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MILD TRAUMATIC BRAIN INJURY - ANTECEDENTS AND AFTERMATH

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Stockholm 2019

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Published by Karolinska Institutet.
Printed by E-Print AB 2019
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ISBN 978-91-7831-393-8

Mild Traumatic Brain Injury – Antecedents and Aftermath

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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This thesis will be publicly defended in lecture hall Hjärtat, Karolinska Institutet, Danderyd Hospital, on March 29, 2019, at 10:00 AM

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To my family

The truth was obscure, too profound and too pure
To live it you have to explode
In that last hour of need, we entirely agreed
Sacrifice was the code of the road

Bob Dylan

ABSTRACT

Mild Traumatic Brain Injury (mTBI) is a frequent, trauma-induced injury, associated with loss of consciousness and/or memory loss for the injury event. Injured individuals experience a wide range of somatic symptoms (e.g. headache, nausea), cognitive symptoms (e.g. poor concentration, memory problems) and affective symptoms (e.g. irritability, depressed mood). These symptoms gradually resolve within days or weeks for the majority of the affected individuals. A minority will however report persisting post-concussion symptoms (PCS). The etiology of these complaints is in dispute, both psychological and organic factors have been proposed. Brain Reserve Capacity theory hypothesize that variations in outcome after seemingly similar brain injuries can be explained by brain "reserves" that acts as buffers. Papers presented herein explores this hypothesis with particular emphasis on cognitive and emotional reserve.

Data comes from two studies. Study 1 have a case-control study design with 24 included mTBI patients referred for neuropsychological assessment (paper 1 and 4). Study 2 is a cohort study with 122 mTBI patients followed prospectively from emergency department visit to follow-up at 3 months (paper 2) and 12 months post injury (paper 3).

In Paper 1 we examined if mTBI patients with persisting PCS exhibits deficits in emotional awareness, decision making or have higher levels of disadvantageous personality traits compared with non-injured controls. No significant differences in performance were noted with regard to emotional awareness or decision making. Patients had significantly higher levels of trait anxiety and stress susceptibility.

In Paper 2 we examined if cognitive performance, particularly attention and memory, in prospectively followed patients with persistent PCS would be more impaired than in those patients who had recovered. We also examined if cognitive reserve, indicated by education level, skill level at work and estimated premorbid intelligence would influence recovery. Three months post injury, mTBI patients regardless of PCS status performed more poorly in a highly challenging memory test compared to non-injured controls and norms. Patients with lower cognitive reserve were 4 times more likely to suffer from persistent PCS.

In Paper 3 we examined if emotional reserve, indicated by previous psychiatric history, personality traits and psychological resilience would influence recovery after mTBI. One-year post-injury, 12 % of the prospectively followed patients had persisting PCS and reported disability in daily life. These patients had reported more psychiatric problems and experienced more stress before and at the time of the injury. They also had lower levels of resilience and exhibited higher levels of personality traits related to somatic trait anxiety, embitterment and mistrust compared to recovered patients.

In Paper 4 we examined pain reporting in a sample of mTBI patients referred for neuropsychological assessment in the post-acute stage and its possible influence on cognitive performance. Patients reported significantly more musculoskeletal pain in the neck and shoulders than non-injured control. In cognitive tests, patients performed on average worse than the controls, but no additive effect of pain was noted. Pain was however associated with

more impaired performance in timed tasks, primarily measuring processing speed, in non-injured controls.

Conclusions: Cognitive deficits in the form of subtle executive problems are still evident in mild traumatic brain injury patients three months post-injury. A pre-injury lower level of cognitive and / or emotional reserve is a considerable risk factor for development of persistent post-concussion symptoms after mild traumatic brain injury. High level of pain, including musculoskeletal pain is common in patients with persisting post-concussion symptoms.

LIST OF SCIENTIFIC PAPERS

I. Oldenburg, C., Möller, M. C., Bartfai, A. Emotional Awareness and Decision Making in Mild Traumatic Brain Injury – A Swedish Case-Control Study. Submitted.

II. Oldenburg, C., Lundin, A., Edman, G., Nygren Deboussard, C., Bartfai, A. Cognitive reserve and persistent post-concussion symptoms - A prospective mild traumatic brain injury (mTBI) cohort study. *Brain Injury*, 2016, 30:2,146-155, doi: 10.3109/02699052.2015.1089598

III. Oldenburg, C., Lundin, A., Edman, G., Nygren Deboussard, C., Bartfai, A. Emotional reserve and prolonged post-concussive symptoms and disability: a Swedish prospective 1-year mild traumatic brain injury cohort study *BMJ Open,* 2018;8**:** e020884. doi: 10.1136/bmjopen-2017-020884

IV. Oldenburg, C., Möller, M. C., Lundeberg, T. & Bartfai, A. Does pain influence cognitive performance in patients with Mild Traumatic Brain injury? Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ABI	Acquired Brain Injury
AUDIT	Alcohol Use Disorders Identification Test
BRC	Brain Reserve Capacity
CCS	California Concussion Scale
CI	Confidence Interval
CT	Computerized Tomography
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Emergency Department
ES	Effect Size
FIT	Rey Fifteen Item Test
GAF	Global Assessment of Function
GCS	Glasgow Coma Scale
HADS	Hospital Anxiety and Depression Scale
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
IES-R	Impact of Event Scale - Revised
IGT	Iowa Gambling Task
ISCED	International Standard Classification of Educational Degrees
ISCO	International Standard Classification of Occupations
KSP	Karolinska Scales of Personality
LEAS	Level of Emotional Awareness Scale
LOC	Loss of Consciousness
MMPI	Minnesota Multiphasic Personality Inventory
MRI	Magnetic Resonance Imaging
mTBI	Mild Traumatic Brain Injury
OR	Odds Ratio
PASAT	Phased Auditory Serial Addition Test
PCS	Post-concussion symptoms
PCD	Postconcussional Disorder

PTA	Post-Traumatic Amnesia
PTSD	Posttraumatic Stress Disorder
RDS	Reliable Digit Span
RHFUQ	Rivermead Head Injury Follow-Up Questionnaire
SRT	Selective Reminding Test
STAI	State and Trait Anxiety Inventory
SOC	Sense of Coherence Scale
SSP	Swedish Universities Scales of Personality
TBI	Traumatic Brain Injury
TMT	Trail Making Test
WAIS	Wechsler Adult Intelligence Scale
ÖMSPQ	Örebro Musculoskeletal Screening Pain Questionnaire

1 PROLOGUE

The name of this thesis, *Mild traumatic Brain Injury – Antecedents and Aftermath*, was chosen to reflect the key starting point for this thesis, namely that each individual affected by brain injury is bringing into the injury his or her unique life history and characteristics (*antecedents*) that will shape the experience and outcome of the injury (i.e. the *aftermath*). This is also true for this thesis. I brought my personal history and learning experience into the work of this thesis, and it shaped the process and the final outcome.

I am a licensed psychologist and completed my studies at the Psychology Institution at Stockholm University in 2001. During my study time, I had, at best, a moderate interest in neuropsychology. Instead I was leaning towards cognitive psychology and wrote two papers during these years with professor Lars-Gunnar Lundh as my supervisor, that were subsequently published [1, 2]. The topic Lars-Gunnar introduced to me concerned the "repressive coping style" and the study of cognitive biases associated with that style. The repressive coping style is a personality trait, characterized by low reporting of experienced anxiety or distress, but high objective signs of anxiety and arousal (e.g. palm sweat) [3]. One could say that people with this coping style show a classic sign of dissociation between subjective and objective signs of distress. One paper in this research field that in particular made a deep impact on me was written by Shedler, Mayman & Manis and had the name "The illusion of mental health" [4]. In this paper the authors argued that psychological self-report scales could not reliably distinguish between "genuine mental health and the façade of or illusion of mental health created by psychological defenses" (p. 1117). The importance of this work that predated my doctoral studies cannot be sufficiently stressed. I developed a deep interest in people's perception and reporting of subjective symptoms. It was clear to me that results from most self-report scales could not be taken at face value but had to be interpreted in the light of which emotional coping-style the individual answering them were prone to.

Despite my ambition to become a psychotherapist, I did my psychologist training year in a Neuropsychology unit at the Rehabilitation Medicine Clinic at Danderyd Hospital. My primary role was to assess cognitive functions in patients with "mild brain injuries". Our working definition of "mild" was primarily based on outcome. I met patients who had suffered strokes, traumatic brain injuries, tumors and encephalitis but had made a fairly good recovery. They would seldom have problems with speaking or walking, and many were back to work, at least part time. They still experienced disabling symptoms though, mostly cognitive and emotional symptoms. The largest group was patients who had suffered a mild traumatic brain injury. These patients had often been on sick-leave for months or even years after their injury. They reported a fair number of lingering symptoms, and our neuropsychological assessments often concluded that they also had discernable cognitive impairments.

I was offered a permanent job at the unit and for several years I kept doing this work. One could say that I was constantly seeing the most severe cases of the mTBI population. This shaped my view of mTBI. I regarded it as an injury with sometimes dire consequences.

The phenomenon of mostly meeting the more severe cases in a population and then draw conclusions to all cases has been described by Cohen & Cohen as the clinician's illusion [5]. The illusion is created by a selection bias. Clinicians tend to see people who are ill and not those who are healthy. In prolonged medical conditions clinicians also tend to see patients only when they are ill, and they tend to see patients with the worst condition more often. Thus, many affected individuals are not seen at all, and the ones who are most affected are seen disproportionally more often than other patients. The illusion explains why many clinicians are pessimistic about future prognosis for a particular condition, since he or she only infers outcome based on experiences from the patients he or she meets.

I definitely had this illusion but was not aware of it at the time. However, when I started to read more about outcome after mTBI from well-designed studies my view of mTBI got challenged. For instance, several meta-analyses [6-9] of studies of mTBI patients that were prospectively followed from emergency department visits (i.e. not prone to selection bias) did not find evidence of any appreciable long lasting cognitive impairment. This lack of evidence is obviously hard to grasp for a neuropsychologist whose primary job was to assess cognition in mTBI patients. One key question I wrestled with was what distinguished the patients I met from the overwhelming majority of individuals with mTBI in research studies who apparently recovered fully without ever getting in touch with a rehabilitation setting?

I had ideas. One idea was that routine cognitive assessment performed in all those studies did not take into account or measured emotional deficits. Maybe they just had looked for deficits in the wrong place. Another idea I had was that pre-injury personality traits, including emotional coping styles, would significantly shape the experience and, more importantly, the reporting of symptoms after injury. In effect this would mean that two individuals could have a very similar brain injury, but still the outcome could be vastly different. This line of thinking is absolutely not new in brain injury rehabilitation. In fact, as early as 1937 British neurologist Charles Symonds famously wrote:

> "*The later effects of head injury can only be properly understood in the light of a full psychiatric study of the individual patient, and in particular, his constitution. In other words, it is not only the kind of injury that matters, but the kind of head*." (p.1092) [10].

This will be the starting point for this thesis. It very much resembles a more recent formulation of the Brain Reserve Capacity theory, by Paul Satz [11], where it is postulated that each brain varies in its capacity to withstand the initial brain injury, and in the subsequent phase compensate for acquired deficits.

2 BACKGROUND

2.1 TRAUMATIC BRAIN INJURY

Traumatic brain injury can be defined as an ”acute brain injury resulting from mechanical energy to the head from external physical forces” [12] (p. 115), or ”an alteration in brain function, or other evidence of brain pathology, caused by an external force” [13], (p.1637). Each year approximately 70 million people [14] suffers from a TBI, and around 10 millions of these results in death or requires treatment in hospital [15]. TBI is the leading cause of disability among children and younger adults [16]. The most common causes are falls, motor vehicle accidents, assaults, and being struck by or against an object. Being near a blast explosion have been recognized as a cause among active military personal [17].

Traumatic brain injury is classified into three different severities, mild, moderate and severe and the clear majority is mild, roughly 70 to 90 % [18]. The classification is based on acute injury characteristics, most commonly the presenting status at the emergency department (ED) or hospital, assessed by the Glasgow Coma Scale (GCS) [19]. Other acute characteristics include the length of loss of consciousness (LOC) and length of post-traumatic amnesia (PTA), see Table 1. The classification is not based on results from brain imaging techniques. It is also not based on outcome, such as experienced symptoms or disability at any given point in time.

Table 1: Classification of severity for traumatic brain injury

Measure	Severe	Moderate	Mild
Glasgow Coma Scale	3-8	9-12	13-15
Loss of Consciousness	> 36 hours	30 min – 36 hours	< 30 minutes
Post-traumatic amnesia	> 7 days	1-7 days	< 24 hours

2.2 MILD TRAUMATIC BRAIN INJURY

There is today no well-established definition of mTBI. The most commonly used definition is provided by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine [20]. Their definition states that mTBI is a “traumatically induced physiological disruption of brain function” (p.86), 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

- loss of consciousness of approximately 30 minutes or less
- after thirty minutes an initial Glasgow Coma Scale (GCS) of 13-15 and
- post-traumatic amnesia not greater than 24 hours.

There are other notable definitions of mTBI. The World Health Organization Collaborating Centre Task Force on Mild Traumatic Brain Injury definition is comparable in criterions but also explicitly states that the manifestations of mTBI "should not be due to drugs, alcohol, medications; caused by other injuries or treatment for other injuries (e.g., systemic injuries, facial injuries, or intubation); caused by other problems (e.g., psychological trauma, language barrier or coexisting medical conditions); or caused by penetrating craniocerebral injury." [12] (p. 115). Another similar definition is offered by the Centers for Disease Control and Prevention (CDC) working group [21] who defines mTBI as "an injury to the head as a result of blunt trauma or acceleration or deceleration forces" (p. 2). Common acute symptoms such as headache, nausea, dizziness, difficulties with concentration, and emotional lability, are not generally included in the diagnosis of mTBI. One exception is the consensus statement on concussion in sport from the 4th International Conference on Concussion in Sport [22] that includes subjective symptoms (e.g. headache, lability, feeling like in a fog).

Table 2: Glasgow Coma Scale

Score	Motor response	Eye Opening	Verbal Response
6	Obeys		
5	Localizes pain		Normal conversation
4	Flexion – withdraw pain	Spontaneous	Disoriented conversation
3	Flexion abnormal	To Voice	Words, but not coherent
2	Extension	To Pain	No words, only sound
1	None	None	None

The mTBI definition is broad. It encompasses blows to the head that only for a few moments disrupts normal brain functioning to high impact traumas that render the individual unconscious for up to 30 minutes. Some attempts have therefore been made to divide mTBI into sub-categories. A common distinction is between complicated and uncomplicated mTBI [23]. In its original definition the term complicated mTBI was used for those with skull fractures and/or intracranial injury (e.g., edema, contusion or hemorrhage) visible on brain imaging. Today the term is commonly reserved just for those who have signs of intracranial injury. The number of mTBI patients who have a complicated mTBI varies according to initial Glasgow Coma Scale values. For patients who presents with a maximum of 15 points around 5 % have intracranial injury related to the trauma on computerized tomography (CT), and it goes up to 20 % for those with GCS 14 and 30 % for those with GCS 13 [24].

MTBI is not a diagnose per se in either the International Classification of Diseases, 10th revision, ICD-10 [25] or the Diagnostic and Statistical Manual of Mental Disorders -5th edition, DSM-5 [26]. In ICD-10 any uncomplicated mTBI would fit into S06.0: concussion

(commotio cerebri). Complicated mTBIs could potentially fit into the other subcategories in S06, intracranial injuries. In the DSM-5 traumatic brain injury is mentioned in relation to neurocognitive disorder. The definition and criterions for a traumatic brain injury are an "impact to the head or other mechanism of rapid movement or replacement of the brain within the skull" (p. 624) and with one or more of the following signs: loss of consciousness, posttraumatic amnesia, confusion and disorientation, neurological signs.

2.3 EPIDEMIOLOGY

2.3.1 Incidence

Incidence relates to the relative risk in a population to sustain a particular condition. Estimates of the annual incidence of mTBI hospitalized patients in the industrialized world range from 100-300 per 100,000 [18]. The number of hospitalizations has decreased over the last decades due to changes in routines. It is becoming increasingly common that patients with mTBI are observed only at the emergency department and then sent home, especially if a brain scan (CT) does not show signs of intracranial injury. Estimates of emergency department visits show much higher numbers, around 5-600 per 100,000 [27-29]. Not all individuals however visit the emergency or become hospitalized and they represent a large number of unrecorded cases. A previous report has estimated that 14 % of individuals with mTBI instead seek medical attention in other clinics or general practitioner's offices and that 25 % do not seek medical attention at all [21]. MTBI is also often overlooked in hospitalized patients with other prominent injuries [30].

2.3.2 Prevalence

Prevalence relates to the number or percentage of people in a population who have the disease in interest, which in the case of mTBI refers to the percentage of individuals who have *ever* experienced an mTBI. Self-report data are available in a few studies. In a study by Segalowitz and Brown of 18 year old's (n = 616) 31 % reported having suffered an mTBI during their lifetime [31]. Another self-report study by Body and Leathem [32] who asked 14-15 year old's if they had suffered an mTBI during the last three years, 44 % reported that they had sustained one or more head injuries. Retrospective self-reporting may not however be accurate. Thirty-one % of previous American football players reported having sustained more concussions during their active career than they reported in a previous survey 10 years before [33]. In a New Zealand birth cohort study (n = 1265) where TBI was verified in records of medical attendance (including visits to general practitioners) 38 % of the males and 24 % of the women experienced at least one verified TBI up until age 25 [34].

2.3.3 Risk Factors

Basic sociodemographic factors are all associated with the risk of sustaining a TBI. Age shows a bimodal distribution where children and older adults are overrepresented [35]. The highest incidence is seen in children below the age of five years. Older adults over 75 years of age have the highest rates of TBI related hospitalization and death [36]. Male sex is related to

an increased risk of sustaining a TBI. Men run around twice the risk of sustaining a TBI [37]. Higher rates of TBI have also been linked to lower socioeconomic level [38, 39].

Frequent alcohol drinking is associated with a higher risk of sustaining a future TBI [40]. Studies have shown that around 10-18 % of all patients who attend EDs are under the influence of alcohol [41], which may be even higher for mTBI. Concerns have been raised [42] that alcohol intoxication can complicate the diagnosis of mTBI, especially by lowering GCS scores. This has not been confirmed except for those cases when alcohol level is very high, above 200 mg per dl [43, 44].

Lower cognitive ability is also associated with a higher risk for sustaining an mTBI. Based on results from countries where men are conscripted into the army and where different IQ tests have been used, lower performance on these tests have been shown to be predictive of sustaining a future mTBI [45, 46]. Individuals with ADHD also have higher risk for accidents, especially driving accidents have been investigated, which is a common cause of mTBI [47].

2.4 GENERAL OUTCOME

2.4.1 Symptoms

The online Merriam-Webster dictionary defines *symptom* as the "subjective evidence of disease or physical disturbance" [48]. Symptoms can be contrasted to medical *signs* which are indications of a disease that are objectively discernable in an examination. For example, headache is a symptom, fever is a medical sign. Symptoms and signs are often non-specific, but certain constellations that occur together may be highly specific and are then commonly referred to as *syndromes*.

Acute symptoms after mTBI are dominated by a range of somatic symptoms including headache, nausea (sometimes accompanied by vomiting), double and/or blurred vision, but also cognitive symptoms (poor memory and attention) and emotional (depressed mood). In both children and adults, these symptoms are often transient and have a gradual resolution within days or weeks after the injury [49].

Post-injury pain, its incidence and characterization, is an understudied topic in TBI research in general [50]. This is particularly true for mTBI since studies shows that mTBI patients actually report *more* post-injury headache than patients with moderate and severe TBI [51]. In a US-study of ED management of mTBI patients, less than half had any assessment or documentation of their pain [52]. Assessment of pain may be of particular importance in neuropsychological assessments of mTBI patients, since increased pain is known to have an adverse effect on cognition [53-56]. A few studies have examined pain and its relation to cognition in mTBI patients with conflicting results, where some have found an association [57] while others have not [58]. The role of pain was highlighted as a future research priority by The WHO Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury in 2004 [12], and by the International Collaboration on Mild Traumatic Brain Injury Prognosis ten years later [59] since pain may be modifiable in post-injury treatment.

2.4.2 Cognition

The acute effect on cognition (within 24 hours) has mostly been studied in concussed athletes. A meta-analysis reported an overall large effect size of 1.42 on global cognitive functioning. The most affected areas were memory acquisition and delayed memory [60]. Studies of mTBI trauma patients within the first week after injury have shown a global effect size of around 0.4 [61].

Meta-analysis including only prospectively followed mTBI samples have not provided evidence that mTBI is associated with any appreciable long-term associated cognitive deficits. The first meta-analyses, performed by Binder, Rohling and Larrabee [7] included 11 studies with a total of 314 mTBI patients and 308 control subjects. The mean effect size (ES) on cognition at three months or later was 0.12 after controlling for sample size in the included studies. To convert this to a more meaningful number it represents roughly 2 points on an IQ-scale (M = 100, SD =15). This is a difference that most cognitive measurements would not be able to capture since measurement error is usually higher. The number of meta-analysis is now substantial, essentially showing the same pattern of significant acute effects on cognition, followed by rapid recovery and no evidence of cognitive deficits past three months [6, 8, 60-64]. However the quality of these meta-analysis has been questioned [65]. A recent systematic review by the International Collaboration on Mild Traumatic Brain Injury Prognosis found no studies supporting an association between mTBI and chronic cognitive impairment in adults, defined as residual deficits one year or more after injury [66].

Most clinical neuropsychologists working with this patient group would testify that acquired long-term cognitive deficits is indeed possible, especially in the case of patients with complicated mTBI. A debate on whether this group of patients actually exists and if meta-analysis hides them have been subject to a heated discussion [61, 67-69].

2.4.3 Psychiatric disorders

Outcome in terms of psychiatric disorders have been studied particularly with reference to posttraumatic stress disorder (PTSD) and depression. In a recent report [70] from the large TRACK-TBI study [71] with prospectively enrolled adult mTBI patients from EDs, around 10 percent screened positive for depressive disorder and 20 percent for PTSD at follow-up at three months and six months post-injury. This is in line with a prior prospective study by Gil et al who found that 14 % of mTBI patients developed PTSD by six months. Interestingly, different prevalence rates were found if the patient had amnesia for the injury event or not, with those remembering the injury were more likely to develop PTSD [72]. Previous studies with smaller mTBI samples have yielded estimates from 10 to 50 percent for depression after mTBI [73-78].

2.5 PERSISTENT POST CONCUSSION SYMPTOMS

If an individual continues to experience symptoms after an mTBI for an extended period of time, it is typically labeled persistent post-concussion symptoms (PCS). Research studies have used different criteria for this condition, but common is a requirement of at least three remaining symptoms, and at least extended past three months after injury. A formal diagnosis

in ICD-10 is sometimes used for this condition, the *postconcussional syndrome* (F 07.2). The previous edition of DSM, the DSM-IV, included the proposed diagnosis *postconcussional disorder* (PCD). This diagnosis required apart from remaining symptoms also disability and evidence from neuropsychological testing of difficulties in attention and memory. A few studies found limited agreement between these diagnosis' [79-82]. In DSM-5 the diagnosis of postconcussional disorder were removed, and the most fitting diagnosis is now *mild neurocognitive disorder* following TBI. Questions have been raised whether the ICD-10 diagnose postconcussional syndrome actually constitutes a genuine syndrome [83].

The number of mTBI patients with persistent PCS is substantial. Prospectively followed patients from emergency departments who report three or more symptoms is 24 % when only including patients with GCS 15 [84] and higher, from 32 to 41 % when including the whole spectrum of mTBI patients [85, 86]. Several long-term follow up studies, more than one year after injury, also report a high prevalence [87, 88].

2.5.1 Peri-injury factors association with persistent PCS

Given the fact that there is a considerable variation in acute injury characteristics within the mTBI spectrum, it is surprising that most studies report very little, if any, effect on worse subjective outcome. Factors such as initial GCS score, length of loss of consciousness, and length of posttraumatic amnesia has not been shown to predict which individuals who will develop persistent PCS [89-94]. Results from several studies also indicate that patients with complicated mTBIs are not reporting more symptoms when compared to patients with uncomplicated mTBIs [95-98]. A recent study examining the predictive value of MRI-based measures found no added value over and above basic clinical features [99].

2.5.2 Pre-injury factors association with persistent PCS

A number of pre-injury factors have been identified or suggested in the vast mTBI literature.

There are mixed findings regarding sex differences, where some studies have found an association between female sex and persistent PCS [85, 89, 100-103], while other studies have not [104, 105]. The reasons for possible sex differences are unclear. Bazarian et al suggests that it could be due to disruption of endogenous estrogen and progesterone production since the peak of disability is during the child-bearing years [106]. Older age is also associated with persistent PCS. Children tend to have better outcome than adults, and adults under the age of 40 tend to have a better outcome than those over 40 [107].

Pre-injury mental health problems have been found to influence outcome in some studies, but not all. Using psychiatric interviews, Luis et al found that US war veterans with a history of pre-combat psychiatric disorders were more likely to develop persistent PCS after mTBI sustained in combat [108]. In civilians Meares et al found an association between pre-injury depressive or anxiety disorder and development of persistent PCS after mTBI [100, 109]. Other studies have not found an association [110, 111].

Personality traits, especially those concerned with managing life stresses such as injuries and illnesses, is thought to play a role in the development of persistent PCS. An earlier attempt to

categorize vulnerable personality styles based on clinical experience is presented by Kay et al [112] who lists five personality traits: overachievement, dependency, insecurity, grandiosity, and borderline related to the development of persistent PCS. They also describe a hypothetical process for an individual with mTBI for developing persistent PCS. It starts with the injury causing cognitive problems. When the individual tries to return to function again he/she experiences failures, frustration and inability to perform as usual. If this situation is not managed well the individual experiences a "shaken sense of self" (p.378), which in turn lead to loss of control and anxiety and possibly depression. These emotional states then feed back into the cognitive system and worsen the situation. Empirical studies of associations between personality traits and recovery from mTBI are sparse however. Rush et al [113] found no association between symptom reporting and personality traits as measured by the revised NEO Personality Inventory in a prospectively followed mTBI cohort. This is in contrast to a recent study by Yuen et al [114] where associations were found between anxious / depressive traits and higher symptom reporting in mTBI patients.

Another formulation of how emotions and motivation influence the disease process from mTBI into PCS is formulated by King [115] who describes different windows of vulnerabilities after a mTBI for the development of PCS. In particular he points out "unhelpful premorbid schemas and coping responses related to managing abnormal life events" (p.277) as a possible emerging factor for persisting PCS in the post-acute phase (1-6 months). Recent empirical research has demonstrated that measures of psychological resilience and mood predicts persistent PCS [116].

2.5.3 Post-injury factors association with persistent PCS

Numerous factors influence how symptoms and disabilities are experienced and communicated following an mTBI.

Emotional states such as anxiety and worry, and the experience of high level of stress is a central feature in slow subjective recovery after mTBI [117-119]. The relationship between these emotional states and subjective recovery is reciprocal. Post-concussion symptoms influence emotional states, and emotional states influence the perception and experience of post-concussion symptoms [120].

Several studies indicate that symptom reporting after mTBI can be subject to a special kind of recall bias called the "good-old-days" bias. Individuals who are susceptible to this bias tend to overestimate their pre-injury level of functioning and health by reporting significantly less pre-injury symptoms than the base rate of symptoms in the general population or in healthy controls [121-125].

Individuals who have suffered an mTBI are often involved in litigation in the aftermath of the injury. In the 2004 systematic review of prognosis for mTBI by the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury, the most consistent predictor across studies for slower recovery was litigation status [49]. Litigation is also associated with lower performance in cognitive testing [126]. Recent studies have highlighted the significance of this factor in post-injury recovery [127, 128].

2.6 BRAIN RESERVE CAPACITY THEORY

The starting point for this thesis is the hypothesis that individual differences at the time of injury will moderate recovery after brain injury. This is not a novel idea. In fact, observations of striking differences in outcome after seemingly similar brain pathologies are common in medical practice. This led Paul Satz to propose the Brain Reserve Capacity (BRC) theory [11]. The theory proposes that individuals have different amounts of "reserves" that acts as buffers when the brain is injured. The buffers are either *protective* and moderate the brain's ability to withstand the initial injury, or *promoting* that facilitate repair and recovery after injury [129]. The protective factors refer to quantitative physical characteristics, typically indexed by total intracranial volume or ventricle-to-brain ratio, whereas the promoting factors refer to the processing efficiency of neuronal networks [130]. This latter aspect of brain reserve capacity is commonly labeled *cognitive reserve* and is typically indexed by measures of intelligence and socioeconomic variables such as educational and occupational attainment [131].

Cognitive reserve has been studied in neurodegenerative diseases, such as Alzheimer's Disease [132], Huntington's Disease [133], Parkinson's Disease [134] and Multiple Sclerosis [135] supporting its role as a moderating factor for clinical outcome. There is a growing body of evidence that suggest that cognitive reserve also moderates outcome in moderate and severe TBI [136-138]. There is some support for the role of cognitive reserve in recovery after mTBI. Hypothesis that mTBI patients in the acute phase would need to recruit more neural resources to maintain a pre-injury level of cognitive performance has found support in studies using positron emission tomography (PET) [139], and functional magnetic resonance imaging (fMRI) [140]. With regard to persistent PCS after mTBI, lower cognitive reserve has been associated with higher symptom reporting in male veterans [141] and in children [142]. Few attempts have been made to broaden the concept of cognitive reserve to also include emotional and personality factors. One notable exception is an Israeli study by Sela-Kaufman et al who investigated attachment styles, temperament and personality traits as moderators for outcome after TBI [143].

3 AIMS

The overall aim of this work was to study and evaluate prognostic factors association with persistent post-concussion symptoms (PCS) after mild traumatic brain injury (mTBI). Particular emphasis was put on pre-injury cognitive and emotional functioning as potential "reserves" against developing persistent PCS, according to the Brain Reserve Capacity (BRC) theory.

Specific aims for each paper:

- Is emotional awareness and decision making reduced in patients with persistent PCS after mTBI?
- Is lower level of cognitive reserve associated with persistent PCS after mTBI?
- Is lower level of emotional reserve associated with persistent PCS after mTBI?
- Is pain associated with worse cognitive performance in patients with persistent PCS after mTBI?

4 METHODS

This thesis contains four papers, derived from two separate mTBI studies with different study designs. Many of the measures used were the same in both studies.

4.1 STUDY DESIGNS AND SETTINGS

Study 1 was a collaboration research project between brain injury rehabilitation clinics in two counties in Sweden (Stockholm and Södermanland). The principal investigator was professor Aniko Bartfai, and the study has so far provided one publication concerning methodological aspects on capturing fatigue with neuropsychological tests [144]. It has a case-control study design and all patient and control assessments took place in outpatient settings at the involved clinics.

Study 2 was a prospective inception cohort study with professor Jörgen Borg as principal investigator. Patients were recruited from emergency departments in close proximity to the actual injury. The study was based at the Danderyd Hospital where most patients (75 %) were recruited. For a limited time, patients were also recruited from the EDs of Karolinska University Hospital and Södersjukhuset. The study has generated three previous publications concerning the biomarker S100B, symptom development until three months and cognitive impairment as assessed by an automated psychological test [145-147].

4.2 INCLUSION AND EXCLUSION CRITERIA

In Study 1 inclusion required a documented injury consistent with the criteria for mTBI by the American Congress of rehabilitation medicine [20], age between 18 and 50, and proficiency in Swedish. Patients were excluded if they had a previous diagnosis of severe psychiatric disease or disorder (e.g., Bipolar Disorder, Schizophrenia), a previous significant acquired brain injury, including an mTBI that had required ED-visit or hospitalization. Furthermore, if CT or MRI images were available from time of injury, those who had subdural hematomas were excluded, since it was considered evidence of a more severe injury. A non-injured control group was collected through advertisements and friends of staff. The controls were offered a gift card of 500 SEK for their participation as well as an optional feedback session.

In Study 2, patients between ages 15 and 65 who attended the EDs with head injury were consecutively considered for inclusion if the admission to the ED was within 24 hours after injury. The mTBI had to be associated with loss of consciousness for no more than 30 minutes and/or post traumatic amnesia not exceeding 24 hours. Inclusion further required an initial GCS score of 14 or 15. Other significant body injury, major neurological disorder (e.g. Multiple Sclerosis), and previous significant brain injury were exclusion criteria. Previous mTBI was allowed. A non-injured healthy control group was collected through local advertisements. No financial or other compensation were offered for their participation.

4.3 STUDY SAMPLES

4.3.1 Study 1

A total of 24 patients and 31 controls were included in the study. The gender distribution (M/F) in the mTBI group (12/12) was similar in the control group (13/18), $\chi 2 = 0.36$, $p = 0.551$. The average age at assessment for the mTBI group ($M = 35.7$, $SD = 9.8$, range 18-51) was not significantly different from the controls ($M = 36.7$, $SD = 8.8$, range 20-49), $t\ (53) = 0.41$, $p = 0.683$. Years in formal education for the mTBI group ($M = 12.0$, $SD = 1.5$, Range 9-16) was however fewer than the controls ($M = 13.1$, $SD = 1.9$, Range 11-18), $t\ (53) = 2.33$, $p = 0.024$. The injury characteristic for the mTBI patient can be seen in table 3.

Table 3: Injury characteristics for the 24 mTBI patients in Study 1, n (%)

Characteristic		Characteristic	
Loss of consciousness		Retrograde amnesia	
None	7 (29)	None	16 (67)
< 1 min	1 (4)	<1 min	2 (8)
1-5 min	6 (25)	1-5 min	3 (12)
6-30 min	5 (21)	> 5 min	2 (8)
Uncertain but <30 min	5 (21)	Missing	1 (4)
Post traumatic amnesia		Type of injury	
None	4 (17)	Car accident	9 (38)
1-5 min	2 (8)	Falls	8 (33)
6-45 min	7 (29)	Bicycle / MC accident	2 (8)
>45 min	4 (17)	Assault	2 (8)
Uncertain but <60 min	7 (29)	Hit by object	2 (8)
Injury related CT/MRI findings	4 (20)	Kicked by horse	1 (4)

Note: Injury related signs of abnormality were found in four patients. Three had intracranial hemorrhages, one patient a fractured skull. In two additional patients, abnormalities were found (white matter lesions) that the radiologist did not consider caused by injury. Four patients had not undergone CT or MRI at time of injury. Percentage calculation has been adjusted to reflect only those with imaging data.

4.3.2 Study 2

A total of 122 patients and 35 controls were included in the study. The gender distribution (M/F) in the mTBI group (71/51) was similar in the control group (17/18), $\chi 2 = 1.02$, $p =$

0.312. The average age for the mTBI group (M = 37.3, SD = 14.6, range 15-65) was not significantly different from the controls (M = 39.0, SD = 14.9, range 16-62), t (155) = 0.61, p = 0.541. Years in formal education for the mTBI group (M = 11.9, SD = 4.0, Range 3-19) was not significantly different from the controls (M = 13.2, SD 2.5, Range 9-17), t(147) = 1.81, p = 0.072. The injury characteristic of the cohort at inception can be seen in table 4.

Table 4: Injury characteristics for the 122 mTBI patients in Study 2, n (%)

Characteristic		Characteristic	
Glasgow Coma Scale		Alcohol intoxication	
15	109 (89)	None	92 (75)
14	13 (11)	<0.20 ‰	20 (16)
Loss of consciousness		>0.20 ‰	10 (9)
<1 min	56 (46)	Injury related CT/MRI findings	8 (7)
1-5 min	47 (39)	Type of accident	
6-30 min	19 (16)	Fall from heights	24 (20)
Post traumatic amnesia		Fall same level	48 (39)
<1 min	21 (17)	Traffic	23 (19)
1-5 min	29 (24)	Assault	9 (7)
6-45 min	45 (37)	Collisions in sport	6 (5)
>45 min	27 (22)	Hit by object	6 (5)
Retrograde amnesia		Other	6 (5)
None	111(91)	Kicked by horse	3 (3)
< 5 min	7 (6)	Run into objects	3 (3)
> 5 min	4 (3)		

4.4 PROCEDURES

4.4.1 Study 1

Each referral was handled by normal clinical routines that each clinic had established at that time. If the referral was accepted, the patient was subsequently transferred to the unit where neuropsychological assessments were conducted. Neuropsychologists involved in the research project carefully analyzed the referral and medical records at hand to establish that all inclusion criteria were matched and that no obvious exclusion criteria could be applied. Each patient was then booked for assessment according to normal routines.

At the patient's first visit to the neuropsychologist he or she was informed about the research project, and a signed consent form was collected for patients who accepted to be part of the

study. A detailed history was then taken using a structured interview form. If any ambiguities regarding injury severity remained after the interview (e.g., length of LOC or PTA) further requests of medical records were ordered (e.g. ambulance reports or ED-records).

After the interview, the neuropsychological assessment was performed by neuropsychologists in the research project that had been trained to administer all the tests according to manuals and a protocol including the order to administer the tests. Since the assessment was comprehensive, several sessions were needed with a total assessment time between 4 to 6 hours. Self-report questionnaires were filled in by the patients between sessions.

4.4.2 Study 2

Patients who matched the inclusion criteria were approached at the ED and was given information about the study. If informed consent was obtained, the ED staff recorded GCS score, duration of loss of consciousness, duration or amnesia (both post-traumatic and retrograde), the results from a breath alcohol test, and requested CT scan of the brain. The follow-up schedule consisted of six occasions.

4.4.2.1 Day one

At day one the patients had their blood samples and completed the Rivermead Post Concussion Symptoms Questionnaire (RPQ). They also went through a computerized automated psychological test, the APT [148], which consisted of measures of attention, memory and reaction time.

4.4.2.2 Day seven

One-week post-injury an experienced neuropsychiatrist performed a multi-axial assessment according to the Diagnostic and Statistical Manual of Mental Disorders – IV (DSM-IV) [149] and established current and previous psychiatric diagnosis (axis 1 and 2). The general medical condition (axis 3) was assessed by a checklist. The *Severity of Psychosocial Stressors Scale* [150] was used to assess axis 4. This scale consists of eleven potential areas of stress that the participant marks as present or not present during the last year, and then grades the overall stress level from "none" to "catastrophic". Finally, Axis V, global assessment of function (GAF) was assessed by use of self-report GAF-scales from 0 to 100.

At this occasion the patients completed the pre-injury measures Swedish Universities Scales of Personality (SSP) and Sense of Coherence Scale (SOC). They were specifically instructed to base their answers on these questionnaires according to their pre-injury level of functioning. They also completed the Hospital Anxiety and Depression Scale (HADS), Impact of Event Scale – Revised (IES-R), the Alcohol Use Disorders Identification Test (AUDIT) and the RPQ. In addition, a magnetic resonance imaging of the brain was undertaken.

4.4.2.3 Day 14

Two weeks post injury the patients had their blood sampled, completed the RPQ and went through the APT once again.

4.4.2.4 Three months follow-up

Three months post-injury, the patients went through a one-session neuropsychological assessment performed by experienced neuropsychologists (see Table 6 for complete list for tests). Patients also had their blood sampled, completed the RPQ and the Rivermead Head Injury Follow-Up Questionnaire (RHFUQ), and performed the APT:

4.4.2.5 Six- and twelve-months follow-ups

These follow-ups consisted of mailed questionnaires (RPQ, HADS, RHFUQ) that the patient completed and mailed back.

The non-injured controls followed a limited schedule with blood sampling, completion of RPQ and performed the APT at day 1, day 14 and three months. The final occasion also included the same neuropsychological assessment as the patients.

4.5 SELF-REPORT MEASURES

4.5.1 Alcohol Use Disorders Identification Test

The Alcohol Use Disorders Identification Test (AUDIT) contains 10 items for which the subject marks his or her alcohol consumption and drinking behaviour. It also asks about adverse reactions to alcohol and problems related to alcohol during the last 12 months. Items are scored from 0-4, and a cut-off score of 8 or higher is used for identification of hazardous alcohol use [151].

4.5.2 California Concussion Scale

The California Concussion Scale (CCS) is a measure of injury severity exclusively for mTBI. The scale consists of three variables (PTA duration, LOC and neurological symptoms) and possible scores range from 3 to 15 where lower scores reflects a more severe injury, similar to the Glasgow Coma Scale. The scale can be administered retrospectively [152].

4.5.3 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a brief self-report questionnaire and consists of fourteen items measuring common symptoms of depression and anxiety. It has been developed primarily to be used in non-psychiatric settings. Each item is rated on a four-point scale, ranging from 0 to 3. The scale is then evaluated for depression and anxiety separately, where scores ranging from 0-7 is considered normal, 8-10 mild, 11-14 moderate, and 15-21 severe [153].

4.5.4 Impact of Event Scale – Revised

The Impact of Event Scale – Revised (IES-R) assesses stress reactions after traumatic events. The scale consists of 22 items where the subject rates frequency of stress reactions during the last week. The scale uses a four options scale where 0 = not at all, 1 = rarely, 3 = sometimes, and 5 = often. Apart from the overall score, The IES-R measures three subcomponents associated with PTSD: intrusion, avoidance and hyperarousal [154].

4.5.5 Rivermead Head Injury Follow Up Questionnaire

The Rivermead Head Injury Follow Up Questionnaire (RHFUQ) measures perceived change and disability in ten different areas (e.g. coping with family demands, previous work load). It uses a five-point scale ranging from 0 = no change, to 5 = a very marked change [155].

4.5.6 Rivermead Post Concussion Symptoms Questionnaire

The Rivermead Post Concussion Symptoms Questionnaire (RPQ) consists of 16 common symptoms in a five-point scale that the subject is asked to rate as present or not during the last 24 hours. Those who do not experience a symptom can mark 0 or 1 on the scale which indicates either that the symptom is not present and has not been present since the injury (0), or mark 1 which indicates that the symptoms has been present since the injury, but no longer is. If the symptom is present, the subject rates the severity as mild (2), moderate (3) or severe (4). In the instructions the subjects are told that the symptoms occur normally and that they should compare themselves with before the injury. When calculating the score, ratings of 1 (symptoms no longer present) are excluded. Total scores ranges from 0 to 64 [156].

4.5.7 Sense of Coherence Scale

The Sense of Coherence Scale (SOC) measures psychological resilience to stressful events. The scale is composed of 39 statements that the subjects marks his or her agreement with on a 7-point Likert scale. The scale, which was developed by Aaron Antonovsky measures three underlying constructs: comprehensibility, manageability, and meaningfulness as well as provides a global summary score for psychological resilience [157].

4.5.8 State-Trait Anxiety Inventory

The Spielberger State and Trait Anxiety Inventory (STAI) is a commonly used measure of anxiety. It consists of two sub scales for anxiety, one for state anxiety which can be defined as the current level of anxiety that the person is experiencing, and one for trait anxiety, which can be defined as the level of anxiety that the person generally experiences. Each scale consists of twenty items, rated on a 4-point Likert Scale. Scores ranges from 20 to 80 [158].

4.5.9 Swedish Universities Scales of Personality

The Swedish Universities Scales of Personality (SSP) is a personality inventory that consists of thirteen scales, each consisting of seven statements, for a total of 91, that the respondent marks his or her agreement with. The SSP is the successor of the previous Karolinska Scales of Personality (KSP), which was developed by Schalling et al [159] from a biological perspective on personality. The SSP was standardized on a representative sample (n = 714) of the Swedish population [160], and the factor analysis resulted in a three-factor model that corresponds to neuroticism, aggressiveness and extraversion. Raw scores are summed and transformed into T-scores for men and women separately.

4.5.10 Örebro Musculoskeletal Screening Pain Questionnaire

The Örebro Musculoskeletal Screening Pain Questionnaire (ÖMSPQ) consists of 25 items measuring subjective pain, as well as psychological and social factors with the aim to predict development of chronic pain. The first 7 items consist of background questions, location of musculoskeletal pain (neck, shoulder, upper back, lower back and legs), length of sick leave and duration of pain. The remaining 18 items in the questionnaire uses a Likert scale format (0-10), with questions about pain levels, fear-avoidance beliefs, emotional states, coping and activities of daily living [161].

Table 5: List of self-report measures included in the studies

Measure	Study 1	Study 2
Alcohol Use Disorders Identification Test	-	x
California Concussion Scale	x	-
Hospital Anxiety and Depression Scale	x	x
Impact of Event Scale - Revised	-	x
Rivermead Post Concussions Symptoms Questionnaire	x	x
Rivermead Head Injury Follow Up Questionnaire	-	x
Sense of Coherence Scale	-	x
Trait and State Anxiety Inventory	x	-
Swedish Universities Scales of Personality	x	x
Örebro Musculoskeletal Pain Screenings Questionnaire	x	-

Note: Study 1 also included tests that were not used for this thesis: The Fatigue Severity Scale, The Pittsburg Sleep Index Questionnaire, and the original Impact of Event Scale.

4.6 PERFORMANCE MEASURES

4.6.1 Level of Emotional Awareness Scale

The Level of Emotional Awareness Scale (LEAS) consists of short written scenarios with two people interacting. The subject's task is to write down how he or she thinks the protagonist in the scenario feels, and how he or she imagines the other person in the scenario is feeling. Each scenario is scored using a model of emotional development that was developed by Richard Lane and co-workers [162, 163], inspired by the work of Piaget and his model of cognitive development. To score LEAS protocols each scenario is coded by awarding emotion words: 0 = cognitive thoughts (e.g. "I feel it is expensive") or no answer at all, 1 = words describing somatic sensations (e.g. tired), 2 = words describing undifferentiated affect or action tendencies (e.g. "feel good"), 3 = single emotion words (e.g. "sad"), and 4 =

two or more emotion words. A total score for each scenario is also calculated by awarding it the highest attained score for either “self”, or “other”, unless both have been awarded 4 points, then the total score is set to 5. The shortened version consists of 10 scenarios, and scores range from 0 to 40 for self and other scores, and 0 to 50 for total score.

4.6.2 Iowa Gambling Task

The Iowa Gambling Task (IGT) measures decision making in a simulated card game involving a symbolic sum of money. The participant is seated in front of four decks of cards, labeled A, B, C and D and is asked to pick a card from the decks one at a time for a total number of 100 trials. The participant is initially given a loan of money (2000 US dollars in the American version) and is then asked to earn as much as possible by choosing cards from deck. The decks vary in the amount of monetary gains they give, and also infrequently gives monetary punishments. Deck A and B gives large short-term rewards but are not beneficial for long-term benefits. The opposite is true for deck C and D. The participant is not told about this beforehand and will have to learn this by experience during the 100 trials to make an overall gain [164].

4.6.3 Selective Reminding Test

The Buschke Selective Reminding Test (SRT) is a verbal learning test where the participant is presented with 12 words and asked to recall as many as possible. The test continues for 12 trials but can be stopped prior to that if the participant has succeeded recalling the complete list for two consecutive trials. For each subsequent trial after the first, the participant is only reminded of those words he or she could not recall in the previous trial. The participants memory of the words is tested with a 30-minute delayed recall condition. The test also includes a cued recall test and a multiple-choice recognition format [165, 166].

4.6.4 Paced Auditory Serial Addition Test

The Paced Auditory Serial Addition Test (PASAT) is a measure of speed of information processing. It consists of a pre-recorded string of 61 single-digits that are presented to the participant at varying speed, where the interval between numbers are shortened for subsequent trials. The participants task is to add the two most recent numbers and ignore previous numbers and his or her own previous answers (e.g. for the following sequence 4-5-3-1, a correct verbal response would be 9, 8 and 4). The score is calculated as the sum of all correct responses during each trial [167]. The PASAT was reviewed by Tombaugh [168].

4.6.5 Stroop Color and Word Test

The Stroop Color and Word test is a test of cognitive flexibility and inhibition. The participant is presented with a sheet of paper with rows of color words, but each are printed in a different color. The task is to read out loud the printed color, while ignoring the semantic meaning of the written word. The test also contains a baseline condition where the subject is just asked to read color words, and one condition with just naming the color of printed strings of X’s. Score is calculated based on time to complete each trial [169, 170].

4.6.6 Trail Making Test

The Trail Making Test (TMT) is a paper and pencil test where the participant is asked to connect 25 encircled numbers (part A) and 25 encircled numbers and letters (part B) that are randomly spread out on a paper. It measures visual scanning, graphomotor speed and mental flexibility. Time to complete each part is the raw score used for calculating T-scores [171].

4.6.7 Verbal Fluency

In the Verbal Fluency test, the participant is asked to produce as many words as possible starting with the same initial letter. The test consists of three one-minute trials with different letters (i.e. F, A and S) and measures the participants ability to produce words using a restricted search condition [172].

4.6.8 Design Fluency

The Design Fluency test was developed as a non-verbal alternative to tests of verbal fluency. It is a paper- and pen based test where the participant is asked to produce unique designs using an imposed restriction of only using four lines or components. The time limit is set to four minutes, and each unique design is awarded one point [173].

4.6.9 Rey Fifteen Item Test

The Rey fifteen-item test (FIT) is a brief performance validity test [174]. The participant is shown a card with 15 items for 10 seconds and asked to memorize them. The items are presented as five rows with strings of well-known sequences (e.g. A-B-C) making the test very easy for most individuals. A cut-off score of <9 is suggested by Lezak et al [171] as evidence of low effort to perform to the best of one's ability. ß

4.6.10 Wechsler Adult Intelligence Scale

The Wechsler Adult Intelligence Scale (WAIS) is a test battery for measuring general intelligence and considered the gold standard in its field. In Study 2, the following subtests were used from WAIS-R [175]: *Information*, a measure of acquired general knowledge and a good proxy for crystallized intelligence, *Digit span*, a measure of working memory, and *Digit Symbol,* a measure of processing speed. From the WAIS-R Neuropsychological Instrument (NI) the *Digit Symbol A* was chosen which is a test of incidental memory, and the *Block Span*, a spatial equivalent to the Digit span subtest [176].

In Study 1 the WAIS-III was used [177]. As in Study 2, Information, Digit Span, Block Span and Digit Symbol was used. In addition, subtest *Letter-Number Sequences*, a measure of working memory, and Matrix reasoning, a measure of non-verbal abstract problem solving was included.

The Digit span sub-test was also used to calculate Reliable Digit Span (RDS) in Study 2, which is an embedded performance validity test. The RDS score is computed by adding the number of digits from the longest errorless sequence from the forward and backward

condition [178]. A cut-off score of <7 was used, as suggested by Greve et al [179] for indication of low effort.

Table 6: List of performance measures included in the studies

Measure	Study 1	Study 2
Level of Emotional Awareness Scale	x	-
Iowa Gambling Task	x	-
Selective Reminding Test	x	x
Phased Auditory Serial Addition Test	-	x
Trail Making Test	x	x
Verbal Fluency	x	-
Design Fluency	x	-
Stroop Color and Word test	x	x
Wechsler Adult Intelligence Scale		
Digit Span	x	x
Block Span	x	x
Information	x	x
Digit Symbol	x	x
Digit Symbol A	-	x
Letter-Number Sequences	x	-
Matrix Reasoning	x	-

Note: Study 1 also included the following tests that are not included in this thesis: Ruff 2 & 7 Selective Attention Test, Grooved Pegboard, Motor functions from the Luria Battery, Rey-Osterreith Complex Figure Test with Boston Qualitative Scoring System, Stroop Color and Word Test and Sniffn' Sticks test (screening 12 version).

4.7 STATISTICS

Data from the two studies were entered into and analyzed with the IBM Statistical Package for the Social Sciences (SPSS). Variables were first checked for outliers or wrongly entered data. Variables were then summarized with descriptive statistics (e.g. frequencies, means, standard deviations) and checked for outliers or wrongly entered data.

Inferential statistical analysis for continuous variables were either standard parametric methods (Student's t-test, ANOVA, ANCOVA) or non-parametric analysis (Mann-Whitney, Kruskal-Wallis). Categorical data were analyzed with chi-square. Fisher's exact test was used when expected cell frequencies were less than 6. Associations between variables were analyzed with Pearson correlational analysis, or Spearman rank correlational analysis if variables were skewed. Logistic regression analysis was used in paper 2 and 3. Significance level was set to $p < 0.05$, and all tests were two-tailed. Effect sizes were provided when appropriate, either Cohen's *d*, or odds ratios.

4.8 ETHICS

4.8.1 Ethical permissions

Study 1 was approved by the regional ethical board in Stockholm, Sweden (registration number: 04-415/2). Study 2 was approved by the Karolinska Institutet Research ethical committee (registration number: 00-013). All participants received oral and written information and gave their informed written consent to take part in the study.

4.8.2 Ethical considerations

According to the influential work of Beauchamp and Childress [180] there are four principles in medical ethics: autonomy, non-maleficence, beneficence, and justice. In the present studies the respect for autonomy was reached by giving the participants detailed information and collecting informed consent. In study 2, consent was collected at the ED where most patients likely were still cognitively affected by the mTBI. This is potentially an ethical dilemma, but patients were told they could at any time abort their participation in the study with no negative effect on clinical management. The principle of *beneficence* say that research should be of use and promote health and well-being for patients. As stated in the background, mTBI is common, and although most recover many do not. The sheer volume of patients makes it necessary to find prognostic factors that can be of used to predict which patients who will develop persistent PCS to target interventions. The third principle, *non-maleficence*, is the principle of do no harm. In study 2, a delicate problem concerns the continuous self-reporting of symptoms for one year. This could potentially increase self-awareness and focus on symptoms that may have been neglected otherwise, essentially creating a nocebo effect. Studies have shown that patients report more symptoms when administered self-report scales compared to when they are only asked to spontaneously report them [181]. The principle of *justice* deals with equality of opportunity implying that people from a certain group in society is not either privileged or abused in the research. In both studies participants were included as long as they fulfilled inclusion criteria. No regard was payed for gender, ethnicity or socio-economic status.

5 RESULTS

5.1 POST CONCUSSION SYMPTOMS (PAPER 1- 4)

The mTBI sample in Study 1 reported on average 9.5 remaining symptoms in RPQ, and all but two patients (92 %) reported three or more symptoms. In the prospective Study 2, follow-up data were available for 102 patients by three months (84 %) and 94 patients by 1-year (77 %). The final drop-out analysis at the 1-year follow up showed that drop-outs had fewer years of education (M = 10.8, SD = 3.6) than remaining patients (M = 12.6, SD = 2.6), t = 2.46, p = 0.015. The drop-outs did however not differ in any of the acute injury characteristics (LOC, PTA, GCS, alcohol intoxication at admission, previous psychiatric history or initial symptom severity as measured by the RPQ). In Table 7 the results from RPQ can be seen for the two follow-up assessments compared to the clinical sample in Study 1. In paper 3, an additional criterion of two or more disabilities as reported in RHFUQ was added for classification of persistent PCS. Eleven patients (12 %) matched these more restricted criteria.

Table 7: Results from the Rivermead Post Concussional Symptoms Questionnaire at 3- and 12-months post injury in Study 2 and the clinical sample in Study 1.

Variable	3 months	12 months	Clinical sample
Persistent PCS, %	33	19	92
Number of symptoms, *M* (*SD*)	2.5 (3.9)	2.2 (4.1)	9.5 (4.0)
Average score, *M* (*SD*)	6.5 (11.3)	6.0 (13.3)	26.9 (12.6)

Note: Persistent PCS is defined as reporting three or more remaining symptoms in RPQ. In the prospective cohort study 102 patients were still in the study by 3 months and 94 by 12 months. The clinical sample were assessed on average 2 years post-injury and consisted of 24 patients.

5.2 EMOTIONAL AWARENESS AND DECISION MAKING (PAPER 1)

Since education differed between the two groups in Study 1, associations between education and performance measures were first analyzed. Education was associated with total-score in LEAS (r = 0.42, p = 0.001) but not with total net score in IGT (r = 0.10, p = 0.465).

To adjust for this, analysis of covariance (ANCOVA) with education as covariate were performed for group comparisons on the LEAS. No effect was found for group in total score (F = 0.81, p = 0.373), Self-score (F = 1.24, p = 0.270), or Other-score (F = 0.67, p = .0418).

As can be seen in Figure 1, both groups improved their performance over the 100 trials in IGT. However, no significant differences in performance were noted with regard to total net score, number of cards drawn from each deck, block scores, or classification of participants performances into impaired vs non-impaired ($\chi 2$ = 0.01, p = 0.993).

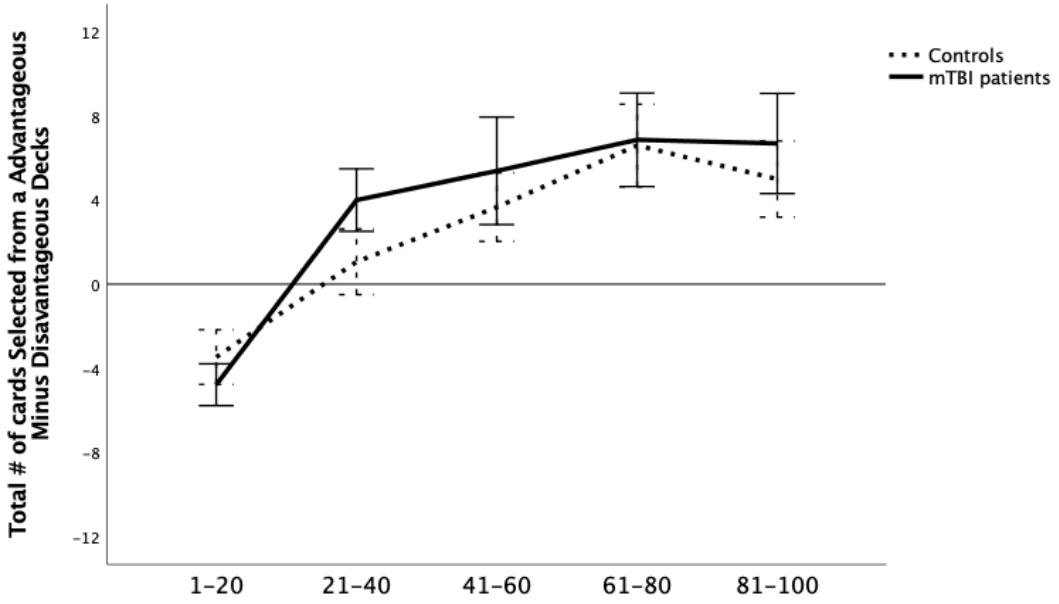

Figure 1: Mean scores (± SEM) on the Iowa Gambling Task for each block of cards for mild traumatic brain injury patients (n = 23) and non-injured controls (n = 30)

5.3 PERSONALITY TRAITS (PAPER 1 AND 3)

The personality inventory, SSP, revealed significant differences between the clinical sample of mTBI patients in Study 1 and the controls (Paper 1). Specifically, the mTBI patients, compared to controls, had elevated levels of somatic trait anxiety ($M = 55.9$, $SD = 12.9$) compared to controls ($M = 45.5$, $SD = 6.8$), $t = 3.58$, $p = 0.001$, $d = 1.01$. Patients also had higher levels of psychic trait anxiety ($M = 47.8$, $SD = 9.3$), than controls ($M = 42.9$, $SD = 7.2$), $t = 2.23$, $p = 0.003$, $d = 0.59$, although not elevated compared to the Swedish norms. The strongest effect was found for the trait stress susceptibility where patients ($M = 60.5$, $SD = 13.8$) had much higher levels than controls ($M = 41.7$, $SD = 11.7$), $t = 5.47$, $p < 0.001$, $d = 1.47$. All these traits are associated with the broader construct of neuroticism. Traits related to extraversion or aggression-hostility were not significantly different in the two groups.

In Study 2 (paper 3), the results on SSP at one-week post-injury were compared for patients who developed persisting PCS and disability and those who had recovered by 1-year post-injury. The PCS group ($n = 11$) had significantly elevated levels of somatic trait anxiety ($M = 53.8$, SD = 11.0), compared to recovered patients ($M = 45.3$, $SD = 7.8$), $t = 2.48$, $p = 0.030$, $d = 0.89$. The PCS group also had elevated levels of the trait embitterment ($M = 59.3$, $SD = 15.3$), compared to those who had recovered ($M = 46.7$, $SD = 8.4$), $t = 2.66$, $p = 0.022$, $d = 1.02$. Finally, the PCS group had higher levels of the trait mistrust ($M = 55.1$, $SD = 13.2$), than recovered patients ($M = 44.5$, $SD = 10.7$), $t = 3.00$, $p = 0.004$, $d = 0.88$.

5.4 COGNITIVE RESERVE (PAPER 2)

Three cognitive reserve indicators were used in paper 2 to examine possible association with persistent PCS: 1) Premorbid IQ estimated from sub-test Information from WAIS-R, 2) highest completed level of education according to the International Standard Classification of Educational Degrees, ISCED-2011 [182] and 3) current occupational skill level as defined by the International Standard Classification of Occupation, ISCO-08 [183].

A one-way ANOVA showed significant differences in scores on Information from WAIS-R, F= 5.17, p = 0.007. Post-hoc analysis revealed that patients with persistent PCS (M = 8.1, SD = 3.0) had lower average score than both the recovered group (M = 10.6, SD = 2.8) and the control group (M = 11.1, SD = 2.5). Higher level of education was associated with recovery (linear-by-linear association 4.2, p = 0.032, as well as higher occupational skill level (linear-by-linear 7.70, p = 0.006). A final logistic regression analysis showed a fourfold increased risk of developing persistent PCS for those with lower estimated premorbid IQ, see Table 8.

Table 8: Results from Logistic regression analysis (adjusted) of cognitive reserve measures and PCS outcome by three months

Cognitive reserve measure	*p*	*OR*	95% *CI*
Low premorbid IQ	0.010	4.14	1.39 - 12.26
Low educational level	0.583	1.40	0.42 - 4.65
Low occupational skill level	0.870	0.90	0.26 - 3.11

Note: Measures were dichotomized. Low premorbid IQ was set at a scaled score of 10 or less in subtest Information from WAIS-R, Low educational level at upper secondary school or lower, and low occupational skill at skill level 2 or lower based on ISCO-08 categorization.

5.5 COGNITIVE DEFICITS (PAPER 2 AND 4)

Although 102 mTBI patients were still in study 2 by the time of the three months follow-up, only 88 patients participated in the neuropsychological assessment and 32 controls. The 14 additional mTBI drop-outs did not differ from the other remaining patients except being on average 11 years younger, t = 2.60, p = 0.011). Six patients and four controls did not pass the performance validity test, RDS, and were removed from further analysis. In total, valid neuropsychological assessment data exist for 82 patients and 28 controls. Comparison between the patients with persistent PCS (n = 27), patients who had recovered (n= 55) and controls are shown in Table 9.

Table 9: Cognitive outcome three months post injury for mild traumatic brain injury patients with persistent post-concussion symptoms (PCS), patients who had recovered (R) and controls (C).

	PCS	Recovered	Controls		
Domain	*M (SD)*	*M (SD)*	*M (SD*	*p*	Post-Hoc
Executive function					
Stroop Color-Word	51.8 (7.7)	51.1 (7.7)	53.8 (10.0)	.375	
Trail Making, Part B	49.5 (8.3)	51.3 (9.2)	51.7 (8.1)	.386	
Memory and learning					
SRT Total Recall	40.3 (15.5)	44.4 (11.8)	51.6 (10.8)	.004	PCS, R < C
SRT Consistent LTR	38.5 (14.6)	42.2 (12.4)	50.8 (11.8)	.001	PCS, R < C
SRT Delayed Recall	43.8 (17.3)	46.1 (14.5)	52.0 (9.3)	.073	
SRT Cued Recall	10.5 (1.5)	10.7 (1.8)	11.5 (0.8)	.004	PCS < C
SRT Multiple Choice	11.7 (0.5)	12.0 (0.2)	11.9 (0.4)	.002	PCS < C
WAIS-R Digit Symbol A	6.6 (2.2)	6.9 (2.2)	7.3 (2.0)	.454	
Attention					
WAIS-R Digit Span	9.4 (3.1)	9.8 (2.8)	10.1 (2.9)	.673	
WAIS-R Block Span	15.7 (3.7)	16.8 (2.8)	17.0 (3.1)	.236	
PASAT (2.4 sec)	51.6 (8.4)	55.4 (7.0)	54.3 (7.0)	.102	
PASAT (1.6 sec)	52.4 (6.1)	54.3 (8.4)	54.6 (5.8)	.526	
Processing speed					
Trail Making, Part A	53.2 (7.8)	52.9 (8.7)	54.1 (7.4)	.943	
WAIS-R Digit Symbol	8.9 (2.8)	10.7 (3.3)	10.5 (2.5)	.024	PCS < R, C
Stroop Word	47.2 (9.2)	48.3 (6.3)	48.5 (6.6)	.766	
Stroop Colour	44.7 (5.4)	44.9 (6.1)	45.8 (7.9)	.810	

Note: SRT = Selective Reminding Test. WAIS-R = Wechsler Adult Intelligence Scale – Revised. PASAT = Phased Auditory Serial Addition Test. Data were heavily skewed for SRT and Trail Making, thus non-parametric analysis was used (Kruskal-Wallis).

In Study 1 (paper 4), the performance in the neuropsychological test battery for the mTBI patients (n = 23) was compared with the non-injured controls (n = 29). Patients, who were assessed on average two years post injury performed worse than controls on all cognitive tests, except for WAIS-III Information, Design Fluency, and the multiple-choice test in Selective Reminding Test. Largest effect sizes (*d*) were noted for WAIS-III Digit Symbol (1.25), WAIS-III Digit Span (1.06), Verbal Fluency (1.06) and WAIS-III Letter Number Sequences (0.98). All, by convention, signifies large effects [184].

5.6 PRE- AND POSTINJURY FACTORS ASSOCIATED WITH PERSISTENT PCS (PAPER 3)

One-year post injury, 94 patients were still in the Study, and 11 (12 %) matched the combined criteria for persistent PCS (three or more symptoms in RPQ and two or more disabilities in RHFUQ). Pre-injury factors association with PCS are shown in table 10. On average, patients with PCS also had lower psychological resilience (M = 142, SD = 26), than recovered patients (M = 158, SD = 20), t = 2.44, p = 0.017, d = 0.69, as measured by SOC.

Table 10: Pre-injury variables for mild traumatic brain injury patients with persisting PCS and disability (n = 11) and those who had recovered (n = 83).

Variables	PCS	Recovered	p	OR (95 % CI)
Female gender	8 (73)	29 (35)	.022	5.0 (1.2 – 20.2
Pre- or concurrent psych disorder, n (%)	9 (82)	20 (24)	.001	14.2 (2.8 – 71.1)
Previous psych disorder	7 (64)	16 (19)	.004	7.3 (1.9 – 28.1)
Concurrent psych. disorder	7 (64)	8 (10)	<.001	16.4 (3.9 – 68.5)
Family history of psych disorder	4 (36)	17 (20)	.077	2.4 (0.9 – 6.3)
Self-assessed GAF, Mean (SD)				
The year before the injury	67 (22)	86 (12)	<.001	0.9 (0.8 – 1.0)
The two weeks before the injury	73 (20)	87 (11)	.003	0.9 (0.8 – 1.0)
Previous mild traumatic brain injury	2 (18)	4 (5)	.117	4.3 (0.6 – 27.1)
Alcohol consumption (Audit)				
Mean (SD)	5.5 (8.1)	5.0 (4.2)	.748	1.0 (0.8 -1.2)
Eight or above, n (%)	1 (10)	13 (17)	.573	0.5 (0.0 – 4.7)
# of psychosocial stressors, M (SD)	3.7 (2.2)	1.3 (1.4)	<.001	2.1 (1.4 – 3.1)

Post-injury anxiety and depression at 1 week were significantly elevated in the group who later developed persistent PCS. Specifically, on the HADS, PCS patients rated anxiety significantly higher (M = 8.4, SD = 5.7) than recovered patients (M = 2.7, SD = 3.3), U = 730, Z = 3.3, p = 0.001, and depression (M = 6.7, SD = 4.7) than recovered patients (M = 2.2, SD = 2.6), U = 735, Z = 3.3, p = 0.001. Large differences were also noted on post-traumatic stress, as measured by the IES-R. PCS patients had higher total score (M = 37, SD = 30), than recovered patients (M = 14.5, SD = 14.5), U = 687, Z = 2.72, p = 0.007. Further analysis of the subscales in IES-R revealed that only the hyperarousal subscale was significantly elevated for the PCS patients compared to recovered patients, U = 769, Z = 3.74, p < 0.001.

5.7 MILD TRAUMATIC BRAIN INJURY AND PAIN (PAPER 4)

The results from the pain screening questionnaire (ÖMSPQ) revealed significant differences between mTBI patients and controls. Patients had higher total score (M = 102.9, SD = 36.8) than controls (M = 38.5, SD = 27.8), t (50) = 7.19, p <0.001, d = 1.97. Twelve patients (52 %) scored over the suggested clinical cut-off (>105) for high risk of chronic pain, versus 2 (7 %) in the control group, $\chi 2 = 13.37$, $p < 0.001$. Compared to the controls, mTBI patients reported neck and shoulder pain more often, but not back or leg pain, see Table 11.

Table 11: Presence of musculoskeletal pain for patients with mild traumatic brain injury (n = 23) and controls (n = 29) as reported in The Örebro Musculoskeletal Screening Pain Questionnaire.

	mTBI		Controls					
Location	n	%	n	%	χ^2	p	OR	95%, CI
Neck	14	60.9	1	3.4	20.61	< .001	43.6	5.0 - 378.9
Shoulder	13	56.5	3	10.3	12.84	< .001	11.3	2.6 – 48.1
Upper back	5	21.7	1	3.4	4.20	.076	7.8	0.8 – 72.1
Lower Back	9	39.1	6	20.7	2.13	.145	2.4	0.7 – 8.1
Legs	7	30.4	4	13.8	2.13	.144	2.7	0.7 – 10.9

Note: mTBI = Mild traumatic brain injury.

MTBI patients rated on average their currently experienced pain as 5.3 (SD = 2.7) on the 0 to 10 scale in ÖMSPQ, significantly higher than controls (M = 1.3, SD = 2.0), t = 6.2, p < 0.001. Average pain experienced by the mTBI patients during the last three months was also significantly elevated, rated at 5.8 (SD = 2.5) compared to controls (M = 1.7, SD = 2.3), t = 6.17, p < 0.001. Finally, mTBI patients rated on average the frequency of pain as 5.9 (SD = 2.6), significantly higher than the controls (M = 1.6, SD = 2.1), t = 6.56, p < 0.001. These three variables from ÖMSPQ (item 9-11) was summed to create a pain index score for further analyses. On average, mTBI patients received an index score of 17.0 (SD = 7.1), significantlty higher than the controls (M = 4.6, SD = 6.2), t = 6.75, p < 0.001, d = 1.86.

Pain index was not associated with mTBI patient's performance in any of the cognitive tests. However, in the control group, higher pain index was associated with lower scores in Digit Symbol (r = -0.45, p = 0.015), fewer produced correct words in Verbal Fluency (r = -0.50, p = 0.005), and longer time to complete Trail Making A (r = 0.55, p = 0.002). Unexpectedly, a correlation between higher pain index and less severe injury was found, r = 0.47, p = 0.024.

6 DISCUSSION

6.1 PERSISTENT POST-CONCUSSION SYMPTOMS

There is a striking difference between patients in Study 1 and Study 2 with regard to reports of persistent post-concussion symptoms. The clinical sample in Study 1 endorses more symptoms and have higher average score in RPQ, even though they were assessed on average two years after the trauma where most, if not all, spontaneous recovery should have already taken place. We can conclude that the clinical sample is not representative of mTBI patients in general, and vice versa, prospectively followed mTBI patients are not representative of actual mTBI patients seen in rehabilitation settings. In fact, the clinical sample in Study 1 have a higher average score in RPQ than ED-patients in Study 2 had at day 1 after injury. However, a more proper comparison could be made with the patients who developed persistent PCS and disability in study 2, consisting of 12 % of the ED-patients. By one year, their average score was 38 on RPQ, actually higher than the clinical sample's average score of 27.

The results from RPQ were not extreme nor did they deviate from similar studies. Prospectively followed ED-cohort studies report averages around or below 10 in RPQ at 3 months or later post-injury [185-187]. In contrast, King and Kirwilliam, who studied a clinical mTBI sample referred for treatment to a concussion clinic on average seven years after trauma. They reported an average RPQ score of 35 [188], similar to our findings in Study 1. Despite the high symptom reporting in Study 1 we also saw considerable variance, where a few patients reported minimal symptoms. In fact, two patients reported less than three persisting symptoms. It is possible that these two patients were referred primarily on the basis of the referring primary care doctor's concern, rather than the magnitude of the patient's own subjective complaints. This of course needs to be studied separately. We are not aware of any previous study that has examined differences in primary care doctor's underlying reason for referring mTBI patients. This could certainly add to the heterogeneity of mTBI patients in clinical contexts.

One central consideration in this thesis is the question of what constitutes a case of persistent PCS. In paper 2 this was solved by the use of the criteria of three or more remaining symptoms in RPQ. However, most post-concussion symptoms are not specific for mTBI, they are common in many other conditions, even in people who are healthy. Given the high back-ground frequency of these symptoms and the inherent difficulty for an individual to compare his or her symptom level today with a previously experienced symptom level months ago (as is requested by RPQ) we decided to add a criterion of disability, in paper 3. This almost halved the PCS-group, from 19 % to 12 % of the whole mTBI sample. It is this author's belief that the criteria for persistent PCS needs to be sharpened to more closely match the patients who in a sense represent the real cases (i.e. the ones who seek treatment).

6.2 EMOTIONAL AWARENESS AND DECISION MAKING

In paper 1, we failed to find any evidence of deficits in emotional awareness or decision making in mTBI patients. The study sample was mTBI patients with slow recovery who were referred to brain injury rehabilitation clinics, and data represents the chronic stage. We cannot exclude the possibility of acute or subacute effects. Even if we would have found differences between patients and controls, the etiology of these deficits would still be disputable. Given the fact that we did not find any differences we could however cautiously assume that mTBI patients with persistent PCS is not characterized with reduced pre-injury functioning in these areas.

Deficits in emotional awareness is a core feature in alexithymia, which is commonly assessed using the self-report scale Toronto Alexithymia Scale – 20 questions (TAS-20) [189]. Prior studies who have used TAS-20 on patients with moderate and severe TBI have found elevated levels of alexithymia compared to healthy controls [190-193]. Studies concerning mTBI is lacking. Our results thus provide some support for the position that alexithymia is not associated with outcome after mTBI. There are some differences though between TAS-20 and LEAS. TAS-20 is covering a wider spectrum of the alexithymia concept and is based on self-report. Recently Maroti, Lilliengren & Bileviciute-Ljungar performed a meta-analysis of studies that have used both measures and found that LEAS and TAS-20 did not correlate at all. They concluded that LEAS and TAS-20 seem to measure different aspects of emotional functioning [194]. Adding to the complexity, we also found an association between higher LEAS scores and education. It is possible that the LEAS test format, with the high requirements of verbal responses and the use of distinct emotion words disfavor individuals who have shorter education and/or lower general verbal intelligence.

6.3 PERSONALITY TRAITS

Traits related to neuroticism were elevated compared to controls, and norms, for patients developing persistent PCS by 1-year post injury (Study 2), and also in the clinical sample in Study 1. Interestingly, somatic rather than psychic anxiety was elevated, which means that the patients were more prone to experiences of over-reactivity in the autonomous nervous system, restlessness and tension, rather than worrying and ruminating.

In paper 3, the traits of embitterment and mistrust also predicted development of persisting PCS. Individuals who are high on these traits are generally unsatisfied, blames and envy other people, are suspicious and distrust other people's motives. An early finding that has bearing on these findings is a study by Rutherford et al in 1977 [195] who found that those who were slow to recover from concussion more often blamed their employers or large impersonal organizations for their injury. The experience of being treated unfairly, or perceived injustice, has received an increasing interest in the study of development of chronic pain [196].

6.4 COGNITIVE RESERVE

In paper 2 we found that lower cognitive reserve, especially indexed by premorbid intelligence, was associated with persistent PCS. In the final adjusted logistic regression analysis, a fourfold increased risk of developing persistent PCS was found for mTBI patients with lower pre-morbid intelligence. This finding adds to a prior study in the general adult

population [110], and extends prior findings in children [197] and in male veterans [108]. The causal link between cognitive reserve and persistent PCS is not yet established. Speculatively, we think that lower cognitive reserve is linked with a lesser capacity to mobilize compensatory cognitive strategies in the early phase after mTBI which in turns leads to heightened burden and more stress in daily activities.

Cognitive reserve is at the moment a hypothetical construct, where indicators of good life circumstances are used as proxies. At present these proxies are limited to exposure to education and skillful activities at work. However, cognitive reserve is most likely influenced by how leisure time is spent. Being active and having a variety of activities (e.g. playing a musical instrument, reading, recreational walks, socializing with friends) would benefit the development of higher cognitive reserve. Studies that have investigated this has found an association between an actively spent leisure time and better outcome in relation to development of Alzheimer's disease [198, 199] and Multiple sclerosis [200]. There is a need to develop valid measures in this area.

6.5 COGNITIVE DEFICITS

The prospectively followed mTBI patients in Study 2 exhibited reduced memory performance, both compared to controls and published norms three months post-injury. The effect was substantial (d = 0.8), affecting primarily memory acquisition, not storage and recall. This finding is in contrast to general findings of meta-analysis of cognitive performance in unselected mTBI samples where no or very small effects are reported. We think this could be due to that the memory test we used, the Selective Reminding Test, is considerably more challenging than traditional list learning tests. In the SRT the examinee needs to develop a meta-cognitive strategy to remember words that are not presented in the subsequent trial, but also resist the pull of the latest reminders. Both these functions are in the executive domain. Our results are in line with prior studies by Nolin et al [201] and Geary et al [202] who found that mTBI patients used less mnemonic strategies such as clustering than controls when tested with the California Verbal Learning test. Taken together these findings supports a hypothesis of an association between mTBI and subtle executive memory deficits in the post-acute stage.

Interestingly, cognitive performance was not significantly different when patients with or without persistent PCS were compared, although patients with persistent PCS tended to have slightly lower results in general. Given the fact that PCS patients had lower pre-morbid intelligence we think that these small observed group differences more likely reflect lower pre-injury cognitive ability rather than acquired cognitive deficits.

The clinical sample of mTBI patients in Study 1 was assessed on average two years after trauma. Patients performed more poorly in most administered cognitive tests. Strongest effects were found in tests measuring processing speed and working memory. This finding is line with previous studies of clinical samples where moderate effects on cognition are usually observed [6]. The case-control design of the study prevents assumptions on causality, i.e. if the observed deficits is related to the trauma, related to other comorbid factors or if they reflect pre-injury functioning.

6.6 PRE-, PERI- AND POST-INJURY FACTORS ASSOCIATION WITH PERSISTENT PCS

Several pre-injury factors were found to be associated with persistent PCS in paper 3. The frequency of exposure to psychosocial stressors and its associated stress level was significantly higher before injury for patients developing persistent PCS by 1-year post-injury. This is in line with an earlier study by Veldhoven et al [203] who found that lifetime exposure to traumatic events as reported in the Stressful Life Events Questionnaire was a significant predictor of outcome. Further, in our study we found that patients who suffered or had suffered previously to a psychiatric disorder were at higher risk for developing persistent PCS, as was a lower self-rated Global Assessment of Function (GAF) for the two weeks before injury and the year preceding the injury. Taken together, these findings emphasize the importance of psychiatric history as an important source for prediction of symptom development after mTBI. A major strength of our study is that the psychiatric evaluation was performed by an experienced neuro-psychiatrist which lends validity to the findings. However, it may not be feasible to implement this in routine mTBI management.

Lower pre-injury levels of psychological resilience were associated with development of persistent PCS. This adds to a growing body of evidence linking resilience and outcome after mTBI. In a 2016 systematic review of this field [204] five studies were accepted, and among those, only two were cohort studies where the prospective course after mTBI could be followed [116, 205]. These two studies used different questionnaires for assessing resilience, and our study adds a third one, the SOC. Needless to say, these instruments have different operationalizations and theoretical underpinnings of resilience, demanding a more detailed analysis of response patterns. The SOC used in our study measures three sub-components of resilience: manageability, meaningfulness and comprehensibility. Interestingly, patients who developed persistent PCS only showed reduction in manageability, a subscale measuring sense of mastery and being in control.

Female gender was associated with almost a fivefold increased risk for developing persistent PCS and disability, which is significantly higher than previous studies where this association has been found. However, our estimate is surrounded by a large confidence interval, and with other studies in mind it is more likely that the increased risk is in the lower end. Gender differences are important to study since there is increasing evidence that suggests the need for gender-specific approaches to rehabilitation and care [206].

Peri-injury factors (i.e. factors related to the injury itself) was not associated with subjective outcome in paper 2 and 3, such as GCS-score, length of post-traumatic amnesia, loss of consciousness or signs of complicated mTBI. However, patients who developed persistent PCS by 1-year reported more symptoms immediately after injury, which could be construed as a sign of a more severe injury. However, an alternative hypothesis that this author is affiliated to is that pre-injury psychological biases and coping styles shapes symptom reporting even at the earliest stage after mTBI.

In study 1, an unexpected correlation between higher pain and a less severe mTBI as assessed by the CCS was found. It is important to realize that the rating of severity was done

retrospectively in this study, which makes the results less reliable. With that in mind, we think that this finding could be explained by either that lower awareness and memory from the trauma serve as a protection for future adverse subjective health, or a selection bias where patients with the mildest mTBI does not get referred to rehabilitation clinics unless significantly distressed, essentially creating an aggregation of high pain patients at the higher end of the mTBI spectrum.

6.7 MILD TRAUMATIC BRAIN INJURY AND PAIN

In the final paper we examined pain reporting in a sample of mTBI patients. An unexpected high prevalence of neck- and shoulder pain was found, significantly elevated compared to controls, and estimates of these pains in the adult working population [207]. Self-reported pain levels were high, comparable to patients with musculoskeletal pain in the sub-acute phase [161], and more than half scored over the established cut-off for high risk of chronic pain. This finding provides ample support for the necessity of pain assessment for this patient population, since undiagnosed and untreated pain may develop into chronic pain, a major reason for disability worldwide [208].

The main question regarding if pain influenced cognition in mTBI was answered negatively. No correlation was found between pain level and cognitive performance in mTBI patients. Pain did affect cognition though in the control group, where predominantly tests measuring processing speed were affected. Our study thus suggests that in a sample of already cognitively impaired mTBI patients, there is no added effect of pain.

7 LIMITATIONS

Both studies investigated pre-injury factors association with persistent PCS after mTBI. However, all measures of pre-injury status and functioning were collected after the injury. For this to be meaningful, one must assume that participant's reporting is not affected or biased by the injury itself. In Study 1, personality measures were collected on average two years after trauma. It cannot be excluded that the highly distressed and symptomatic mTBI sample responded and described more of their current situation than their pre-injury functioning (although that was stressed by the psychologist before completing the questionnaire). A major strength in Study 2 is that collection of pre-injury factors took place in close proximity to the actual injury (within 1 week). Patients was also told that their answers to the pre-injury measures should reflect their normal pre-injury functioning. This may have reduced any significant recall biases that especially patients who develop persistent PCS are prone to.

To my knowledge very few mTBI studies exists where pre-injury factors has been collected before injury. One notable exception is a study by Greiffenstein and Baker [209] who had access to Minnesota Multiphasic Personality Inventory (MMPI) profiles completed before and after injury in a sample of patients with persistent PCS. These patients had abnormal MMPI profiles before injury with predominantly somatoform symptoms, and importantly, these traits were not changed after injury. In a study of college athletes, high reporting of somatic symptoms pre-season was associated with worse subjective outcome after concussion [210]. In a neighboring research field, research on development of posttraumatic stress disorder (PTSD), studies have shown associations between trait anxiety [211], negative affectivity [212, 213] and neuroticism [214-216] measured before trauma and a subsequent diagnosis. Taken together, this seems to implicate that traits primarily handling negative emotions to a certain degree predicts subjective outcome after trauma.

Both studies wrestled with recruitment. In study 1, patients were highly selected, passing through several filters before the neuropsychological assessment. These filters include, but are not limited to, the discretion of primary care physicians and referral routines at the rehabilitation clinics. Indeed, one of the clinics involved in the study changed their routines on handling mTBI patients during the study period and rejected most mTBI referrals. In study 2, non-participation was only for a brief period systematically investigated. During this period 73 percent of ED-patients with mTBI declined participation in the study. The high attrition rate limits the external validity of the findings, since it cannot be excluded that those who participated differed in important ways from those who volunteered. Previously it has been found that those with more severe injuries tend to volunteer more often in mTBI studies [217].

Both studies used non-injured controls. It has been debated whether it is more proper to use trauma controls (e.g. patients with orthopedic injury) to properly control for the confounding effects of being exposed to *any* trauma [59] rather than mTBI per se. The superiority of trauma controls was recently challenged in a study who compared community controls with

trauma controls and found no discernable differences, except for higher alcohol use among the trauma controls [218].

The problem of low power was particularly evident in the 1-year follow-up in Study 2 where only 11 patients matched the criteria for persistent PCS + disability. This means that important differences may not have been detected (type 2 error). This has implications for future prospective ED studies that aims at studying the group with persisting PCS. If the aim is to have a group of patients with persistent PCS of considerable size, our study provides a rough estimate for future power calculations.

8 SUMMARY OF FINDINGS

- Emotional awareness and decision making is not affected in mTBI patients with persistent PCS in the post-acute stage.

- Mild traumatic brain injury is associated with executive memory deficits at three months post-injury.

- Patients with persistent PCS do not perform worse in cognitive tests three months post injury when compared to patients who have recovered.

- Lower levels of cognitive reserve is associated with higher risk of developing persistent PCS. Especially estimates of premorbid intelligence can be used in prognostic models for finding patients at risk for persistent PCS.

- Lower levels of emotional reserve, as evident in pre-injury or concurrent psychiatric disorders, higher stress levels, disadvantageuos personality traits (neuroticism, embitterment, mistrust) and lower psychological resilience shapes the emergence and persistence of PCS after mTBI.

- Musculoskeltal pain incidence and pain levels are high in mTBI patients with persistent PCS and need to be adressed for proper clinical management.

- Higher levels of pain is not associated with worse cognitive performance in mTBI patients already exhibiting cognitive deficits.

9 CONCLUSION AND FUTURE RESEARCH

This thesis has focused on patients who have suffered a mild traumatic brain injury and, in the aftermath, developed persisting post-concussion symptoms and disability. Although the etiology of this condition is in dispute this thesis shows that it is unlikely caused by a single biomedical factor. Instead a biopsychosocial approach where the weight of pre-injury psychological factors is taken into account is the most viable approach for developing a thorough understanding of poor subjective outcome after mTBI.

Specifically, this thesis has shown that patients who have suffered an mTBI still have cognitive deficits in the form of executive memory problems three months after injury, regardless of whether they report they have recovered or not. Further, lower pre-injury levels of cognitive and emotional reserve are risk factors for development of persistent post-concussion symptoms after mild traumatic brain injury. High level of pain, including musculoskeletal pain is common in patients with persisting post-concussion symptoms.

Although there are literally thousands of studies in the field of mild traumatic brain injury, there is still a need for high-powered well-designed studies in the following area:

- Development of multivariable prognostic models who can be used early to identify patients at risk of poor outcome.

- Development of appropriate cost-effective interventions that can reduce the risk of poor outcome.

- A focus on identifying and reporting data from measures of cogntive and emotional reserve.

- Development of new sensitive neuropsychological measures for assessing non-cognitive complaints like fatigue, fatiguability and emotional functions.

- Larger epidemiological studies that investigates poor outcome beyond self-reports. These can include register-based studies of sickness absence and return-to-work rates following mTBI.

10 SVENSK SAMMANFATTNING

Lätt traumatisk hjärnskada, vilket inkluderar hjärnskakning, är en mycket vanlig skada som drabbar tiotusentals personer i Sverige varje år. Skadan uppstår efter våld mot huvudet, exempelvis vid fallolycka, och åtföljs av kortare medvetslöshet och/eller minnesförlust. Vanliga symtom i efterförloppet såsom huvudvärk, illamående och yrsel och därefter kognitiva och affektiva symtom klingar av inom loppet av dagar eller veckor för majoriteten av de drabbade. En minoritet av de drabbade utvecklar dock långvariga besvär med symtom såsom trötthet, huvudvärk, minnes- och koncentrationssvårigheter.

Orsaken till varför vissa har ett sämre utfall, trots att själva skadan ter sig likartad från en klinisk vinkel är inte klarlagd. Teorin om hjärnreserv (Brain reserve capacity) förklarar skillnad i utfall efter liknande hjärnskada med att hjärnan har reserver som agerar som buffertar vid skada. Artiklarna i denna avhandling undersöker hypoteser utifrån den teorin vid lätt traumatisk hjärnskada, med ett särskilt fokus på kognitiv och emotionell reserv.

Data kommer från två studier, en fall-kontroll studie med 24 vuxna patienter, remitterade till rehabiliteringsklinik för neuropsykologisk utredning (artikel 1 och 4), samt en prospektiv kohortstudie där 122 patienter följdes från akutmottagningsbesök till uppföljning efter tre månader (artikel 2) och tolv månader (artikel 3).

I Artikel 1 undersöktes om patienter med lätt traumatisk hjärnskada uppvisade skillnader i emotionell medvetenhet, beslutsförmåga och ogynnsamma personlighetsdrag jämfört med icke-skadad kontrollgrupp. Patienterna undersöktes i snitt två år efter skada och presterade likvärdigt avseende emotionell medvetenhet och beslutsförmåga, men hade högre grad av personlighetsdragen somatisk trait ångest och stresskänslighet.

I Artikel 2 undersöktes om patienter med kvarstående besvär hade lägre kognitiv reserv än de patienter som tillfrisknat vid tre månaders uppföljning. Studien visade att patienter med bestående besvär presterar likvärdigt i kognitiva test som de som tillfrisknat efter tre månader. Patienter med lägre kognitiv reserv hade en fyrfaldigt ökad risk för att utveckla långvariga besvär. Studien fann också att patientgruppen (oavsett symtomtyngd) presterade sämre i ett exekutivt krävande minnestest.

I Artikel 3 undersöktes om emotionell reserv, indexerad efter exponering för tidigare eller nuvarande psykiatrisk åkomma, ogynnsamma personlighetsdrag och psykologisk motståndskraft. Vid ett-årsuppföljningen hade 12 procent av kohorten långvariga besvär och begränsningar i vardagen. Dessa patienter hade vid tiden för skadan fler tidigare och aktuella psykiatriska åkommor, och upplevde mer stress i vardagen. De hade därtill lägre psykologisk motståndskraft och högre skattning av vissa ogynnsamma personlighetsdrag (somatisk trait ångest, bitterhet och misstro) jämfört med de patienter som tillfrisknat.

I Artikel 4 undersöktes muskuloskeletal smärta och dess påverkan på kognition. Patienterna utreddes i snitt två år efter skada och presterade tydligt sämre än kontrollgrupp i kognitiva test. Cirka 60 procent av patienterna rapporterade nack- och axelsmärta, betydligt oftare än kontrollerna. Smärta var dock inte associerat med försämrad kognitiv prestation i

patientgruppen. En association fanns dock mellan smärta och sämre resultat i ffa snabbhetstest för de friska kontrollerna.

Sammanfattningsvis visar studierna att lägre nivå av kognitiv och emotionell reserv är en betydande riskfaktor för utvecklandet av långvariga besvär efter lätt traumatisk hjärnskada, att kognitiv nedsättning i form av exekutiva minnessvårigheter fortfarande är märkbar på gruppnivå tre månader efter skada, och att hög smärtnivå, inkluderande muskuloskeletal smärta är vanligt hos patienter med långvariga besvär efter skada.

11 ACKNOWLEDGEMENTS

First of all, I want to thank all participants, both patients and controls in Study 1 and 2. Without you volunteering into the studies they simply could not have been carried out, and for this I am very grateful.

My most profound thanks go to my main supervisor, Aniko Bartfai. Aniko encouraged me to become a doctoral student, a possibility I did not even consider to be a viable option at the time. We have spent countless hours going through analyzes and conclusions from the two studies, always with good theoretical insights and deep neuropsychological knowledge provided by Aniko. Aniko has always been very generous with her time for me and for this I am forever very grateful.

I also want to express my gratitude for my co-supervisors. Gunnar Edman, who have helped me with statistical analyses and provided feedback and encouragement. Jean-Luc af Geijerstam whom I always have very stimulating discussions with. Jean-Luc also introduced me to the world of systematic reviews and large epidemiological studies. I hope to work a lot with Jean-Luc in the future. Finally, I want to thank Jörgen Borg who was supervising me earlier in the thesis work. Jörgen has a vast knowledge on mild traumatic brain injury, and an international professional network I can only dream to ever reach. I have thoroughly enjoyed our discussions.

A heartfelt thanks to Anders Lundin, literally my mentor in this project. Anders and I became friends when we worked together at the Neuropsychology unit. He is by far the most skillful clinician I have ever worked with. His thesis, Mild traumatic brain injury - clinical course and prognostic factors for postconcussional disorder, is based solely on the vast data collection in Study 2. His significance and contributions for carrying out this study cannot be overestimated. As a co-author to paper 2 and 3 he was very active and provided helpful and constructive feedback to the smallest details of the manuscript.

My doctoral studies would not have been possible without a supporting clinical context, so I want to express my deepest thanks to the Rehabilitation Medicine Clinic at Danderyd Hospital for supporting me financially and otherwise throughout this work. I am hoping to be able to pay this all back with becoming a skillful collaborator and researcher for the years to come. Specially I want to thank all senior researchers who have been nothing but generous and supportive: Kristian Borg, Monika Löfgren, Ola Svensson and Marie-Louise Schult.

I owe a debt of gratitude to my current unit at the rehabilitation medicine clinic, the Specialist regional insurance medicine center (FMU). I have had immense support and encouragement by unit manager Madeleine Jonsson. I came to the unit almost by accident and circumstances, now I feel that FMU provides the most rewarding clinical and professional experience I have had at the clinic. My thanks also to Thomas Lundeberg whom I love to work with. To my great joy he accepted to become co-author of my final paper for this thesis where his vast knowledge on pain mechanisms and chronic pain development is a huge resource. I also want to thank Marie-Louise Schult, who was head of the section to which FMU previously belonged, for being generous and supportive.

A very special thanks also to co-author Marika Möller. Marika and I have become close friends during this time. She was first a fellow PhD student but completed her PhD in 2013. Marika is creative, have high energy and is more of a neuropsychologist than I will ever become. When we work together, which I hope we will a lot in the future, our different starting points makes a very fruitful combination.

I also want to thank co-author Catharina Nygren Deboussard for being encouraging and supportive throughout the work with this thesis. Catharina was also very much involved in Study 2, with the extensive data-collection.

All co-workers at the FMU unit needs to be mentioned for being supportive and for providing a welcome interruption from all mTBI thinking: Birgitta Hansson, Sten Månsson, Ziad Yanes, Yvonne Sidén Silfver, Helena Iacobaeus, Lisa Lidberg, Amanda Jörgensen, Maria Andersson, Birgitta Tuveson, Caroline Lager, Elin Pella Bergsell, Anna Holmqvist, Ulrika Dahlgren, Julia Eklund, Elisabeth Rignell, Jessica Johansson, Kerstin Adevik, Ebba Norheim and Yvonne Wiik.

I also must thank my institution at Karolinska Insitutet, the Clinical Sciences, Danderyd Hospital. A remarkably steady trio have been supporting us doctoral students: head of the institution Erik Näslund, study director Håkan Wallén, and administrator Nina Ringart.

My deepest gratitude to fellow PhD students at the clinic whom I have shared the very special experience of being part-clinician and part-student. The struggle to combine those existences unites us forever: Anna Tölli, Giedrė Matusevičienė, Kristina Sargénius Landahl, Gaia Pennati, Märta Berthold Lindstedt, Helena Hybbinette, Ann-Christine Persson, Johanna Wallensten, Azra Ramovic, Jeanette Plantin, Anneli Wall, Karin Uhlin and last, but not least, my sister in spirit Gabriela Markovic.

My first clinical home at the rehabilitation clinic was the Neuropsychology unit, started by Aniko. I had my formative years at that unit and worked and learned so much both regarding neuropsychological assessments and cognitive rehabilitation. Let me mention a few of my coworkers at the time: Nina Lorenzen, Pia Linde Runeskog, Inga-Lill Boman, Daniel Karlstedt, Lotta Bolin Hellbom, Lotta Nilsson.

Thanks to Kristina Franzon and Teréz Molnar-Curtis and all other members of the Severe Brain Injury team where I worked for a period of time and learned a lot about the other end of the TBI spectrum.

A very special thanks also to Martin Larsson who introduced me to the gym and showed all those essential exercises. I consider Martin my very own personal trainer.

I also want to express my gratitude to all co-workers at the rehabilitation clinic whom I have had the pleasure to work with during these years, too many to mention all by name.

Thanks to Lars-Gunnar Lundh, professor in psychology, who provided me with my first experiences with stringent research endeavors.

A sincere thanks also to the medical library at Danderyd hospital for first-class service.

I also want to thank friends and colleagues in the Swedish Neuropsychological Society, an organization for professional neuropsychologist.

I want to thank the neuropsychologists involved in Study 1, who helped out with the assessments of both patients and controls: Thomas Mengshoel, Gabriela Markovic, Isa Gustin, Terese Damberg, Cecilia Jönsson, Johanna Philipson and Rebecka Quist.

I am also grateful for the contribution with data collection in Study 2 by research nurse Seija Lund, and neuropsychologists Daniel Karlstedt and Siw Evans.

I also want to thank the organizations who provided grants to the support my thesis work Promobilia foundation, Hjärnkraft - the Swedish organization for people with acquired brain injury, the Swedish Society for medicine and the Swedish Neuropsychological society.

Members of the mighty Merciless kingdom in Utopia: taco, sunspear, sozz, toxic, zhogun, saptz, furiosa and several others. Thanks for providing a very welcome relaxation in between all the writing. See you next wave.

Thanks also to my close friends in the gentlemen's club: Henrik Brånstad, Anders Kandelin and Anders Bergqvist whom I have known since I was a teenager. Thanks for staying in touch and insisting on gentlemen's dinners!

Thanks to Jonn Clemente for mind-expanding discussions for almost 40 years, a true thinker.

Finally, I want to express my deepest gratitude and affection for my family. My wife and life partner Pia and our two daughters Iris and Daphne. Thanks for all understanding and support during the countless hours I have been preoccupied with this work.

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