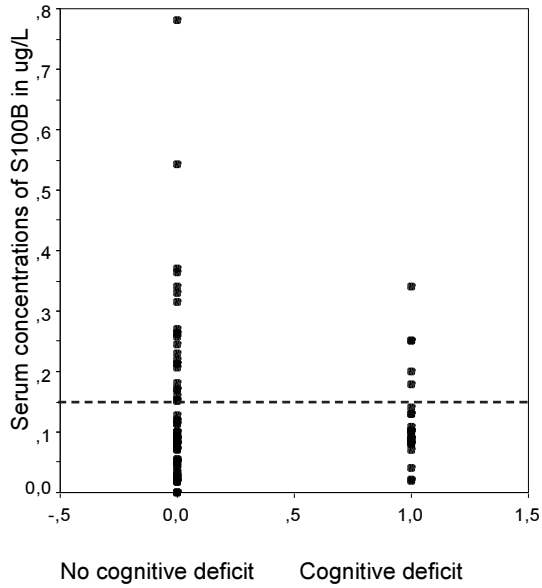
APT results improved significantly over time in several variables. However, self-reported cognitive symptoms were not related to cognitive impairment in the tests, and there was no difference in self-reported symptoms, at any timepoint, between patients with and without S 100 concentrations above cut off. Separate analyses of the relationship between time development of the performance according to APT and pathological S 100B and S 100A1B results did not show any significant interactions. Thus, there was no differ-

Table 6. *Sociodemographic and clinical characteristics of patients (n = 122) and controls (n= 35)*

Characteristic		MTBI patients	Controls
Age	Mean	37.3	39.0
	range	15 - 65	16 - 62
Gender, n (%)			
Men		71 (58)	17 (49)
Women		51 (42)	18 (51)
Education years	Mean	12.3	13.2
	range	3 - 19	9 - 17
Occupation, n (%)			
Working		88 (72)	29 (83)
Unemployed		2 (2)	0 (0)
Student		20 (17)	5 (14)
Sick leave		7 (6)	0 (0)
Disability pension		3 (3)	0 (0)
Retirement pension		2 (2)	1 (3)
Type of accident, n (%)			
Fall (from height)		24 (20)	N/A[2]
Fall (same level)		48 (39)	N/A
Traffic		23 (19)	N/A
Assault		9 (7)	N/A
Other [1]		18 (15)	N/A
Intoxicated by alcohol		30 (25)	N/A
GCS at first examination, n (%)			
15		109 (89)	N/A
14		13 (11)	N/A
Injury-related CT, and/or MRI abnormalities n (%)		8 (7)	N/A
Loss of consciousness, n (%)			
0 – 0.9 min		56 (46)	N/A
1 – 5 min		47 (39)	N/A
6 – 30 min		19 (15)	N/A
Anterograde amnesia, n (%)			
0 – 0,9 min		21 (17)	N/A
1 – 5 min		29 (24)	N/A
6 – 45 min		45 (37)	N/A
> 45 min		27 (22)	N/A
Retrograde amnesia, n (%)			
0 – 5 min		7 (6)	N/A
> 5 min		4 (3)	N/A

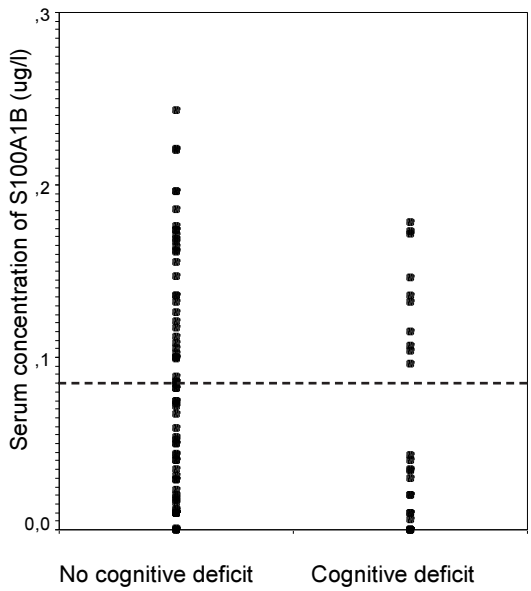
[1] Other types of accidents were: collision with other person in sports (6), hit by falling objects (6), run into objects (3), kicked by horses (3).
[2] Not Applicable

Figure 6. *S100B and cognitive impairment*



S100B in patients with (n=25) and without (n=71) signs of cognitive impairment according to APT or neuropsychological testing at three months. Cut-off level at 97.5 percentile of non-injured persons, 0.15 µg/L (hatched line).

Figure 7. *S100A1B and cognitive impairment*



S100A1B in patients with (n=25) and without (n=72) signs of cognitive impairment according to APT or neuropsychological testing at three months. Cut-off level at 97.5 percentile of non-injured persons, 0.085 µg/L (hatched line).

ence in the pattern of change over the sessions between patients with pathological S 100 and those without.

In summary, the diagnostic accuracy of S 100B and S 100A1B for MTBI was poor. Serum concentrations were not correlated to the severity of injury nor to symptom reports at three months post injury.

Paper II

Symptom character, frequency and course

Poor memory, sleep disturbance and fatigue were the most commonly reported MTBI related symptoms after three months, when frequency as well as intensity were taken into account. At day 1, 7 and 14 respectively, 86, 74 and 56 % of the patients reported one or more MTBI related symptoms. At three months, 49 % of the patients reported at least one such symptom.

A principal component analysis of the symptoms reported at day one yielded a four factor solution – somatic (headache, dizziness, nausea /vomiting and fatigue), cognitive (taking longer to think, poor concentration and poor memory), affective (feeling frustrated, restlessness, sleep disturbance, irritability and feeling depressed) and a fourth ”vision related” factor comprising symptoms related to vision (blurred vision, double vision, sensitivity to light) together with noise sensitivity, with a somewhat weaker loading. This factor solution explained 66 percent of the total matrix variance. The factor structure remained invariant throughout the observation period. The factor analysis is presented in table 7.

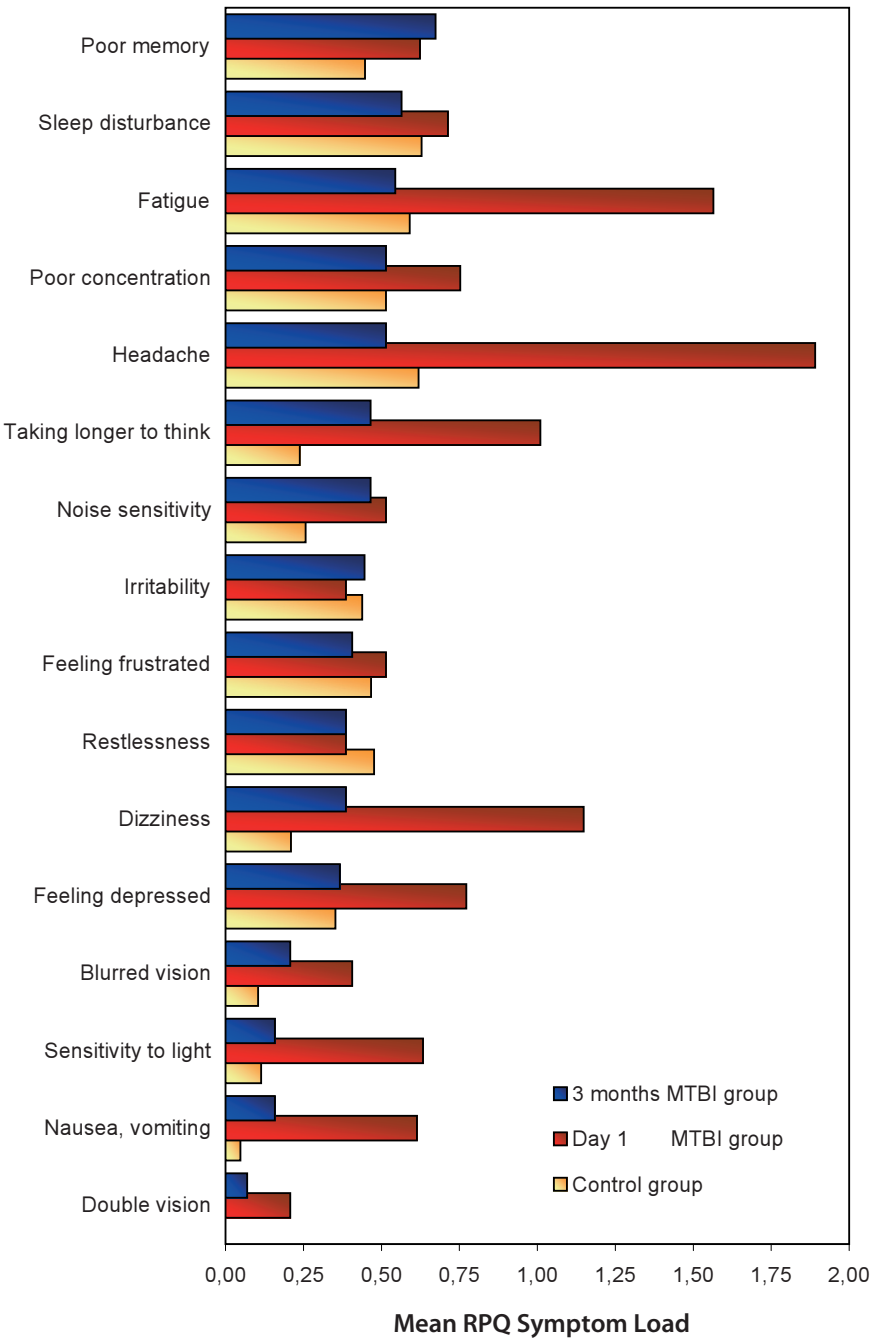
The course from day one to three months varied between symptoms. Some symptoms (headache, fatigue, taking longer to think, dizziness, sensitivity to light and nausea/vomiting) decreased markedly from day one to the assessment at three months. Some symptoms (sleep disturbance, poor concentration, noise sensitivity, feeling frustrated, blurred vision and double vision) decreased less whereas other symptoms (irritability, restlessness and poor memory) increased during the three months follow up. Statistical analysis of the differences between patients and controls was not feasible as the prerequisites for assessment were different – MTBI patients assessed change from baseline whereas controls assessed symptoms at baseline. The most obvious

Table 7. *Four factor structure of MTBI symptoms rated by the patient at the day after the injury.*

	Principal components				
Symptom	**I**	**II**	**III**	**IV**	**h^2**
Somatic symptoms					
Headache	*0.81*	0.05	0.11	0.09	0.67
Dizziness	*0.73*	0.16	0.25	0.06	0.62
Nausea, vomiting	*0.72*	0.14	0.08	0.07	0.55
Fatigue	*0.61*	0.19	0.42	0.11	0.59
Vision related symptoms					
Double vision	0.09	*0.82*	0.21	0.16	0.75
Blurred vision	0.03	*0.82*	0.16	0.10	0.70
Sensitivity to light	0.31	*0.70*	0.12	0.15	0.62
Noise sensitivity	0.42	*0.54*	0.28	0.25	0.60
Cognitive symptoms					
Taking longer to think	0.27	0.16	*0.86*	0.15	0.85
Poor concentration	0.21	0.18	*0.81*	0.23	0.79
Poor memory	0.18	0.28	*0.80*	0.14	0.77
Affective symptoms					
Feeling frustrated	-0.01	0.01	0.19	*0.80*	0.67
Restlessness	0.04	0.38	-0.02	*0.70*	0.65
Sleep disturbance	0.42	0.11	0.21	*0.58*	0.57
Irritability	0.17	0.47	0.26	*0.56*	0.63
Feeling depressed	0.48	0.17	0.24	*0.50*	0.56
Percentage explained variance	*41.0*	*10.4*	*7.5*	*7.4*	*66.3*

Loadings in italics indicate the highest factor loading/correlation for that variable, and those which are underscored a significant loading (>0.40). The proportion of explained variance for a variable is expressed as a communality index (h^2).

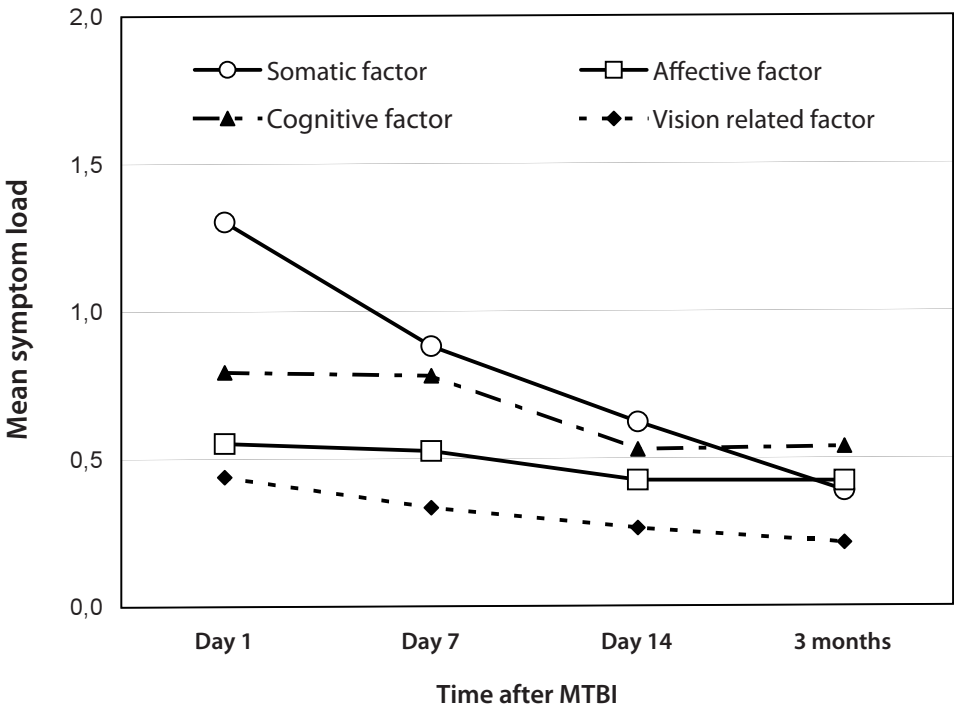
Figure 8. *Rank order of symptoms*



differences, however, between patients and controls at three months were the higher frequency of noise sensitivity, dizziness, blurred vision and slowness of thought in the MTBI group. The rank order of symptom intensity in MTBI patients differed from that in healthy controls, where sleep disturbance and headache had the highest load, see figure 8.

The course of symptoms within the four different factors was similar, with a gradual decline of symptom load. Somatic symptoms were initially more prominent but declined faster than symptoms in the other factors, resulting in a similar symptom load for somatic, cognitive and affective factors at three months. Vision related symptoms were less prominent and reported by few patients only. High symptom load at day ne was significantly correlated with high symptom load at three months ($\tau = 0.38$; $p < 0.01$). The course of symptoms is presented in figure 9.

Figure 9. *Course of symptoms*



Symptoms and disability

A factor analysis of the disability assessed with RHFUQ at three months yielded two factors, which explained 75 % of the total matrix variance. The first factor – "activity factor" – embraced social and professional activities outside the family, and the second factor – "relation factor" – had reference to closer relations, e.g. family and friends. Four items had significant loadings, i.e. correlations, with more than one factor and were thus insufficiently separated by the factors. The only items that were satisfactorily separated were item 5 ("previous leisure activities") and item 9 ("relationship with partner"). The factor analysis is presented in table 8.

Table 8. *Two factor structure of disability rated three months after MTBI.*

	Principal Component		
Disability	**I**	**II**	**h^2**
Activity Factor (I)			
Previous leisure acitivities	*0.83*	0.08	0.70
Previous social acitivities	*0.78*	0.42	0.78
Routine domestic activities	*0.76*	0.28	0.65
Conversation with one person	*0.73*	0.40	0.70
Conversation with two or more persons	*0.72*	0.34	0.64
Previous work load/standard	*0.70*	0.55	0.79
Work more tiring	*0.65*	0.56	0.70
Relation Factor (II)			
Relationship with partner	0.16	*0.94*	0.91
Coping with family demands	0.35	*0.87*	0.88
Relationships with friends	0.48	*0.73*	0.76
Percentage explained variance	*65.0*	*10.3*	*75.3*

Loadings in italics indicate the highest factor loading/correlation for that variable, and those which are underscored a significant loading (>0.40). The proportion of explained variance for a variable is expressed as a communality index (h^2).

At three months, 25 % of the patients reported dysfunction in at least one domain of everyday life, such as work, relations, and social and leisure activities. Subjects with high total RPQ also tended to have high total RHFUQ ($\tau = 0.60$; $p < 0.001$). The four symptom factors (somatic, affective, cognitive, vision related) showed similar correlation with the two disability factors (relations, activity) ($\tau = 0.23 – 0.42$, $p < 0.01$) with a marginally higher correlation between the affective factor and the relation factor as compared to the activity factor (0.42 vs. 0.33), and vice versa for the somatic factor (0.23 vs. 0.34).

Paper III

The number and frequency of cases according to the three different case definitions are presented in table 9.

Table 9. *The number and frequency of cases fulfilling the criteria for PCD and PCS according to the three different definitions. Only 88 (86%) of the patients completed the neuropsychological investigation.*

	Criterion met	yes (%)	n	Case
3 symptoms	S-criterion	37 (36)	102	ICD-10 case
2 disabilities	D-criterion	19 (19)	102	
	S + D criterion	17 (17)	102	”Intermediate case”
Cognitive impairment	NP-criterion	25 (28)	88	
	S + D + NP criterion	4 (5)	88	DSM-IV case

Thirtysix percent (n=37) of the injured patients met the S-criterion for PCD. When the D-criterion was added, only 17 % (n=17) of the patients remained cases. Of the 19 patients that met the D-criterion, 89 % (n=17) also fulfilled the S-criterion. Thus, the addition of the D-criterion narrowed the case definition but the remaining cases were recruited from essentially the same group of patients. The addition of the NP-criterion further reduced the number of cases considerably, from 17 % to 5 %. However, there was poor correlation between the S+D-criterion and the NP-criterion, see table 10.

Sixteen % of the controls were also by the blinded rating procedure classified to meet the NP criterion, although there was no history of head injury or any other disorder or circumstances that explained the cognitive difficulties. The difference between cognitive impairment in the MTBI group as compared to non-MTBI controls did not reach statistical significance (p = 0.16). The agreement in the injured group between reported cognitive problems and demonstrable cognitive deficits in neuropsychological tests was also poor, see table 11.

Table 10. *Correlation between reported symptoms and disability (S+D criterion) and observed cognitive impairment (NP criterion).*

		NP criterion		
		no	yes	total
intermediate case (S+D criterion)	no	52	21	73
	yes	11	4	15
	total	63	25	88

Table 11. *Correlation between reported cognitive problems and observed cognitive impairment (NP criterion).*

		NP criterion		
		no	yes	total
reported cogn problems	no	52	17	69
	yes	11	8	19
	total	63	25	88

Correlation coefficient 0.048 (n.s.)

Paper IV

Seventeen (17 %) of the 102 patients completing the three months follow up fulfilled case criteria for PCD, according to the intermediate case definition previously described. Twenty-four out of the 102 patients had a history of psychiatric disorder, 16 had a current psychiatric disorder and 10 had both. Twelve patients had a concurrent, disabling somatic disorder. The clinical characteristics of the psychiatric and medical disorders are presented in tables 12 and 13.

Table 12. *Previous and concurrent psychiatric disorder (n=102).*

Prior	*n*	*Concurrent*	*n*
Mood disorder	14	Mood disorder	1
Anxiety disorder	1	Anxiety disorder	4
Eating disorder	3	Eating disorder	0
Adjustment disorder	4	Adjustment disorder	1
Somatoform disorder	1	Somatoform disorder	2
Subst related disorder (amphetamine misuse)	1	Subst related disorder (alcohol in all cases)	4
		Personality disorder (narcissistic, obsessive, NUD (2))	4
Sum	24	*Sum*	16

Diagnostic class according to DSM-IV
In each column there is only one diagnosis per individual
Ten of the patients with concurrent disorder also had a history of psychiatric disorder

Table 13. *Concurrent somatic disorders implying disability (n=102).*

Somatic disorder	*n*
Orthopedic conditions (Low back pain (2), knee problems (2), st post whiplash)	5
Miscellaneous (MS, aortic stenosis, sarcoidosis, breast cancer, st post abdominal surgery)	5
Fibromyalgia	2
Sum	12

One diagnosis per patient

Table 14. *Univariate correlation analysis using PCD case as the dependent variable.*

Variables	Cut off	PCD Case	P value
Sociodemographic variables			
Age	> 40 years	.00	1.000
Gender	female/male	.224*	.024
Cohabitation	Yes/no	- .101	.314
Years of education	>12 years	.008	.936
Pre-traumatic variables			
Psychiatric disorder (previous or concurrent)	Yes/no	.289*	.003
Previous psychiatric disorder	Yes/no	.248*	.012
Concurrent psychiatric disorder	Yes/no	.169	.090
Family history for psychiatric disorder	Yes/no	.246*	.013
General medical condition	Yes/no	.407**	<.001
Long term sick-leave prior to the injury	Yes/no	.295**	.003
Previous MTBI	Yes/no	.139	.160
Number of psychosocial stressors	>3	.366**	<.001
Perceived distress from stressors	>moderate	.285*	.017
Self-assessed GAF			
The year before the injury	GAF-1 <71	- .375**	<.001
The two weeks prior to the injury	GAF-2 <71	- .346**	<.001
Swedish Scales of Personality (SSP)			
Somatic trait anxiety	> T-score 55	.202*	.041
Psychic trait anxiety	"	.034	.736
Stress susceptibility	"	.104	.300
Lack of assertiveness	"	- .029	.775
Impulsiveness	"	.030	.765
Adventure seeking	"	- .019	.851
Detachment	"	- .002	.981
Social desirability	"	.008	.933
Embitterment	"	.197*	.047
Trait irritability	"	.072	.471
Mistrust	"	.116	.247
Verbal trait aggression	"	-.120	.231
Physical trait aggression	"	.003	.973
Sence Of Coherence Scale (SOC)	>145	-.152	.129
Audit	>7	- .166	.110
Injury related (precipitating) variables			
Glasgow Coma Scale (GCS)	15/14	- .163	.101
Loss Of Consciousness duration (LOC)	> 5 min	- .003	.978
Posttraumatic amnesia duration (PTA)	> 15 min	.072	.468
Brain imaging changes (CT; MRI)	Yes/no	.087	.386
Alcohol intoxication when injured	Yes/no	-.200	.054
Type of traumatic event			n.s.
Post-traumatic variables			
IES – R			
Intrusion	>14	.374**	<.001
Avoidance	>11	.138	.170
Arousal	>11	.539**	<.001
HADS			
Anxiety	>7	.483**	<.001
Depression	>7	.453**	<.001
RPQ	>17	.637**	<.001

Univariate correlation analysis

Univariate correlation analysis was performed using the sociodemographic, pre-traumatic, injury related and post-traumatic variables as the independent variables and PCD case as the dependent variable. Gender, as well as a number of pre- and posttraumatic variables were correlated with PCD but none of the injury variables. The data are summarized in table 14.

Stepwise logistic regression analysis

To identify the significant predictors and their unique contribution to the outcome, a stepwise logistic regression analysis was performed, in which all variables were entered. Posttraumatic hyperarousal (OR 9.08), presence of a disabling medical condition (OR 6.19), female gender (OR 5.54) and a high number of psychosocial stressors (OR 11.93) all had unique and independent contributions to the outcome, see table 15. The intercorrelations between these predictors were weak, sharing a maximum of 4.5 % of the variance, see table 16.

Table 15.
Odds Ratios for the variables significantly contributing to PCD after MTBI.

Variables	β	*SE*	*p*	*OR*	*95 % CI for OR*
Hyperarousal	***2.21***	***.72***	***.002***	***9.08***	***2.23 to 37.00***
Disabling somatic condition	***1.83***	***.84***	***.029***	***6.19***	***1.21 to 31.78***
Female gender	***1.71***	***.79***	***.030***	***5.54***	***1.18 to 26.02***
Psychosocial stressors	***2.48***	***.92***	***.007***	***11.93***	***1.96 to 72.53***

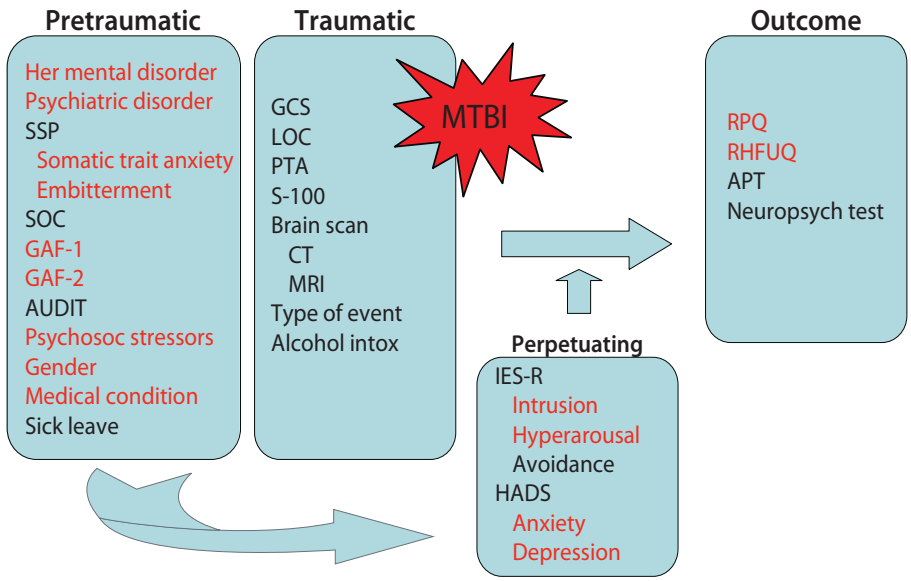
Table 16. *Correlations between the variables in the stepwise logistic regression analysis.*

	Psychosocial stressors	*Female gender*	*Somatic condition*	*Hyperarousal*
Psychosocial stressors	***1***	***-.095***	***.208****	***.180***
Female gender	***-.095***	***1***	***.197****	***.060***
Somatic condition	***.208****	***.197****	***1***	***.226****
Hyperarousal	***.180***	***.060***	***.226****	***1***

Summary of results

The results are summarized in figure 10. Variables with significant univariate correlation to the outcome are highlighted in red.

Figure 10. *Summary of results.*



Discussion

Methodological issues

Outcome measures

In previous research many different outcome measures have been used, which has complicated comparisons between studies. One aim in this study was to explore outcome measures with regard to reliability, validity and utility. In Paper III we investigated the applicability of the two existing definitions of PCD on the investigated cohort of patients. A case definition only based on symptoms, as suggested in the ICD-10, was considered unsatisfactory from clinical points of view, and a measure of disability was added in order to increase clinical validity.

The measures chosen for the study, RPQ and RHFUQ, did not only include frequency of symtoms or disability in a "yes" or "no" fashion but also provided measures of intensity, i.e. if the symptoms were experienced as mild, moderate or severe. Using "three symptoms" as the starting point, as this was the required number of symptoms in the ICD-10 as well as the DSM-IV definition of the disorder, we also considered one mild symptom in combination with a severe symptom, or two symptoms of moderate intensity, as "case criterion", as this combination resulted in the same "symptom load" in terms of RPQ score (6). However, as this represented a deviation from the original criteria, we decided to use the "three symptoms" case criterion. In fact, in our cohort of patients, the two different ways of defining the case criterion resulted in the same number of cases. The mean RPQ score among cases was 27.1 (range 6 – 53) and only one of the cases, with three "mild symptoms", scored 6 on the RPQ.

It should be recognized that the choice of number of symptoms is arbitrary and justified more by conveniance than by research evidence. Moreover, increased symptom reporting is associated with both female gender and chronic distress [86, 87] and, thus, its relation to disease pathology is complex.

A dimensional, non-cathegorical approach to assessment would also be defendable and appropriate, especially in clinical settings, as obvious disease

pathology is rarely at hand and there are no valid objective signs that help the clinician to differ the healthy from the ill. Again, for purposes of research in this study, we arrived at chosing a definite cut off in order to focus on subjects with a severity of illness that was considered clinically relevant.

Further, the use of checklists have been criticized [90] as they have been shown to increase symptom reporting, possibly by increasing attention to possible areas of discomfort, leading to negative expectations and worse outcome [91].

The internal construct validity of the RPQ was recently studied by use of a Rasch Measurement model. The RPQ items were found to represent two separate constructs and it was recommended that they should not be summated in a single score [88]. In another study, a confirmatory factor analysis of the RPQ supported the notion of postconcussion symptoms as a collection of associated but at least partially separable cognitive, emotional and somatic symptoms. The different factors might imply different disease mechanisms, and it is concluded that PCS, as measured with RPQ, might be viewed as an "overarching umbrella term" that describes a range of different symptoms that arise for different reasons subsequent to (although not necessarily directly because of) a TBI [89].

Neuropsychological impairment after MTBI has been demonstrated in several studies [27, 39-41]. However, in most studies cognitive dysfunction resolve within weeks or after a couple of months [38] and in cases with persisting problems, factors other than the MTBI have been associated with worse outcome [28]. DSM-IV suggests "evidence from neuropsychological testing or quantfied cognitive assessment of difficulty in attention or memory" as criterion for PCD. To investigate the applicability of the DSM-IV definition on the current cohort, two different methods of establishing the incidence of cognitive impairment were used, as described in the Methods section. The APT did not show any significant differences between patients and controls. Twenty-seven percent of the patients had cognitive impairment after three months according to the elaborated cognitive impairment case definition. However, 16 % of the controls also had cognitive impairment according to the definition, although they had no recent history of head trauma. Moreover, there was poor correlation between demonstrated and subjectively reported cognitive impairment. Thus, we did not consider "evidence from neuropsychological testing or quantfied cognitive assess-

ment of difficulty in attention or memory" a justified criterion for PCD. One could of course argue that the few individuals fulfilling case criteria according to DSM-IV were the "true cases". However, this would result in decreased descriptive validity by exclusion of the majority of patients attending for problems following MTBI, which would obviously also decrease clinical utility.

Conceptual considerations

Overlapping symptoms or comorbidity or differential diagnoses
It has been recognized that the symptoms charaterizing PCD are unspecific [92] and overlap with the symptoms described in other injured groups [28], in chronic pain patients [35, 93, 94] and even in the general population [34]. In a study of depressed patients, approximately 9 out of 10 patients with depression met liberal ICD-10 self-report criteria for a PCS and more than 5 out of 10 met conservative criteria for the diagnosis. In a retrospective study of history of head injury, cognitive or psychosocial difficulties scores on Postconcussion Checklist did not vary by self-report of head injury but was significantly correlated with Beck Depression Inventory, suggesting that general level of psychological distress is a key factor in postconcussional symptoms [95]. PTSD is another known sequel after MTBI, and postconcussive symptoms are significantly correlated with PTSD symptoms, indicating that postconcussive symptoms may be mediated by an interaction of neurological and psychological stressors after MTBI [96].

It might thus be argued that a clinical investigation would be of crucial importance for a correct classification of the condition at three months. However, to avoid assessment bias on behalf of the investigating doctor, it was decided to accept the patients´ subjective reports of symptoms and disability and their attributions of the symptoms to head injury. One reason for this decision was that hospital doctors find it impractical, partly because of time constraints, to assess emotional problems in patients and many doctors do not refer for psychiatric evaluation because of fear of stigmatising the patient [97]. It is thus likely that in most clinical encounters, i.e. in common clinical practise, the patients symptom reports and attribution of symptoms to the head injury, if not evidently inappropriate, will be accepted at face value by the doctor and that psychiatric differential diagnoses in most cases will not be considered.

If PCD and PTSD or depression overlap phenomenologically, if PCD hardly occur without a significant anxiety/affecitve component, and there is no point of rarity or biological marker to differ between the conditions – what should guide the clinician when establishing the diagnosis? In clinical practise this is less of a problem when the physician can adapt a dimensional approach, summarize the condition in terms of "not only PCD but also…" and taylor the symptomatic treatment regardless of the etiology. In forensic contexts, however, there is often a forced choice situation, when causality has to be approved of or rejected, with substantive consequenses for the patient in terms of financial compensation. For researchers there is no simple, straightforward solution to this dilemma. In this study, the subjective experience of the patients has been recognized and their attributions to the head trauma accepted and not called into question as this attitude probably comes closest to common clinical practise. However, we are aware of the shortcomings of this alternative.

It is this author's personal view that the consequenses of TBI can be interpreted along a biopsychosocial spectrum. In severe TBI, psychological variables will have less impact on the clinical outcome, but the milder the injury, the greater the impact from psychosocial factors. In the mild end of the severity spectrum, brain injury factors will be of less importance and interacting psychological and social factors will account for the majority of the perceived disability, whatever the patient´s attributions. The task for the doctor is to evaluate, in a non-judgemental way, the possible determinants of illness and try to assist in restoring function and well-being.

Strengths of the study

Standard inclusion criteria

The inclusion criteria were in accordance with the currently most commonly used definition proposed by the American Congress of Rehabilitation Medicine [98]. Loss of consciousness or posttraumatic amnesia were required, i.e. not only alteration of consciousness, to ensure a substantial effect of the injury on cerebral function. Focal lesions, visualized with brain imaging, were accepted if they were transient and as long as the clinical course in all other respects was consistent with MTBI and no major neurological loss of functions was present. The definition of MTBI also comprises patients with GCS 13 on arrival, but in this study only patients with GCS 14 – 15 were included. Patients with GCS 13 constitutes only 5 % of the whole

MTBI population[1]. Thus, the patients in our study represent the vast majority of patients within the "mild spectrum". Furthermore, it has been argued that patients with GCS 13 should not be included in the MTBI group, since those patients have a similar risk of intracranial lesions as patients with moderate TBI [3].

Assessment of premorbid factors and the use of prospective design

P remorbid factors were thoroughly assessed immediately after the injury, when recall bias, a major confounder in other studies of premorbid factors [99], is minimal and unlikely to affect the results. The study had a prospective design and included all patients within the first 24 hours after the trauma, when injury related factors could be reliably assessed. The sample consisted of consecutive patients, that were selected on the basis of injury criteria and not for postconcussive complaints. The assessment of premorbid factors was thus performed without knowledge of the outcome, that might otherwise have biased the assessments, from the part of the investigator as well as the patients. The data collection was exhaustive, yielding an opportunity to analyze and compare the impact of a large number of predisposing as well as injury related variables.

The case definition

The elaborated case definition included validated measures of symptoms as well as disability, yielding a more complex outcome measure with increased clinical utility as compared to most previous studies using outcomes only based on symptoms or single neuropsychological measures of cognitive impairment. Clinical assessment of the outcome might have resulted in a more valid diagnosis of PCD. However, as the nature of the condition is ambiguous as well as controversial and, in essence, based on subjective reporting of symptoms and disability, self-assessments were used in order to avoid bias from the part of the investigator (see above). The symptom scale, RPQ, has been shown, though, to be reliable in self-administered as well as clinician-administreded settings [84]. Neither the individual related nor the injury related independent variables correlated with signs of cognitive impairment in neuropsychological tests, and the case definition of PCD did not take neuropsychological test results into account, as these had insufficient specificity and were considered to represent another illness dimension with little association to symptoms and disability, as demonstrated in Paper III.

[1]The proportions in the mild spectrum are: GCS 13 5 %, GCS 14 17 % and GCS 15 78 % (n = 11859), calculated from Servadei et al, 2001.

Limitations of the study

As discussed above, a possible confounder was the overlap of criteria between independent variables that included emotional symptoms (psychiatric disorder, HADS, IES-R) and the outcome variable, as emotional symptoms are also part of the symptom cluster in RPQ. However, the correlation analysis was repeated using the different factors of the RPQ – somatic, cognitive and affective factor [100] – as dependent variables, with basically the same result (data not shown). Thus, the predictors for adverse outcome were the same, irrespective of whether affective symptoms were included or not in the outcome measure.

Non-participation rate was high, 73 % during the three months when attrition was studied in detail, which is a recognised problem in this kind of study. Incentives were not used for the injured population as this was considered a risk for bias in the selection of patients. Non-participants most often claimed lack of time or motivation to adhere to the extensive evaluation programme. The high attrition rate calls the external validity in question. In a follow up of a condition that are oftenly not considered dangerous, there might be a risk to gain a hearing from persons with high concern about their health, which might in turn bias the results towards higher symptom reporting. The proportion of patients in this study with persistant complaints was not higher, though, than in studies with a less demanding design. The high non-participation rate probably reflected the rather exhaustive follow up programme, including several visits, time concuming testings and painful blood samples.

Participants as compared to non-participants had higher hospitalisation rate (80 vs. 53 %), higher CT scan examination rate (93 vs. 60 %) and more CT scan abnormalities (7 vs. 0 %) indicating that the participating MTBI patients represented a more severely injured group than the non-participants. This is in accordance with the findings in a recent Canadian study on the recruitment bias in an outcome study after MTBI, in which the participants group was biased toward those with more significant injuries [101].

Considerable efforts were made to include a control group with orthopedic injuries but without injury to the brain. It was not possible, though, to find volonteers for the extensive follow up programme, as the questions at issue had little reference to the orthopedically injured population. To generate normal data for the neuropsychological tests and for measurements of S 100,

a control group of 35 non injured individuals was included instead. As symptom reporting according to the questionnaire implied that the proband had suffered an injury and was asked to report change in symptoms after the injury, the use of a non injured population rendered quantitative comparisons of symptoms between the injured and the non injured groups irrelevant. An arbitrary comparison between symptom reporting was finally included in the paper, though, to show that the rank order was somewhat different between the groups indicating that the symptoms in the injured group did not only represent a reinforcement of otherwise commonly experienced symptoms in the population.

Paper I

A substantial proportion of the patients with MTBI had S 100B and S 100A1B concentrations above cut off. Furthermore, a considerable proportion reported symptoms and had signs of cognitive impairment. However, we found no statistically significant association between either reported symptoms or signs of cognitive impairment and the S 100 abnormalities. Thus, our data did not support S 100B or S 100A1B as diagnostic tools for predicting cognitive impairment after MTBI. This is in contrast with other studies, where an association between S 100B and persisting symptoms [102], cognitive impairment [103] and disability [104] have been reported in patients with TBI of varying severity. For example, in the study by Herrmann et al, where acute S 100B predicted long term cognitive impairment after MTBI, CT or MRI scan showed abnormalities in 48 % of the patients. In our sample, the frequency of radiological abnormalities were 7 %, which is similar to the frequency reported in studies of unselected patients with MTBI with a GCS score of 15 [6]. It might also be pointed out that the function of the S 100 proteins are not fully characterised, and that S 100B seems to exert, depending on its concentration, neurotrophic as well as toxic effects [19].

The evaluation of cognitive impairment after MTBI is complicated. Meta-analytic studies show only small and non-significant overall effect sizes, that with increasing time post injury tend to zero [105]. Poor correlation between subjective complaints and cognitive performance has also been found in previous studies [106] and conditions such as pain [107] and depression [108, 109] influence cognitive function. In our study, the classification of cognitive impairment was developed in order to minimize the influence of confounding factors such as premorbid function, pain and

depression. Nevertheless we did not find an association between the release of S 100 proteins and cognitive impairment.

Paper II

Factor analysis yielded four symptom domains: a somatic, a cognitive, an affective and a vision related domain. Somatic symptoms predominated in the early phase but at three months somatic, cognitive and affective symptoms had similar weight, whereas vision related symptoms were reported by only few individuals and had lower total impact. Similar findings have been reported in previous studies at follow-up, but to our knowledge the early time course of symptom constellations has not previously been demonstrated.

The vast majority (86 %) of the MTBI patients reported one or more symptoms the day after the injury and about half reported at least one persisting symptom at three months after the injury. The most prominent symptoms experienced after three months were poor memory, sleep disturbance and fatigue. This corresponds well with the findings of the original studies with the RPQ, in which fatigue, irritability, frustration and poor memory were the most prevalent symptoms at six months [84, 110]. The findings differ, however, from other studies reporting headache, dizziness, fatigue and difficulty in concentration [26]; headache, irritability and dizziness [25]; headache, decreased energy and dizziness [27]; concentration problems and restlessness [34] or headache and concentration difficulties [28] as the most common symptoms at follow-up. One reason for this discrepancy might be that RPQ assesses *change in symptoms*, whereas other studies use assessment instruments capturing *total symptom load* which, at least theoretically, is a combination of baseline symptoms and symptom change after the trauma. It might be argued that the total symptom load is a more adequate measure of the patient's suffering. However, with regard to the interpretation of prognostic factors for a poor outcome after MTBI, we consider symptom change after the injury crucial. The total load of MTBI related symptoms at day one correlated significantly with symptom load at three months, indicating that early symptoms, as assessed by the RPQ, might be useful to predict persisting symptoms. This supports the finding in the study by King, in which RPQ score at 7-10 days after injury correlated with RPQ score at three months (τ=0,48; $p<0,01$) [77].

The rank order of symptoms in MTBI patients differed from that in healthy, non-injured subjects. As symptoms were assessed by use of a questionnaire

that was developed for subjects who had suffered an injury, the interpretation of these data must be cautious. However, the observed difference in rank order indicates that symptoms persisting after MTBI are not only an amplification of symptoms that are common in the general population but that the symptoms after MTBI have some specificity, not only in the early post-acute phase as demonstrated in previous studies [111]. In a study comparing MTBI patients 12 months after the injury with chronic pain patients by use of RPQ, some condition specific symptoms were reported. The MTBI patients reported significantly more subjective cognitive symptoms whereas the chronic pain patients showed a trend towards reporting more emotional maladjustment [35].

One fourth of the patients reported injury-related disability at three months after the MTBI. Symptoms correlated significantly with disability. Although disability in the presence of symptoms could be inferred, this issue has only rarely been explicitly addressed in previous studies. In a study by Crawford et al [85], the correlation between the sum of total ratings from the RHFUQ and RPQ after three months was good (τ=0,67; p<0,001). Our findings also support this association between symptoms and disability.

In summary, the study showed that self-reported MTBI related symptoms gradually decline post-injury and that symptoms correlate with disability at three months. Patients with high symptom load in the early post-injury phase are at risk for developing persisting complaints.

Paper III

In the population having suffered an MTBI, our study delineates two possible problem domains with only limited overlap. One domain consists of reported symptoms and disability, the other of demonstrable signs of cognitive dysfunction in neuropsychological assessment, possibly caused by the head trauma. The poor correlation between these two illness dimensions is illustrated by the dramatic drop in case frequency, from 36 to 5 %, when the more complex DSM-IV case definition is employed instead of the symptom based ICD-10 case definition. The result is consistent with previously reported findings [50, 52]. The addition of the NP-criterion, i.e. signs of cognitive dysfunction in neuropsychological tests, according to the DSM-IV definition as compared to the ICD-10 definition thus results in low concordance between the two definitions.

It is not possible to establish a numerical cut-off level as a golden standard in neuropsychology for what is regarded as clinically impaired performance in the borderline region, i e around 1 SD below the mean. For example, a statistically normal performance by a person with previous high intellectual function might imply impairment after trauma. Attempts to quantify impairment through statistical procedures have shortcomings when compared to clinical decision making, where a number of interacting variables, such as premorbid intellectual level, earlier brain trauma, socioeconomic factors and education are taken into account. In the present study a rigorous attempt, as described in the methods section, was made to ensure high reliability of the assessment of cognitive impairment. This was achieved through an a priori standardisation of the clinical decision process and an estimate of the reliability of the process by comparison of two or three independent evaluators. However, there is a possibility that the validity of the neuropsychological assessment was weakened by the blinded rating procedure, since crucial information on history of the head injury was omitted.

Selection of measurement methods and targeting dysfunction is another crucial area. The neuropsychological tests were selected in order to detect possible effects of the trauma, primarily on memory and attention. Another set of tests, assessing for example executive functions, might have been more sensitive to the effects of the trauma as has been suggested [112]. The tests used and the cut off levels chosen for defining "impairment" were in agreement with established clinical neuropsychological praxis. The difference between injured patients and uninjured controls did not reach statistical significance, though, and the high number (16 %) of possible cases in the control group calls into question whether the chosen cut off level was too inclusive. There was, however, a trend towards more signs of dysfunction in the injured group, and the lack of statistically significant differences may also reflect low power due to small sample size. The failure to reliably establish the presence of persistent cognitive deficits at the individual level in the MTBI patients is supported by some previous studies [113]. Some other studies, though, report small but non significant effects in domains like working memory/attention and speed of processing [105]. Although the evidence so far makes the diagnosis of the PCD still rely on subjective reports only, this does not exclude, of course, cognitive deficits as a result of the concussion in individual cases.

In the current study there was also poor correlation between neuropsychological test performance and reporting of cognitive symptoms. Other

researchers have reported corresponding low correlation between reported cognitive symptoms and objective function in healthy subjects [114]. In the current study a majority (68 %) of the patients with demonstrable cognitive dysfunction did not report any subjective cognitive problems. Instead, reported cognitive problems exhibited a strong association with symptoms in the affective and somatic domains. The results of previous studies of patients with mild or moderate TBI are not consistent and indicate good [40, 115] as well as poor [106, 116, 117] correlation between symptoms and objective markers for cognitive dysfunction. In a recent study by Chamelian on patients with TBI, evidence of cognitive dysfunction was found in patients with subjective cognitive complaints. In most, but not all patients, the objective deficits were linked to comorbid major depression. When major depression was controlled for, the differences between those with and without subjective complaints disappeared on most cognitive tests, indicating a close association between mood and cognition [109].

The lack of objective markers for the condition, although commonly considered crucial for the validity of a medical diagnosis, is far from uniqe. It is characteristic for most psychiatric conditions as well as for the so called functional somatic syndromes, that are characterized more by somatic symptoms, suffering and disability than by disease-specific, demonstrable abnormalities of structure or function [118]. Without a marker for the condition the definition of PCD must rely on the reporting of subjective symptoms, as this will be the main reason for most people to seek medical attention. Furthermore, as an indication of clinical significance, a disability criterion should be added to the symptom based definition in ICD-10. Admittedly, the cut off between disorder and non-disorder is arbitrary and "cases" only represents the outer edge on a continuum of distress.

Well defined criteria are necessary for diagnostic reliability and was the unquestionable advantage with the introduction of DSM-III in psychiatry. Diagnostic validity, however, still remains a major problem in psychiatric classification, as specific markers for most disorders are lacking and the evidence for diagnosis is essentially phenomenological and behavioural-descriptive [119]. The same holds for a diagnosis of post-concussional disorder. The face validity of postconcussional problems is high – as most people have problems in the acute phase after the trauma it seems reasonable that some people also develop persistent symptoms. However, although attribution of the symptoms to effects of the head injury seems logical and

straightforward, the association is not uncomplicated and there are diverging opinions within the medical society about the nature of the illness. The criticism for insufficient specificity of the symptom cluster following head injury [28, 34, 35, 53, 93, 94, 120, 121], is another viewpoint, likewise raised for the functional somatic syndromes [42]. Although these obvious shortcomings attenuate the validity of the diagnostic category, it still appears sensible as well as useful to maintain the concept for clinical purposes and to enable further research.

The proposed DSM-IV definition of PCD seemingly tries to avoid the weaknesses inherent in the diagnosis, not only by demanding measurable signs of cognitive deficits but also by requiring a "significant cerebral concussion", as described in the introduction. The suggested severity threshold puts the required injury at a more severe end of the head injury severity spectrum, where posttraumatic sequelae are common and less often give rise to diverging opinions in the clinical assessment. It still, though, leaves out the vast majority of cases with a less severe concussion but nevertheless with persisting symptoms a couple of months post injury. The trend in MTBI research has instead been to adhere to the definition proposed by the American Congress of Rehabilitation Medicine, where neither loss of consciousness nor amnesia is required [98]. The high thresholds of the DSM-IV definition of concussion exclude several of the patients normally comprised in an MTBI population and thus appears less useful.

The label of the condition is a related issue giving rise to diverging opinions. In ICD-10 and DSM-IV the terms "syndrome" and "disorder" are used, respectively. The difference between these two labels is not distinct. According to Merriam Webster Online Medical dictionary "syndrome" means "a group of signs and symptoms that occur together and characterize a particular abnormality or condition", whereas "disorder" is defined just as "an abnormal physical or mental condition". Moreover, "syndrome" is often used for more specific and medically well defined conditions like Rett´s or adrenogenital syndrome, whereas "disorder" is commonly applied to less well defined conditions, often within the psychiatric domain, like bipolar or panic disorder. Given the relatively unspecific and subjective character of the postconcussional problems that are not attributable to any demonstrable pathologic changes, we consider the term "postconcussional disorder" a more appropriate label.

In summary, the addition of a neuropsychological test criterion for a diagnosis of PCD, as proposed in DSM-IV, is not supported by our data. Although there was a tendency to more cognitive deficits in the MTBI group, the test poorly differentiated the injured from the uninjured group. Further, the test results did not correlate with reported symptoms and disability, not even when restricted to symptoms within the cognitive domain. We therefore advocate that the diagnosis of PCD should still be based on reported symptoms, in accordance with the ICD-10 definition, but with the addition of a measure of disability.

Paper IV

This study shows that the development of PCD after an MTBI is significantly influenced by psychosocial and medical factors at hand already at the moment of injury. Female gender, previous and concurrent psychiatric disorder, family history for psychiatric disorder, concurrent disabling somatic disorder, maladaptive personality traits such as somatic trait anxiety and embitterment, globally assessed psychological function the year before as well as the two last weeks before the injury, and an accumulation of psychosocial stressors the year before the trauma, were all significantly correlated to the outcome. These premorbid factors, assessed within a week after the traumatic event, thus seem to act as predisposing factors for the development of PCD. The precipitating, injury related, factors on the other hand, GCS score, duration of loss of consciousness, posttraumatic amnesia and signs of hemorraghe on brain imaging, did not show any significant association to the outcome. This is in accordance with the findings in Paper I, in which no relation between brain injury markers, including two isoforms of the protein S-100, and cognitive outcome after MTBI was observed [122]. Thus, within the mild brain injury severity spectrum, the severity of the trauma is of limited importance for the long term outcome. Moreover, the premorbid psychosocial factors were in most cases strongly associated with high levels of hyperarousal, anxiety, depression and postconcussional symptoms, assessed during the first week post injury.

Predicting PCD

The strongest predictor for adverse outcome at three months was high ratings of postconcussional symptoms one week after the trauma. This is of course of considerable clinical interest when trying to identify persons at risk for developing PCD. But as the postconcussional symptoms are also

part of the outcome measure and are partly assessed with the same instrument, it does not provide much further understanding of the mechanisms leading to late problems. RPQ at one week was therefore excluded from the logistic regression analysis. Early postconcussional symptoms as predictors for late symptoms after MTBI have been demonstrated by King [77, 123]. In the same way, high levels of acute stress symptoms after a traumatic event predict later development of PTSD [124].

When all other relevant pre-traumatic, socio-demographic, injury related as well as post-traumatic variables were entered into a stepwise logistic regression analysis, post-traumatic hyperarousal, disabling somatic condition, female gender and accumulation of psychosocial stressors all contributed significantly and independently to the outcome. Several of the variables, which in the univariate analysis were associated to negative outcome, had high proportions of common variance, why many of them did not enter the regression equation. A high "general distress factor", in combination with somatic disability and female gender, thus seem to be the crucial link between the trauma and poor outcome. The general distress factor is, in addition to hyperarousal and psychosocial stressors, also reflected in pre-injury variables like low GAF the year and the weeks before the injury, the perceived level of distress from psychosocial stressors, and post-injury variables like high HADS scores. Interestingly, in this study it was also possible to show that the distress was not only due to the trauma and to concurrent stressors but also to vulnerability factors as prior psychiatric disorder, family history of psychiatric disorder and to personality traits like anxiety proneness and embitterment (see below).

Impact of negative affect

Two personality factors, Somatic trait anxiety and Embitterment, were associated with the development of PCD. The Somatic trait anxiety scale can be exemplified by items like 'My body often feels stiff and tense', 'I often feel restless, as if I wanted something without knowing what' and 'I sometimes sweat without reason', whereas the Embitterment scale can be exemplified by items like 'I often encounter hardships in my life', 'I envy successful people' and 'I never seem to be able to avoid troubles'. In a factor analysis of the SSP, three factors, Neuroticism, Aggressiveness and Extraversion, have been disentangled. Both Somatic trait anxiety and Embitterment have high loadings to the Neuroticism factor [62]. A comprehensive concept for the personality risk factors might thus be 'neuroticism' or 'negative affect', compris-

ing subjective distress and a propensity to experience a variety of aversive mood states, including anxiety, depressed mood, anger, guilt, fear and nervousness. Negative affect is related to self-reported stress as well as to poor coping [125, 126].

It has previously been described that emotional reactions early after the trauma are important for the development of postconcussional complaints. In one study concurrent neurological or psychiatric problems and the presence of other life stressors were the most important factors associated with poor outcome [28]. Other studies have linked posttraumatic stress, measured after the trauma, to postconcussional symptoms after MTBI [96]. King et al have previously used HADS and IES-R, together with the RPQ and duration of posttraumatic amnesia, to predict the late outcome [123].

It has also been suggested, although difficult to demonstrate, that the emotional as well as the somatic problems occuring after the injury also depend on premorbid personality factors. In one study pre-traumatic neuroticism, assessed by the relatives of the patient, predicted the number of reported symptoms [127]. In yet another study, pre- and postinjury MMPI-2 profiles were compared in a small group of PCD claimants. All had abnormal premorbid MMPI profiles, predominantly characterized by somatoform symptoms, indicating that presence of premorbid psychopathology was a vulnerability factor for postconcussive complaints. However, there was no increase in these symptoms after the injury, suggesting that the reported posttraumatic changes were instead due to a response bias that minimized preinjury problems and that there was a reattribution of the preinjury symptoms to the recent traumatic event [128]. Given the impact from concurrent psychiatric and somatic disorders in our study, such an effect of reattribution of premorbid disability to the recent traumatic injury cannot be excluded. It should be emphasized, however, that the patients were carefully instructed to rate *change* in symptoms after the injury, by that means, at least theoretically, controlling for symptoms present already at baseline.

Impact of concurrent medical conditions

Twelve patients had medical conditions with some disability and seven of those became PCD cases. The two patients with fibromyalgia and one with low back pain also had comorbid psychiatric conditions but, in general, psychiatric comorbidity was not significantly more common in PCD cases with than without concurrent somatic problems. Comorbid somatic conditions

were also found to be more common in PCD cases in the study by Ponsford [28], and in another study, pre-existing physical limitations and a history of brain illness were independent predictors of poor outcome after mild head injuy [31].

Impact of the head trauma

The impact of non injury related factors does not mean, of course, that the head injury is of no importance at all for the late outcome. In our study 86 % of the patients reported symptoms one day after the injury and 49 % reported at least one persisting symptom at three months post injury [100]. This is consistant with the view that the head injury, at least during an initial period, caused considerable, but temporary, suffering in a majority of the patients. At three months post injury, the symptom pattern among patients in our study differed from the spontaneously reported symptoms in uninjured controls, also indicating a symptom modifying effect of the head trauma [100]. However, among the patients reporting several distressing postconcussional symptoms in combination with disability, there was a significant contribution of premorbid psychosocial adversities and of high levels of anxiety and depression already during the first days post injury. In summary, the clinical picture in the PCD seems to emerge as a result of the interplay between the precipitating head trauma, the predisposing personality traits and the perpetuating impact of concurrent strains and reactive anxiety and depression.

Impact of medico-legal factors

PCD cases had significantly more unsettled insurance claims than non cases 6 and 12 months after the trauma (data not shown). However, in this study medico-legal factors were estimated to have been of minor importance as the patients only occasionally were entitled to compensation from motor or liability insurance. In most personal accident insurances the possibilities, in the Swedish insurance system, of making substantial gains from insurance compensation or litigation are limited.

Predisposing and perpetuating variables

How to understand the impact of premorbid psychosocial factors and concurrent psychological distress for the development of postconcussional complaints after an MTBI? The prognosis for recovery after mild head injury is good for most patients [38]. In a majority of studies, most patients are recovered after a couple of months. It might be assumed, therefore, that

a mild brain injury per se is, in most cases, not severe enough to result in longstanding disability. Instead, other vulnerability factors and other concurrent strains, more related to the individual than to the trauma, in the long run seem to act as predisposing and perpetuating factors, as has previously been proposed, for example by Lishman [129]. This pattern of etiological influences has also been demonstrated in studies of the development of psychiatric morbidity after exposure to traumatic events, where longitudinal outcome was better predicted by pre-traumatic variables than by the nature and intensity of the exposure [130-132].

Recent research, looking beyond the scope of traumatic brain injury, has contributed to the understanding of the association between premorbid personality, psychological distress and the development of physical symptoms after health related events. For example, in patients undergoing vaccination before travelling abroad, trait negative affect predicted increased reporting of general, non-vaccination related symptoms that were attributed to the intervention by the patients [133]. In an experimental study, where healthy volunteers were inoculated with a common cold virus, negative affect was associated with reports of more symptoms and reports of symptoms without a physiological basis [134]. Moreover, female gender and psychological distress have been generally acknowledged as the most important determinants for high somatic symptom reporting, especially in medically unexplained conditions [135]. In a previously healthy population, anxiety and depression were the strongest predictors for the development of chronic fatigue syndrome, another medically unexplained condition, six months after an acute episode of infectious mononucleosis [136]. Moreover, it has recently been demonstrated, in a large prospective study, that emotional instability (eg. neuroticism) and premorbid stress were associated with higher risk for chronic fatiguing illness [137]. In conclusion, not only in PCD but in several other medically insufficiently explained conditions, negative affect and psychological stress exert a major impact on the emergence, persistence and interpretation of symptoms and disability after health perturbations, especially in women.

This study highlights the importance of premorbid factors for the development of PCD. It adds to the evidence that PCD after MTBI is a diagnostic entity characterized by a complex of symptoms and disability that could unlikely be explained by a single traumatic factor such as the head injury. Instead, the diversity of variables associated with the outcome in this study

and in previous research indicate that both biological (concussion, concurrent medical condition, female gender), psychological (negative affectivity, previous or concurrent psychiatric disorder) and social (strain from concurrent life adversities, financial motifs) factors are at play. A biopsychosocial etiological model, recognising predisposing and perpetuating factors as well as the precipitating head injury, need to be taken into account for a proper understanding of PCD. This broad view of the problem should guide clinical management of patients with lasting problems after MTBI.

Summary of findings

Concentrations of S 100B and S 100A1B were not related to reported cognitive symptoms nor signs of cognitive impariment in patients with MTBI with an initial GCS score of 14 or 15.

At three months after an MTBI poor memory, sleep disturbance and fatigue were the most common MTBI related symptoms. Forty-nine % of the patients reported at least one symptom, and 25 % reported dysfunction in at least one domain of everyday life, such as work, relations, and social and leisure activities.

High symptom load at day one was significantly correlated with high symptom load at three months, and subjects with high symptom load tended to have more disability.

The addition of a neuropsychological test criterion for a diagnosis of PCD, as proposed in DSM-IV, was not supported, as neuropsychological tests poorly differentiated the injured from the uninjured group, and did not correlate with reported symptoms, not even when restricted to symptoms within the cognitive domain.

PCD did not show any association to injury related factors such as GCS score, duration of loss of consciousness, posttraumatic amnesia and signs of hemorraghe on brain imaging.

PCD, defined in terms of reported symptoms in combination with disability at 3 months after MTBI, was significantly associated with premorbid psychological vulnerability, somatic disorder, concurrent psychosocial stressors and female gender; and premorbid psychological factors were significantly associated with high levels of hyperarousal, anxiety, depression and post-concussional symptoms, assessed during the first week post injury.

Conclusions and future research

PCD after MTBI is a diagnostic entity characterized by a complex of symptoms and disability that could unlikely be explained only by a single traumatic factor such as the head injury. Instead, the diversity of variables associated with the outcome in this study and in some previous research indicate that biological (concussion, concurrent medical condition, female gender), psychological (negative affectivity, previous or concurrent psychiatric disorder) as well as social (strain from concurrent life adversities, financial motifs) factors are simultaneously at play. A biopsychosocial etiological model, recognising predisposing and perpetuating factors as well as the precipitating head injury, need to be taken into account for a proper understanding of PCD. This broad view of the problem should guide future research and clinical management of patients with unfavourable recovery after MTBI.

There is a need for future research on MTBI in several areas, three of which deserve special attention:

Studies of the validity of outcome measures, also with regard to contextual factors, such as employment market and insurance systems.

Studies of new and more sensitive imaging techniques as well as biological and clinical markers of vulnerability factors, to attain a deeper understanding of the biological and psychosocial variables discussed in this thesis.

Randomized controlled trials, targeting already identified factors to prevent and to treat PCD in high risk groups, as identified by prognostic markers for unfavourable recovery after MTBI.

Populärvetenskaplig sammanfattning på svenska

Varje år sjukhusvårdas 20 000 personer i Sverige på grund av skallskada. 80 – 90 procent av dessa har ”lätt skallskada”, d.v.s. hjärnskakning. Skallskador drabbar företrädesvis unga vuxna, män dubbelt så ofta som kvinnor. Efter hjärnskakning besväras de flesta av symtom som huvudvärk, yrsel, dimsyn, uttröttbarhet, minnes- och koncentrationsproblem, irritabilitet, rastlöshet, nedstämdhet och nedsatt tolerans för stress. Dessa symtom klingar normalt av inom loppet av några månader, men somliga får långvariga besvär, s.k. postcommotionellt syndrom (PCS).

Trots omfattande forskning saknas kunskap om vad som förorsakar PCS efter hjärnskakning. Detta ger upphov till en kontrovers, där vissa forskare betonar betydelsen av hjärnskada medan andra forskare lägger större tonvikt vid psykologiska och sociala faktorer.

Studiens syfte var att undersöka vilka faktorer som har störst betydelse för utveckling av PCS. 122 personer (71 män, 51 kvinnor) med hjärnskakning undersöktes med datortomografi och magnetröntgen av hjärnan. Hjärnskakningens svårighetsgrad bedömdes utifrån minnesluckans längd samt medvetslöshetens längd och djup. Ett cellprotein, S 100B, som utsöndras i blodet efter skallskada, mättes med blodprov på akutmottagningen. Under första veckan intervjuades de skadade beträffande tidigare sjuklighet, personlighet, psykisk funktionsnivå och psykosociala belastningsfaktorer före skadan samt copingförmåga. Dessutom undersöktes de psykologiska effekterna av hjärnskakningen. För att få ett jämförelsematerial följdes 35 friska försökspersoner under tre månader med vissa av testerna.

Tre månader efter hjärnskakningen undersöktes patienterna med avseende på kvarstående hjärnskakningssymtom, social och yrkesmässig funktionsnedsättning samt kognitiva funktioner som minne, uppmärksamhet och mentalt tempo. Vid bedömningen av kognitiv funktionsnedsättning till följd av skallskadan vägde man in den kognitiva förmågan före skadan och andra faktorer som, utöver skallskadan, kunde ge kognitiva problem.

Kan S 100B i blodet förutsäga kognitiv funktionsnedsättning?
S 100B var akut förhöjt, som ett tecken på hjärnpåverkan, hos totalt 42 % av

de skallskadade patienterna och hos 60 % av dem som vid röntgen hade blödning i hjärnan. S 100B hade dock ingen koppling till vare sig upplevd kognitiv funktionsnedsättning eller till prestationerna i de kognitiva testen efter tre månader. Det var också dålig överensstämmelse mellan upplevd kognitiv funktionsnedsättning och prestationerna i de kognitiva testen.

Hur ser det kliniska förloppet ut efter hjärnskakning?
Hälften av patienterna hade minst ett kvarstående symtom efter tre månader – mest framträdande var minnesproblem, störd sömn och trötthet. De som hade mest problem i akuta skedet hade också mest problem tre månader senare och hade också mest uttalad funktionsnedsättning. En fjärdedel av patienterna rapporterade social eller yrkesmässig funktionsnedsättning.

Hur ska PCS definieras?
Enligt WHO-definitionen i ICD-10 krävs tre symtom för diagnosen PCS. Enligt DSM-IV, den amerikanska psykiatrins diagnosmanual, krävs tre symtom i kombination med social och/eller yrkesmässig funktionsnedsättning samt tecken på kognitiv funktionsnedsättning i neuropsykologiska test. Kriterierna i ICD-10 bedömdes för vida, eftersom symtom utan funktionsnedsättning inte ansågs tillräckliga för en kliniskt meningsfull diagnos. I neuropsykologiska test bedömdes 27 % av patienterna och 16 % av kontrollpersonerna ha kognitiv funktionsnedsättning, vilket talade för att testen inte tillräckligt väl kunde skilja ut kognitiva problem p.g.a. skallskada från kognitiva problem av andra orsaker. Den sammanfattande bedömningen blev att resultaten från neuropsykologiska test inte kunde användas som kriterium för diagnosen PCS. Ingen av de två definitionerna av PCS bedömdes därför användbar, och den definition av PCS som tillämpades i de följande analyserna var tre symtom i kombination med social och yrkesmässig funktionsnedsättning.

Vilka riskfaktorer har koppling till utvecklingen av PCS?
Den psykologiska sårbarheten innan olyckan (ångestbenägenhet; tidigare psykiatrisk diagnos) samt högt antal psykosociala påfrestningar året innan olyckan var de viktigaste riskfaktorerna för PCS. Mest utslagsgivande för utveckling av sena besvär var hur stark stress man upplevde veckan efter olyckan. Kvinnor fick oftare PCS. Annan samtidig kroppslig sjukdom påverkade också utvecklingen av PCS. Däremot fanns ingen koppling till själva skallskadans svårighetsgrad, medvetslöshetens eller minnesluckans längd, nivån av S 100B eller om det fanns tecken till hjärnblödning p.g.a. skadan.

Sammanfattningsvis finns både kliniska och laboratoriemässiga tecken på hjärnskada eller påverkad hjärnfunktion hos många av dem som drabbas av hjärnskakning, men prognosen för utläkning av hjärnskaderelaterade symtom är god. Ett mindre antal personer får kvarstående besvär och dessa tycks utvecklas genom ett samspel av tidigare psykologisk sårbarhet, skallskadesymtom och stressymtom i det tidiga skedet samt andra samtidiga psykosociala påfrestningar. Vid utredning och behandling efter hjärnskakning bör därför en helhetssyn tillämpas, där lika stor tonvikt läggs vid såväl utredning av den psykologiska sårbarhet och de psykosociala stressfaktorer som förstärker och vidmakthåller PCS, som vid den skallskada som utlöst besvären.

Acknowledgements

My sincere thanks and appreciation to:

The MTBI patients and the voluntary control subjects, for their unselfish readiness to participate.

Professor Jörgen Borg, principal supervisor, for bringing me on the scientific journey, for generosity, indulgence and for skilfully steering me past the hidden dangers in the research process.

Assistant professor Gunnar Edman, co-supervisor and the Quentin Tarantino of confidence intervals, for generously sharing with me his time for discussions on statistics and movies.

Dr Catharina Nygren Deboussard, colleague and fellow researcher, for nice collaboration in the head trauma project and fighting spirit at the tennis court.

Research nurse Seija Lund for excellent, dutiful, warm and indispensable care of patients, logistics and data collection throughout the study.

Assistant professor Aniko Bartfai and psychologists Daniel Karlstedt and Siw Evans for constructive cooperation in the neuropsychology parts of the research project.

Poet Niels Jamber for IT support and mind expanding discussions.

Professor Olle Nyrén and dr Johanna Adami at the Department of Medical Epidemiology and Biostatistics at Karolinska Institutet, for generously and enthusiastically sharing their epidemiological skills with me.

Professor Åke Nygren, professor David Cassidy, associate professor Linda Carroll and Lena Holm, all members of the WHO task force on MTBI, for valuable discussions and stimulating encounters.

Agneta Bagge, Per Borgå, Johan Cullberg, Lena Flyckt, Magnus Flyckt, Maria Mattson, Christina Norberg, Nina Raab, Anne Tiainen and Birgitta Westerman, co-workers at the Research Unit of the Department of Psychiatry at Danderyd University Hospital, for providing a warm, cheerful, stimulating and encouraging work environment.

Colleagues at PsykiatriCentrum at the Karolinska University Hospital and Karolinska Institutet – Lars Farde, Petter Gustafsson, Jörgen Herlofson, Per Mindus, Björn Mårtensson, Göran Sedvall, Pär Svanborg, Hans Peter Söndergaard, Alexander Wilzcek and Marie Åsberg, to name but a few – that have been important, helpful, supportive and encouraging mentors and friends during different periods throughout my psychiatric career.

Colleagues at the Departments of Audiology and Neurology at Karolinska University Hospital – Johan Bergenius, Lars Edström, Jan Hannerz, Torbjörn Tomson and many others – that have likewise been supportive and stimulating co-workers and partners in discussion in the field of neuropsychiatry.

Colleagues and friends in the European Association for Consultation-Liaison Psychiatry and Psychosomatics – Ulrik Fredrik Malt, Per Fink and many others – for influential mentoring and teaching in the field of liaison psychiatry.

Co-workers at the Unit of Neuropsychology at Danderyd University Hospital, for stimulating companionship and skilful collaborative clinical work with brain injured patients.

Colleagues at the Rehabilitation Medicine University Clinic Stockholm at Danderyd University Hospital, for generously accommodating me during the research project.

The Medical Library at Danderyd University Hospital, for excellent and unobtrusive service.

Henrik Löfgren, for graphic design of this thesis book and long term friendship.

Bengt Carlsson, for precious IT support, even in out of office hours, and for walks and talks.

Mrs Lena Niedzwiedska, for opening her "word kiosk".

Dr Björn Lundin, brother and colleague, for always being there.

My wife Åsa, for encouragement and precious love, and our daughters, Maria, Cecilia and Agnes for being my dearest ones.

The study was supported by a grant from the Swedish insurance company AMF, grant nr T-27:99.

References

1. Peloso, P.M., H. von Holst, and J. Borg, *Mild traumatic brain injuries presenting to Swedish hospitals in 1987-2000.* J Rehabil Med, 2004(43 Suppl): p. 22-7.
2. Cassidy, J.D., L.J. Carroll, P.M. Peloso, et al., *Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury.* J Rehabil Med, 2004(43 Suppl): p. 28-60.
3. Servadei, F., G. Teasdale, and G. Merry, *Defining acute mild head injury in adults: a proposal based on prognostic factors, diagnosis, and management.* J Neurotrauma, 2001. **18**(7): p. 657-64.
4. Stein, S.C. and C. Spettell, *The Head Injury Severity Scale (HISS): a practical classification of closed-head injury.* Brain Inj, 1995. **9**(5): p. 437-44.
5. Borg, J., L. Holm, J.D. Cassidy, et al., *Diagnostic procedures in mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury.* J Rehabil Med, 2004(43 Suppl): p. 61-75.
6. Stiell, I.G., G.A. Wells, K. Vandemheen, et al., *The Canadian CT Head Rule for patients with minor head injury.* Lancet, 2001. **357**(9266): p. 1391-6.
7. Doezema, D., J.N. King, D. Tandberg, et al., *Magnetic resonance imaging in minor head injury.* Ann Emerg Med, 1991. **20**(12): p. 1281-5.
8. Rugg-Gunn, F.J., M.R. Symms, G.J. Barker, et al., *Diffusion imaging shows abnormalities after blunt head trauma when conventional magnetic resonance imaging is normal.* J Neurol Neurosurg Psychiatry, 2001. **70**(4): p. 530-3.
9. Vik, A., K.A. Kvistad, T. Skandsen, et al., *[Diffuse axonal injury in traumatic brain injury.].* Tidsskr Nor Laegeforen, 2006. **126**(22): p. 2940-4.
10. Garnett, M.R., A.M. Blamire, B. Rajagopalan, et al., *Evidence for cellular damage in normal-appearing white matter correlates with injury severity in patients following traumatic brain injury: A magnetic resonance spectroscopy study.* Brain, 2000. **123 (Pt 7)**: p. 1403-9.
11. Jantzen, K.J., B. Anderson, F.L. Steinberg, et al., *A prospective functional MR imaging study of mild traumatic brain injury in college football players.* AJNR Am J Neuroradiol, 2004. **25**(5): p. 738-45.

12. Jacobs, A., E. Put, M. Ingels, et al., *One-year follow-up of technetium-99m-HMPAO SPECT in mild head injury.* J Nucl Med, 1996. **37**(10): p. 1605-9.
13. Ruff, R.M., J.A. Crouch, A.I. Troster, et al., *Selected cases of poor outcome following a minor brain trauma: comparing neuropsychological and positron emission tomography assessment.* Brain Inj, 1994. **8**(4): p. 297-308.
14. de Kruijk, J.R., P. Leffers, P.P. Menheere, et al., *S-100B and neuron-specific enolase in serum of mild traumatic brain injury patients. A comparison with health controls.* Acta Neurol Scand, 2001. **103**(3): p. 175-9.
15. Shaw, G.J., E.C. Jauch, and F.P. Zemlan, *Serum cleaved tau protein levels and clinical outcome in adult patients with closed head injury.* Ann Emerg Med, 2002. **39**(3): p. 254-7.
16. Ingebrigtsen, T., B. Romner, P. Kongstad, et al., *Increased serum concentrations of protein S-100 after minor head injury: a biochemical serum marker with prognostic value?* J Neurol Neurosurg Psychiatry, 1995. **59**(1): p. 103-4.
17. Skogseid, I.M., H.K. Nordby, P. Urdal, et al., *Increased serum creatine kinase BB and neuron specific enolase following head injury indicates brain damage.* Acta Neurochir (Wien), 1992. **115**(3-4): p. 106-11.
18. Yamazaki, Y., K. Yada, S. Morii, et al., *Diagnostic significance of serum neuron-specific enolase and myelin basic protein assay in patients with acute head injury.* Surg Neurol, 1995. **43**(3): p. 267-70; discussion 270-1.
19. Van Eldik, L.J. and M.S. Wainwright, *The Janus face of glial-derived S100B: beneficial and detrimental functions in the brain.* Restor Neurol Neurosci, 2003. **21**(3-4): p. 97-108.
20. Townend, W. and T. Ingebrigtsen, *Head injury outcome prediction: A role for protein S-100B?* Injury, 2006. **37**(12): p. 1098-108.
21. Anderson, R.E., L.O. Hansson, O. Nilsson, et al., *Increase in serum S100A1-B and S100BB during cardiac surgery arises from extracerebral sources.* Ann Thorac Surg, 2001. **71**(5): p. 1512-7.
22. de Boussard, C.N., P. Fredman, A. Lundin, et al., *S100 in mild traumatic brain injury.* Brain Injury, 2004. **18**(7): p. 671-683.
23. Sundstrom, A., P. Marklund, L.G. Nilsson, et al., *APOE influences on neuropsychological function after mild head injury: within-person comparisons.* Neurology, 2004. **62**(11): p. 1963-6.
24. Chamelian, L., M. Reis, and A. Feinstein, *Six-month recovery from*

mild to moderate Traumatic Brain Injury: the role of APOE-epsilon4 allele. Brain, 2004. **127**(Pt 12): p. 2621-8.
25. Rutherford, W.H., J.D. Merrett, and J.R. McDonald, *Symptoms at one year following concussion from minor head injuries.* Injury, 1979. **10**(3): p. 225-30.
26. Lidvall, H., B. Linderoth, and B. Norlin, *Causes of the postconcussional syndrome.* Acta Neurol Scand, 1974. **50**(Suppl. 56).
27. Levin, H.S., S. Mattis, R.M. Ruff, et al., *Neurobehavioral outcome following minor head injury: a three-center study.* J Neurosurg, 1987. **66**(2): p. 234-43.
28. Ponsford, J., C. Willmott, A. Rothwell, et al., *Factors influencing outcome following mild traumatic brain injury in adults.* J Int Neuropsychol Soc, 2000. **6**(5): p. 568-79.
29. Alves, W., S. Macciocchi, and J. Barth, *Postconcussive symptoms after uncomplicated mild head injury.* J Head Trauma Rehabil, 1993. **8**(3): p. 48-59.
30. Middelboe, T., H. Andersen, M. Birket-Smith, et al., *Minor head injury: impact on general health after 1 year. A prospective follow-up study.* Acta Neurol Scand, 1992. **85**: p. 5-9.
31. Thornhill, S., G.M. Teasdale, G.D. Murray, et al., *Disability in young people and adults one year after head injury: prospective cohort study. [see comments.].* Bmj, 2000. **320**(7250): p. 1631-5.
32. Ingebrigtsen, T., K. Waterloo, S. Marup-Jensen, et al., *Quantification of post-concussion symptoms 3 months after minor head injury in 100 consecutive patients.* J Neurol, 1998. **245**(9): p. 609-12.
33. Fox, D., L.-H. PR., K. Earnest, et al., *Base Rates of Postconcussive Symptoms in Health Maintenance Organization Patients and Controls.* Neuropsychology, 1995. **9**(4): p. 606-611.
34. Gouvier, W., M. Uddo-Crane, and L. Brown, *Base Rates of Post-Concussional Symptoms.* Archives of Clinical Neuropsychology, 1988. **3**: p. 273-278.
35. Gasquoine, P., *Postconcussional Symptoms in Chronic Back Pain.* Applied Neuropsychology, 2000. **7**(2): p. 83-89.
36. Kashluba, S., C. Paniak, T. Blake, et al., *A longitudinal, controlled study of patient complaints following treated mild traumatic brain injury.* Arch Clin Neuropsychol, 2004. **19**(6): p. 805-16.
37. Bohnen, N. and J. Jolles, *Neurobehavioral aspects of postconcussive symptoms after mild head injury.* Journal of Nervous & Mental Disease, 1992. **180**(11): p. 683-92.

38. Carroll, L.J., J.D. Cassidy, P.M. Peloso, et al., *Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury.* J Rehabil Med, 2004(43 Suppl): p. 84-105.
39. Hugenholtz, H., D.T. Stuss, L.L. Stethem, et al., *How long does it take to recover from a mild concussion?* Neurosurgery, 1988. **22**(5): p. 853-8.
40. Bohnen, N., J. Jolles, and A. Twijnstra, *Neuropsychological deficits in patients with persistent symptoms six months after mild head injury.* Neurosurgery, 1992. **30**(5): p. 692-5; discussion 695-6.
41. Killam, C., R.L. Cautin, and A.C. Santucci, *Assessing the enduring residual neuropsychological effects of head trauma in college athletes who participate in contact sports.* Arch Clin Neuropsychol, 2005. **20**(5): p. 599-611.
42. Nimnuan, C., S. Rabe-Hesketh, S. Wessely, et al., *How many functional somatic syndromes?* J Psychosom Res, 2001. **51**(4): p. 549-57.
43. Fann, J.R., W.J. Katon, J.M. Uomoto, et al., *Psychiatric disorders and functional disability in outpatients with traumatic brain injuries.* American Journal of Psychiatry, 1995. **152**(10): p. 1493-9.
44. Mobayed, M. and T.G. Dinan, *Buspirone/prolactin response in post head injury depression.* J Affect Disord, 1990. **19**(4): p. 237-41.
45. Jorge, R.E., R.G. Robinson, D. Moser, et al., *Major depression following traumatic brain injury.* Arch Gen Psychiatry, 2004. **61**(1): p. 42-50.
46. Mayou, R.A., J. Black, and B. Bryant, *Unconsciousness, amnesia and psychiatric symptoms following road traffic accident injury.* Br J Psychiatry, 2000. **177**: p. 540-5.
47. Parshall, A.M. and R.G. Priest, *Nosology, taxonomy and the classification conundrum of the functional psychoses.* Br J Psychiatry, 1993. **162**: p. 227-36; discussion 237-8.
48. Iverson, G.L. and R.T. Lange, *Examination of "postconcussion-like" symptoms in a healthy sample.* Appl Neuropsychol, 2003. **10**(3): p. 137-44.
49. Kashluba, S., J.E. Casey, and C. Paniak, *Evaluating the utility of ICD-10 diagnostic criteria for postconcussion syndrome following mild traumatic brain injury.* J Int Neuropsychol Soc, 2006. **12**(1): p. 111-8.
50. McCauley, S.R., C. Boake, C. Pedroza, et al., *Postconcussional disorder - Are the DSM-IV criteria an improvement over the ICD-10?* Journal of Nervous & Mental Disease, 2005. **193**(8): p. 540-550.
51. Mittenberg, W. and S. Strauman, *Diagnosis of mild head injury and the postconcussion syndrome.* 2000: p. 783-91, 2000 Apr.

52. Boake, C., S.R. McCauley, H.S. Levin, et al., *Limited Agreement Between Criteria-Based Diagnoses of Postconcussional Syndrome.* Journal of Neuropsychiatry & Clinical Neurosciences, 2004. **16**(4): p. 493-499.
53. Boake, C., S.R. McCauley, H.S. Levin, et al., *Diagnostic criteria for postconcussional syndrome after mild to moderate traumatic brain injury.* J Neuropsychiatry Clin Neurosci, 2005. **17**(3): p. 350-6.
54. World Health Organization, *International Classification of Functioning, Disability and Health (ICF)*. 2001, Geneva.
55. Kroenke, K. and A.D. Mangelsdorff, *Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome.* American Journal of Medicine, 1989. **86**(3): p. 262-6.
56. Engel, G.L., *The need for a new medical model: a challenge for biomedicine.* Science, 1977. **196**(4286): p. 129-36.
57. Gallagher, R.M., *Rational integration of pharmacologic, behavioral, and rehabilitation strategies in the treatment of chronic pain.* Am J Phys Med Rehabil, 2005. **84**(3 Suppl): p. S64-76.
58. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*. Third ed. 1987, Cambridge.
59. Skodol, A.E. and P.E. Shrout, *Use of DSM-III axis IV in clinical practice: rating etiologically significant stressors.* Am J Psychiatry, 1989. **146**(1): p. 61-6.
60. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. 1994, Washington: American Psychiatric Association.
61. Bodlund, O., G. Kullgren, L. Ekselius, et al., *Axis V—Global Assessment of Functioning Scale. Evaluation of a self-report version.* Acta Psychiatr Scand, 1994. **90**(5): p. 342-7.
62. Gustavsson, J.P., H. Bergman, G. Edman, et al., *Swedish universities Scales of Personality (SSP): construction, internal consistency and normative data.* Acta Psychiatr Scand, 2000. **102**(3): p. 217-25.
63. Gustavsson J.P, *Stability and validity of self-reported personality traits. Contributions to the evaluation of the Karolinska Scales of Personality*, in *Dep of Clin Neuroscience*. 1997, Karolinska Institute: Stockholm.
64. Bergdahl, J., *Psychologic aspects of patients with symptoms presumed to be caused by electricity or visual display units.* Acta Odontol Scand, 1995. **53**(5): p. 304-10.

65. Ponzer, S., B. Bergman, B. Brismar, et al., *A study of patient-related characteristics and outcome after moderate injury.* Injury, 1996. **27**(8): p. 549-55.
66. Antonovsky, A., *The structure and properties of the sense of coherence scale.* Soc Sci Med, 1993. **36**(6): p. 725-33.
67. Ristkari, T., A. Sourander, H. Helenius, et al., *Sense of coherence among Finnish young men—a cross-sectional study at military call-up.* Nord J Psychiatry, 2005. **59**(6): p. 473-80.
68. Ristner, G., R. Andersson, L.M. Johansson, et al., *Sense of coherence and lack of control in relation to outcome after orthopaedic injuries.* Injury, 2000. **31**(10): p. 751-6.
69. Saunders, J.B., O.G. Aasland, A. Amundsen, et al., *Alcohol consumption and related problems among primary health care patients: WHO collaborative project on early detection of persons with harmful alcohol consumption—I.* Addiction, 1993. **88**(3): p. 349-62.
70. Isaacson, J.H., R. Butler, M. Zacharek, et al., *Screening with the Alcohol use Disorders Identification Test (AUDIT) in an inner-city population.* J Gen Intern Med, 1994. **9**(10): p. 550-3.
71. Stigbrand, T., L. Nyberg, A. Ullen, et al., *A new specific method for measuring S-100B in serum.* Int J Biol Markers, 2000. **15**(1): p. 33-40.
72. Sundin, E.C. and M.J. Horowitz, *Impact of Event Scale: psychometric properties.* Br J Psychiatry, 2002. **180**: p. 205-9.
73. Weiss, D.S. and C.R. Marmar, *The Impact of Event Scale - Revised*, in *Assessing Psychological Trauma and PTSD: A Practitioner's Handbook.*, J. Wilson and T. Keane, Editors. 1996, Guilford: New York. p. 399-411.
74. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
75. Bjelland, I., A.A. Dahl, T.T. Haug, et al., *The validity of the Hospital Anxiety and Depression Scale. An updated literature review.* J Psychosom Res, 2002. **52**(2): p. 69-77.
76. Andrews, H., P. Barczak, and R.N. Allan, *Psychiatric illness in patients with inflammatory bowel disease.* Gut, 1987. **28**(12): p. 1600-4.
77. King, N.S., S. Crawford, F.J. Wenden, et al., *Early prediction of persisting post-concussion symptoms following mild and moderate head injuries.* Br J Clin Psychol, 1999. **38**(Pt 1): p. 15-25.
78. Wechsler D, *WAIS-R. Manual*. 1981, New York: The Psychological Corporation.
79. Kaplan E, Fein D, Morris R, et al., *WAIS-R as a neuropsychological instrument*. 1991, San Antonio: The Psychological Corporation.

80. Spreen O and Strauss E, *A compendium of neuropsychological tests. Administration, norms and commentary.* 1991, New York: Oxford University Press.
81. Golden, C.J., *A group version of the stroop color and word test.* J Pers Assess, 1975. **39**(4): p. 386-8.
82. Gronwall, D. and P. Wrightson, *Delayed recovery of intellectual function after minor head injury.* Lancet, 1974. **2**(7881): p. 605-9.
83. Levander, S., *An Automated Psychological Test Battery: IBM-PC-version*, in *Research Reports from Department of Psychiatry and Behavioural Medicine*. 1988, University of Trondheim.
84. King, N.S., S. Crawford, F.J. Wenden, et al., *The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability.* J Neurol, 1995. **242**(9): p. 587-92.
85. Crawford, S., F.J. Wenden, and D.T. Wade, *The Rivermead head injury follow up questionnaire: a study of a new rating scale and other measures to evaluate outcome after head injury.* J Neurol Neurosurg Psychiatry, 1996. **60**(5): p. 510-4.
86. Ladwig, K.H., B. Marten-Mittag, B. Formanek, et al., *Gender differences of symptom reporting and medical health care utilization in the German population.* Eur J Epidemiol, 2000. **16**(6): p. 511-8.
87. Kroenke, K. and R.K. Price, *Symptoms in the community. Prevalence, classification, and psychiatric comorbidity.* Arch Intern Med, 1993. **153**(21): p. 2474-80.
88. Eyres, S., A. Carey, G. Gilworth, et al., *Construct validity and reliability of the Rivermead Post-Concussion Symptoms Questionnaire.* Clin Rehabil, 2005. **19**(8): p. 878-87.
89. Potter, S., E. Leigh, D. Wade, et al., *The Rivermead Post Concussion Symptoms Questionnaire : A confirmatory factor analysis.* J Neurol, 2006.
90. Mulhern, S. and T.M. McMillan, *Knowledge and expectation of post-concussion symptoms in the general population.* J Psychosom Res, 2006. **61**(4): p. 439-45.
91. Hahn, R.A., *The nocebo phenomenon: concept, evidence, and implications for public health.* Prev Med, 1997. **26**(5 Pt 1): p. 607-11.
92. Gunstad, J. and J.A. Suhr, *Perception of illness: nonspecificity of post-concussion syndrome symptom expectation.* J Int Neuropsychol Soc, 2002. **8**(1): p. 37-47.

93. Smith-Seemiller, L., N.R. Fow, R. Kant, et al., *Presence of post-concussion syndrome symptoms in patients with chronic pain vs mild traumatic brain injury.* Brain Inj, 2003. **17**(3): p. 199-206.
94. Iverson, G.L. and L.M. McCracken, *'Postconcussive' symptoms in persons with chronic pain.* Brain Inj, 1997. **11**(11): p. 783-90.
95. Sawchyn, J.M., M.M. Brulot, and E. Strauss, *Note on the use of the Postconcussion Syndrome Checklist.* Arch Clin Neuropsychol, 2000. **15**(1): p. 1-8.
96. Bryant, R.A. and A.G. Harvey, *Postconcussive symptoms and post-traumatic stress disorder after mild traumatic brain injury.* J Nerv Ment Dis, 1999. **187**(5): p. 302-5.
97. Morgan, J.F. and M. Killoughery, *Hospital doctors' management of psychological problems - Mayou & Smith revisited.* Br J Psychiatry, 2003. **182**: p. 153-7.
98. Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine, *Definition of mild traumatic brain injury.* J Head Trauma Rehabil, 1993. **8**: p. 86-87.
99. Ferguson, R.J., W. Mittenberg, D.F. Barone, et al., *Postconcussion syndrome following sports-related head injury: expectation as etiology.* Neuropsychology, 1999. **13**(4): p. 582-9.
100. Lundin, A., C.N. de Boussard, G. Edman, et al., *Symptoms and disability until three months after Mild TBI.* Brain Injury, 2006. **20**(**8**): p. 799–806.
101. McCullagh, S. and A. Feinstein, *Outcome after mild traumatic brain injury: an examination of recruitment bias.* J Neurol Neurosurg Psychiatry, 2003. **74**(1): p. 39-43.
102. Savola, O. and M. Hillbom, *Early predictors of post-concussion symptoms in patients with mild head injury.* Eur J Neurol, 2003. **10**(2): p. 175-81.
103. Herrmann, M., N. Curio, S. Jost, et al., *Release of biochemical markers of damage to neuronal and glial brain tissue is associated with short and long term neuropsychological outcome after traumatic brain injury.* J Neurol Neurosurg Psychiatry, 2001. **70**(1): p. 95-100.
104. Townend, W.J., M.J. Guy, M.A. Pani, et al., *Head injury outcome prediction in the emergency department: a role for protein S-100B?* J Neurol Neurosurg Psychiatry, 2002. **73**(5): p. 542-6.
105. Frencham, K.A., A.M. Fox, and M.T. Maybery, *Neuropsychological studies of mild traumatic brain injury: a meta-analytic review of research since 1995.* J Clin Exp Neuropsychol, 2005. **27**(3): p. 334-51.

106. Lannoo, E., F. Colardyn, T. Vandekerckhove, et al., *Subjective complaints versus neuropsychological test performance after moderate to severe head injury.* Acta Neurochir (Wien), 1998. **140**(3): p. 245-53.
107. Nicholson, K., M.F. Martelli, and N.D. Zasler, *Does pain confound interpretation of neuropsychological test results?* NeuroRehabilitation, 2001. **16**(4): p. 225-30.
108. Austin, M.P., P. Mitchell, and G.M. Goodwin, *Cognitive deficits in depression: possible implications for functional neuropathology.* Br J Psychiatry, 2001. **178**: p. 200-6.
109. Chamelian, L. and A. Feinstein, *The effect of major depression on subjective and objective cognitive deficits in mild to moderate traumatic brain injury.* J Neuropsychiatry Clin Neurosci, 2006. **18**(1): p. 33-8.
110. Wade, D.T., N.S. King, F.J. Wenden, et al., *Routine follow up after head injury: a second randomised controlled trial.* J Neurol Neurosurg Psychiatry, 1998. **65**(2): p. 177-83.
111. Paniak, C., S. Reynolds, K. Phillips, et al., *Patient complaints within 1 month of mild traumatic brain injury: A controlled study.* Arch Clin Neuropsychol, 2002. **17**(4): p. 319-34.
112. Nolin, P., *Executive memory dysfunctions following mild traumatic brain injury.* J Head Trauma Rehabil, 2006. **21**(1): p. 68-75.
113. Schretlen, D.J. and A.M. Shapiro, *A quantitative review of the effects of traumatic brain injury on cognitive functioning.* Int Rev Psychiatry, 2003. **15**(4): p. 341-9.
114. Wang, Y., R.C. Chan, and Y. Deng, *Examination of postconcussion-like symptoms in healthy university students: relationships to subjective and objective neuropsychological function performance.* Arch Clin Neuropsychol, 2006. **21**(4): p. 339-47.
115. Leininger, B.E., S.E. Gramling, A.D. Farrell, et al., *Neuropsychological deficits in symptomatic minor head injury patients after concussion and mild concussion.* J Neurol Neurosurg Psychiatry, 1990. **53**(4): p. 293-6.
116. Kapur, N. and D. Pearson, *Memory symptoms and memory performance of neurological patients.* Br J Psychol, 1983. **74 (Pt 3)**: p. 409-15.
117. Landre, N., C.J. Poppe, N. Davis, et al., *Cognitive functioning and postconcussive symptoms in trauma patients with and without mild TBI.* Arch Clin Neuropsychol, 2006. **21**(4): p. 255-73.
118. Barsky, A.J. and J.F. Borus, *Functional somatic syndromes.* Ann Intern Med, 1999. **130**(11): p. 910-21.

119. Jablensky, A., *The nature of psychiatric classification: issues beyond ICD-10 and DSM-IV.* Aust N Z J Psychiatry, 1999. **33**(2): p. 137-44.
120. Lees-Haley, P.R. and R.S. Brown, *Neuropsychological complaint base rates of 170 personal injury claimants.* Arch Clin Neuropsychol, 1993. **8**(3): p. 203-9.
121. Wong, J.L., R.P. Regennitter, and F. Barrios, *Base rate and simulated symptoms of mild head injury among normals.* Arch Clin Neuropsychol, 1994. **9**(5): p. 411-25.
122. de Boussard, C.N., A. Lundin, D. Karlstedt, et al., *S100 and cognitive impairment after mild traumatic brain injury.* J Rehabil Med, 2005. **37**(1): p. 53-7.
123. King, N.S., *Emotional, neuropsychological, and organic factors: their use in the prediction of persisting postconcussion symptoms after moderate and mild head injuries.* J Neurol Neurosurg Psychiatry, 1996. **61**(1): p. 75-81.
124. Harvey, A.G. and R.A. Bryant, *The relationship between acute stress disorder and posttraumatic stress disorder: a 2-year prospective evaluation.* J Consult Clin Psychol, 1999. **67**(6): p. 985-8.
125. Kanner, A.D., J.C. Coyne, C. Schaefer, et al., *Comparison of two modes of stress measurement: daily hassles and uplifts versus major life events.* J Behav Med, 1981. **4**(1): p. 1-39.
126. Hotopf, M., R. Mayou, M. Wadsworth, et al., *Temporal relationships between physical symptoms and psychiatric disorder. Results from a national birth cohort.* Br J Psychiatry, 1998. **173**: p. 255-61.
127. Keshavan, M.S., S.M. Channabasavanna, and G.N. Reddy, *Post-traumatic psychiatric disturbances: patterns and predictors of outcome.* Br J Psychiatry, 1981. **138**: p. 157-60.
128. Greiffenstein, F.M. and J.W. Baker, *Comparison of premorbid and postinjury mmpi-2 profiles in late postconcussion claimants.* Clin Neuropsychol, 2001. **15**(2): p. 162-70.
129. Lishman, W.A., *Physiogenesis and psychogenesis in the 'post-concussional syndrome'.* British Journal of Psychiatry, 1988. **153**: p. 460-9.
130. McFarlane, A.C., *The aetiology of post-traumatic stress disorders following a natural disaster.* Br J Psychiatry, 1988. **152**: p. 116-21.
131. North, C.S., E.M. Smith, and E.L. Spitznagel, *Posttraumatic stress disorder in survivors of a mass shooting.* Am J Psychiatry, 1994. **151**(1): p. 82-8.
132. Kelly, B., B. Raphael, F. Judd, et al., *Posttraumatic stress disorder in response to HIV infection.* Gen Hosp Psychiatry, 1998. **20**(6): p. 345-52.

133. Petrie, K.J., R. Moss-Morris, C. Grey, et al., *The relationship of negative affect and perceived sensitivity to symptom reporting following vaccination.* Br J Health Psychol, 2004. **9**(Pt 1): p. 101-11.
134. Feldman, P.J., S. Cohen, W.J. Doyle, et al., *The impact of personality on the reporting of unfounded symptoms and illness.* J Pers Soc Psychol, 1999. **77**(2): p. 370-8.
135. Kroenke, K. and R.L. Spitzer, *Gender differences in the reporting of physical and somatoform symptoms.* Psychosom Med, 1998. **60**(2): p. 150-5.
136. Moss-Morris, R. and M. Spence, *To "lump" or to "split" the functional somatic syndromes: can infectious and emotional risk factors differentiate between the onset of chronic fatigue syndrome and irritable bowel syndrome?* Psychosom Med, 2006. **68**(3): p. 463-9.
137. Kato, K., P.F. Sullivan, B. Evengård, et al., *Premorbid Predictors of Chronic Fatigue.* Arch Gen Psychiatry, 2006. **63**: p. 1267-1272.

Appendix

Frågeformulär symtom

Frågeformulär ”Rivermead” för symtom efter skallskada

Instruktion: Efter en skallskada kan man drabbas av symtom som kan oroa eller besvära. Vi vill veta om du har upplevt några av nedanstående symtom. Många av symtomen uppträder även normalt, så försök att jämföra upplevelsen av symtom före och efter olyckan. Sätt ett kryss i den ruta som bäst överensstämmer med ditt svar.

	Jämfört med innan olyckan har du nu (eller de senaste 24 timmarna) upplevt:	***Har inga sådana symtom***	***Haft symtom men är nu besvärsfri***	***Mindre problem***	***Måttliga problem***	***Stora problem***
A	***Huvudvärk***	☐	☐	☐	☐	☐
B	***Yrsel***	☐	☐	☐	☐	☐
C	***Illamående eller kräkningar***	☐	☐	☐	☐	☐
D	***Ljudöverkänslighet, lättretad av höga ljud***	☐	☐	☐	☐	☐
E	***Sömnproblem***	☐	☐	☐	☐	☐
F	***Utmatning, uttröttbarhet***	☐	☐	☐	☐	☐
G	***Känsla av irritation, lättretlighet***	☐	☐	☐	☐	☐
H	***Känsla av nedstämdhet eller gråtmildhet***	☐	☐	☐	☐	☐
I	***Känsla av frustration eller otålighet***	☐	☐	☐	☐	☐
J	***Glömska, dåligt minne***	☐	☐	☐	☐	☐
K	***Koncentrationssvårigheter***	☐	☐	☐	☐	☐
L	***Långsam i tanken***	☐	☐	☐	☐	☐
M	***Dimsyn***	☐	☐	☐	☐	☐
N	***Ljuskänslighet, lättretad av ljus***	☐	☐	☐	☐	☐
O	***Dubbelseende***	☐	☐	☐	☐	☐
P	***Rastlöshet***	☐	☐	☐	☐	☐
	Har du haft andra symtom? Specificera, gradera som ovan	☐	☐	☐	☐	☐

Frågeformulär funktionsnedsättning

Frågeformulär ”Rivermead” för funktionsnedsättning efter skallskada

Instruktion: Efter en skallskada kan man drabbas av symtom som kan oroa eller besvära. Vi vill veta om du har upplevt några av nedanstående symtom. Många av symtomen uppträder även normalt, så försök att jämföra upplevelsen av symtom före och efter olyckan. Sätt ett kryss i den ruta som bäst överensstämmer med ditt svar.

	Jämfört med innan olyckan/skadan har det skett en förändring beträffande:	***Ingen förändring***	***Ingen förändring men svårare jfrt med tidigare***	***Mindre förändring***	***Måttlig förändring***	***Stor förändring***
A	***Förmågan att konversera med en person***	☐	☐	☐	☐	☐
B	***Förmågan att konversera med två eller flera personer***	☐	☐	☐	☐	☐
C	***Förmågan att utföra dagliga aktiviteter i hemmet***	☐	☐	☐	☐	☐
D	***Förmågan att delta i tidigare sociala aktiviteter***	☐	☐	☐	☐	☐
E	***Förmågan att uppskatta tidigare fritidsaktiviteter***	☐	☐	☐	☐	☐
F	***Förmågan att upprätthålla tidigare arbetsbelastning/standard***	☐	☐	☐	☐	☐
G	***Upplevelsen av att arbete är tröttande***	☐	☐	☐	☐	☐
H	***Relationer till tidigare vänner***	☐	☐	☐	☐	☐
I	***Relationen till din partner***	☐	☐	☐	☐	☐
J	***Förmågan att hantera krav från familjen***	☐	☐	☐	☐	☐
	Har du upplevt andra svårigheter? Specificera och gradera som ovan:	☐	☐	☐	☐	☐