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The Role of Neuroimaging Findings and Preinjury Risk Factors

Doctoral thesis

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Norwegian University of Science and Technology
Thesis for the Degree of Philosophiae Doctor
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Norsk sammendrag

Prognose etter lett hodeskade – Hjerneavbildning og premorbide risikofaktorer

Mange rammes hvert år av lette hodeskader, også kalt hjernerystelser. De fleste kommer seg raskt etter en slik skade, men noen sliter med symptomer i lang tid. Et viktig spørsmål er hvorfor noen rammes så hardt, mens andre klarer seg bra. Temaet for denne avhandlingen har vært hvilken betydning funn fra hjerneavbildning og premorbide faktorer har for prognose. Fire artikler inngår i avhandlingen, der data fra en stor longitudinell studie som ble gjennomført i Trondheim fra 2014 til 2017 ble brukt. Alle pasienter med lett hodeskade i alderen 16.0-59.9 år som ble behandlet ved akuttavdelingen ved St. Olavs hospital eller ved Trondheim kommunale legevakt ble identifisert, og 378 av disse ble inkludert i en oppfølgingsstudie der senfølger ble målt på ulike måter. I tillegg ble 199 av disse pasientene del av en utvidet oppfølgingsstudie, der avansert hjerneavbildning og kognitiv testing ble gjennomført. To kontrollgrupper inngikk i studien: 82 trauma-kontroller med ortopediske skader, men ikke hodeskader, og 83 friske kontroller uten skader.

I den første artikkelen studerte vi sambandet mellom selvrapporterte symptomer og resultat på kognitive tester. Vi undersøkte om pasienter som rapporterte forbedring av kognitive plager fra to uker til tre måneder etter skaden også hadde forbedrede testresultat, men vi fant kun et meget svakt samband. Derimot fant vi at forbedring av kognitive plager var sterkt forbundet med forbedring av emosjonelle og somatiske plager.

I den andre artikkelen undersøkte vi hvilke faktorer som var forbundet med rapportering av plager tre måneder etter skade. Vi fant at en rekke premorbide faktorer var assosierte med symptomrapportering, deriblant å ikke arbeide eller studere på fulltid, å ha smerter og dårlig søvnkvalitet før skaden, og å være kvinne. Vi fant også at intrakranielle funn på CT-undersøkelse økte risikoen for symptomer.

I den tredje artikkelen brukte vi avanserte MR-teknikker (eng. *diffusion tensor imaging* og *diffusion kurtosis imaging*) for å undersøke om mikroskopiske skader i hjernens hvite substans var assosiert med symptomer tre måneder etter skade. De fleste pasienter med lette hodeskader har ikke intrakranielle funn ved typiske CT- eller kliniske MR-undersøkelser, derfor er nye avanserte metoder som kan oppdage mindre skader av stor interesse. Vi fant at pasienter som rapporterte symptomer ved tre måneder hadde tegn på forandringer i hjernens hvite substans, men det kunne også se ut til at de allerede før skaden hadde noe dårligere integritet i hvit substans.

I den fjerde artikkelen undersøkte vi effekten av kognitiv reserve på kognitiv testprestasjon etter lette hodeskader. Tidligere studier på demenssykdommer har vist at personer med bl.a. høyere intelligens og utdanning (høyere kognitiv reserve) klarer seg bedre i tidlige stadier av sykdommen. Vi ville undersøke om disse faktorene var beskyttende også etter lette hodeskader. Når vi sammenlignet kognitiv testprestasjon hos deltagere med høy kognitiv reserve, fant vi ingen forskjeller mellom pasienter med lette hodeskader, trauma-kontroller og friske kontroller. Vi fant derimot forskjeller da vi sammenlignet deltagere med lavere kognitiv reserve i de samme tre gruppene, der resultatene viste at pasienter med lette hodeskader hadde svakest prestasjon på de kognitive testene.

Oppsummert har denne avhandlingen vist at både hjerneavbildningsfunn og en rekke premorbide faktorer er assosierte med dårligere prognose etter lette hodeskader. Pasienter med slike risikofaktorer, som lav kognitiv reserve og smerter før skaden, ser ut til å være ekstra sårbare for senfølger hvis de rammes av en lett hodeskade.

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Turid Follestad, my go-to statistician. Tell me again, how are factor variables with more than two levels handled in Stata *lasso*? Thank you for always being available.

When I entered this project, most of the data were already collected. Cathrine Einarsen, Rune Hatlestad Karlsen, Simen Saksvik, Migle Karaliute, Lena Hoem Nordhaug, John André Nebb Ek, and Hanna Lillehaug, to mention a few, had done most of the job, and I felt spoiled... Some work remained, however, such as annoying ourselves over participants choosing to place the "X" in-between two alternatives in questionnaires…

Alexander Olsen, for valuable contributions on two of my papers.

Last but not least, Linda Fordal, among many things, my English teacher.

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Change in self-reported cognitive symptoms after mild traumatic brain injury is associated with changes in emotional and somatic symptoms and not changes in cognitive performance

Jonas Stenberg, Justin E Karr, Douglas P Terry, Asta K Håberg, Anne Vik, Toril Skandsen, Grant L Iverson.

Neuropsychology, 2020; 34: 560-568. DOI: 10.1037/neu0000632

Paper 2:

Personal factors associated with postconcussion symptoms three months after mild traumatic brain injury

Toril Skandsen, ***Jonas Stenberg***, Turid Follestad, Migle Karaliute, Simen B Saksvik, Cathrine E Einarsen, Hanna Lillehaug, Asta K Håberg, Anne Vik, Alexander Olsen, Grant L. Iverson.

Archives of Physical Medicine and Rehabilitation, 2020; In Press.

DOI: 10.1016/j.apmr.2020.10.106

Paper 3:

Acute diffusion tensor and kurtosis imaging and outcome following mild traumatic brain injury

Jonas Stenberg, Live Eikenes, Kent G Moen, Anne Vik, Asta K Håberg, Toril Skandsen.

Manuscript

Paper 4:

Cognitive reserve moderates cognitive outcome after mild traumatic brain injury

***Jonas Stenberg*,** Asta K Håberg, Turid Follestad, Alexander Olsen, Grant L Iverson, Douglas P Terry, Rune H Karlsen, Simen B Saksvik, Migle Karaliute, John A N Ek, Toril Skandsen, Anne Vik.

Archives of Physical Medicine and Rehabilitation, 2020; 101: 72-80.

DOI: 10.1016/j.apmr.2019.08.477

Other Papers on MTBI Published During the PhD Period

Developing cognition endpoints for the CENTER-TBI neuropsychological test battery
Jonas Stenberg, Justin E Karr, Douglas P Terry, Simen B Saksvik, Anne Vik, Toril Skandsen, Noah D Silverberg, Grant L Iverson.
Frontiers in Neurology, 2020; 11:670. DOI: 10.3389/fneur.2020.00670.

Examining test-retest reliability and reliable change for cognition endpoints for the CENTER-TBI neuropsychological test battery
Jonas Stenberg, Justin E Karr, Rune H Karlsen, Toril Skandsen, Noah D Silverberg, Grant L Iverson.
Frontiers in Neurology, 2020. DOI: 10.3389/fneur.2020.541533

Examining the subacute effects of mild traumatic brain injury using a traditional and computerized neuropsychological test battery
Rune H Karlsen , Simen B Saksvik , ***Jonas Stenberg*** , Astri J Lundervold , Alexander Olsen , Ida V Rautio , Line Folvik , Asta K Håberg, Anne Vik , Justin E Karr, Grant L Iverson, Toril Skandsen.
Journal of Neurotrauma, 2020; Epub ahead of print. DOI: 10.1089/neu.2019.6922

Abbreviations

AD	Axial Diffusivity
ASRS	Adult ADHD (Attention Deficit Hyperactivity Disorder) Self-Report Scale
AUDIT	Alcohol Use Disorders Identification Test
BC-PSI	The British Colombia Postconcussion Symptom Inventory
BFI	Big Five Inventory
CC	Community Controls
CENTER-TBI	Collaborative European NeuroTrauma Effectiveness Research
CI	Confidence Interval
COWAT	Controlled Oral Word Association Test
CT	Computed Tomography
DKI	Diffusion Kurtosis Imaging
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale - Extended
ICD-10	International Classification of Diseases, 10th edition
IQR	Interquartile Range
ISI	Insomnia Severity Index
Kax	Axial Kurtosis
KFA	Kurtosis Fractional Anisotropy;
Kmean	Kurtosis Mean
Krad	Radial Kurtosis
LOC	Loss of Consciousness
LOT-R	Life Orientation Test-Revised;
LTE-Q	List of Threatening Events Questionnaire;
MD	Mean Diffusivity
Mdn	Median
MRI	Magnetic Resonance Imaging
MTBI	Mild Traumatic Brain Injury
OTBM	Overall Test Battery Mean
PCS	Postconcussion Symptoms
PTA	Post-Traumatic Amnesia
RAVLT	Rey Auditory Verbal Learning Test
RD	Radial Diffusivity
ROI	Region of Interest
RPQ	The Rivermead Post Concussion Symptoms Questionnaire
RSA	Resilience Scale for Adult
SD	Standard Deviation
TAI	Traumatic Axonal Injury
TBI	Traumatic Brain Injury
TBSS	Tract-Based Spatial Statistics
TC	Trauma Controls
TMT	Trail Making Test
TFCE	Threshold-Free Cluster Enhancement
TRACK-TBI	Transforming Research and Clinical Knowledge in Traumatic Brain Injury Study

Summary

Mild traumatic Brain Injury (MTBI) is common. It is estimated that out of 100 000 individuals, 300 adults will seek medical care for an MTBI in Norway each year. Although most patients with MTBI recover rapidly over the first days or weeks after the injury, a considerable minority of the patients continues to report symptoms for months, or even years. MTBI has been studied extensively over the last decades, but much is still unknown regarding *who* is at risk for poor outcome, and *why* this is. Previous research has not found consistent associations between CT- and MRI-identified brain pathology and outcome, and most clinicians would agree that outcome can differ substantially between two patients, despite similar neuroimaging findings. Research suggests that preinjury factors, such as age, sex, and somatic and mental health, are important for outcome, but it is largely unknown *how* these factors are related to outcome.

The overall aim of this thesis is to investigate the role of neuroimaging findings and preinjury factors on outcome after MTBI. More specifically, this thesis will (1) investigate the association between cognitive test performance and self-reported postconcussion symptoms (PCS); (2) investigate whether macrostructural brain pathology and microstructural integrity are associated with PCS; and (3) investigate which preinjury factors are associated with outcome. These questions have been examined through 4 papers, all using data from the Trondheim MTBI follow-up study.

In paper 1, the associations between self-reported PCS and cognitive test performance were examined. These are both commonly evaluated after MTBI, but the relation between them is not well understood. The study included 135 patients with MTBI and focused on the association between self-reported *cognitive* symptoms and cognitive test performance. Unlike previous studies, a longitudinal examination was conducted and it was examined whether improvement in self-reported cognitive symptoms from 2 weeks to 3 months was associated with improvement in cognitive test performance. Results showed that at 3 months, 27% reported cognitive symptoms to some extent. At both assessments, greater severity of self-reported cognitive symptoms was very weakly associated with worse cognitive test performances (2-week *rho* range: -0.19 to -0.01; 3-month *rho* range: -0.20 to -0.10), but strongly related to greater somatic and emotional symptoms. Change in self-reported cognitive symptoms from 2 weeks to 3 months was not associated with

change in cognitive test performance, but change in self-reported cognitive symptoms was strongly associated with change in emotional (*rho*=0.58) and somatic symptoms (*rho*=0.57).

In paper 2, the associations between several preinjury and injury-related factors and PCS were examined. Patients with MTBI (*n*=378), trauma controls (*n*=82), and healthy community controls (*n*=81) were included. Results revealed that there were few differences in preinjury factors between the MTBI group, the trauma controls, and the community controls. At 3 months, 20.8% of the patients with MTBI, 8.0% of the trauma controls, and 1.3% of the community controls reported PCS. In the MTBI group, there were differences between patients with and without PCS on most preinjury factors and injury-related variables in univariable comparisons. In a penalized multivariable regression model, working less than full time before injury, having preinjury pain, poor sleep quality, and being female were among the selected predictors, but also resilience and some personality traits contributed in the model. Intracranial abnormalities on CT were also a risk factor for PCS.

Paper 3 focused on associations between microstructural integrity in white matter, assessed with advanced MRI, and PCS. Patients with MTBI (*n*=176) underwent diffusion tensor (DTI) and diffusion kurtosis (DKI) imaging within 72 hours after the injury and assessment of PCS 3 months after the injury. All analyses were performed in the total sample, in patients without intracranial findings on clinical MRI sequences (i.e., uncomplicated MTBI), and with estimated intelligence both included and excluded from the statistical models. Results showed that the prevalence of PCS was higher in patients with complicated MTBI than in patients with uncomplicated MTBI. Tract-based spatial statistics showed that patients with PCS had lower fractional anisotropy and kurtosis fractional anisotropy, and higher radial diffusivity, than patients without PCS. Compared to healthy controls, patients with PCS had widespread differences in all 8 DTI and DKI metrics examined. In the uncomplicated MTBI sample, significant differences in fractional anisotropy between patients with and without PCS remained. When including estimated preinjury intelligence in the statistical models, no significant differences in DTI or DKI metrics between patients with and without PCS were present, but patients with PCS still had significantly higher mean, radial, and axial diffusivity than controls.

Paper 4 focused on the effect of cognitive reserve on cognitive test performance. The cognitive reserve hypothesis postulate that the effect of a brain injury depends on a patient's cognitive reserve. The study investigated whether cognitive reserve moderated differences in cognitive test performance between patients MTBI (n=160) and controls (trauma controls n=71, community controls n=79). A cognitive composite score was used as outcome measure. The Vocabulary subtest was used as a proxy of cognitive reserve. Results demonstrated that the effect of cognitive reserve on cognitive test performance was larger in patients with MTBI than in community controls at 2 weeks and at 3 months after injury. Thus, group differences in cognitive test performance varied as a function of cognitive reserve, with the biggest differences seen among participants with lower cognitive reserve.

In sum, this thesis has demonstrated the importance of both neuroimaging findings and preinjury factors on outcome after MTBI. First, outcome after MTBI is multidimensional and patients can present with good cognitive test performance, but still self-report several symptoms. Both macrostructural brain pathology, identified with CT and MRI, and poor microstructural integrity in white matter, identified with DTI and DKI, seem to be risk factors for later PCS. Preinjury factors such as unemployment and physical and mental health seem to be of particular importance for the development of PCS after MTBI. Low cognitive reserve was found to be a risk factor for reduced cognitive test performance. Importantly, the prevalence of PCS was considerably higher in patients with MTBI than in trauma and community controls, despite these groups being similar on the preinjury factors that predicted PCS. Further, the effect of cognitive reserve on cognitive test performance was greater in patients with MTBI than in uninjured individuals. Thus, the findings do not suggest that patients with symptoms had these problems already before the injury, or that the symptoms are largely unrelated to the MTBI. Rather, the combined effect of an MTBI and preinjury risk factors seems to be particularly critical.

1. General Introduction

Traumatic brain injury (TBI) has been described as *the most complex disease in the most complex organ* (1, p. 87). It is an injury caused by an external force that can lead to brain contusions, hemorrhages, and traumatic axonal injury, and around 2.5 million people experience a TBI in Europe each year (2,3). TBI can be seen as a continuum, ranging from very mild head injuries, without loss of consciousness and visible brain pathology, to very severe forms, causing prolonged disorders of consciousness and lifelong disability or death. *Mild* Traumatic Brain Injury (MTBI), by definition, is in the milder end of this continuum, and is the most common form of TBI (4). Despite the word "mild" in its name, outcome after MTBI is unfavorable in a substantial minority of the patients. Why this is, is a question researchers have been struggling with over the last decades. Even if the research on MTBI has grown exponentially the last decades, much is still unknown, and the field is characterized by debate and controversies. This thesis will investigate the role of neuroimaging findings and preinjury factors on outcome after MTBI.

1.1. Mild Traumatic Brain Injury

1.1.1. MTBI Definition

Many definitions for MTBI exist. Common for most of them are the reliance on Glasgow Coma Scale score (GCS), presence and length of loss of consciousness (LOC), length of posttraumatic amnesia (PTA), and in some definitions, intracranial imaging findings (5). The GCS consists of 3 subscales measuring eye-opening response, motor response, and verbal response. The total score, which is used for TBI classification, varies from 3 to 15, where 3 indicates deep unconsciousness, and a score of 15 means that the patient is fully awake, orientated, and follows commands (6,7). Length of LOC is commonly defined as the time from injury to return of the ability to follow commands (8). The definition of PTA differs somewhat between studies, with different focus on impaired orientation, retrograde amnesia, and anterograde amnesia (9). Orientation and continuous memory are naturally dependent, and the length of self-reported PTA is usually established by asking the patient questions like how long it was before they started remembering things consistently again (10). GCS, LOC and PTA are not independent measures. For example, a person who is unconscious (i.e. has LOC), will have a low GCS-score. Therefore, when interpreting the

GCS-score, it is essential to consider time since injury. A commonly used MTBI definition is the one proposed by the WHO Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury:

> "MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (1) 1 or more of the following: confusion or disorientation, LOC for 30 minutes or less, posttraumatic amnesia for less than 24 hours, and/or other transient neurologic abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (2) GCS score of 13-15 after 30 minutes post-injury or later upon presentation for health care. (3) These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (eg, systemic injuries, facial injuries, or intubation), caused by other problems (eg, psychological trauma, language barrier, or coexisting medical conditions), or caused by penetrating craniocerebral injury" (11, p. 115)

In their review of the literature, the WHO task force notes a profound variability between studies in the criteria used to define MTBI, which hampers the understanding of MTBI (5). Most important, some definitions of MTBI do not include a GCS-score of 13 (i.e., a GCS-score of 13 equals moderate TBI) (12), and some do not allow for intracranial lesions on imaging (5). Studies excluding patients with a GCS-score of 13 and patients with intracranial findings will obviously end up with a milder sample of patients with MTBI than studies adopting the definition suggested by the WHO task force. The term concussion is often used interchangeably with MTBI (13), but in some definitions, a concussion is considered to be in the mild end of MTBI, such as in the definition suggested by the American Medical Society for Sports Medicine (14).

1.1.2. Prevalence of MTBI

The prevalence of MTBI is difficult to estimate because it is expected that a large portion of people experiencing an MTBI does not seek medical care. Based on data from the Trondheim MTBI study, the incidence of persons 16-60 years seeking medical care for MTBI in Norway is estimated to be 302 per 100,000 person-years (15). A systematic review found that, internationally, the

incidence of hospital-treated MTBIs is around 100-300 per 100,000 person-years, but if also persons not seeking medical care are counted, the incidence is probably above 600 per 100,000 person-years (16). Consistently, it has been shown that MTBI is more common among males, teenagers and young adults (15,16).

1.2. Outcome After MTBI

Cognitive test performance and self-reported cognitive, emotional, and somatic symptoms are routinely evaluated in MTBI research. The tests used to evaluate cognitive test performance, such as tests of memory, attention, and executive functioning, are often referred to as neuropsychological tests. However, clinical neuropsychology, in its most general meaning, is the science of the behavioral expression of brain dysfunction (17); a definition that includes considerably more than cognitive test performance. With this definition, a self-report questionnaire where people rate their own symptoms after an MTBI, could also be considered a neuropsychological instrument, and consequently, neuropsychological outcome after MTBI can refer to both test performance and self-reported symptoms. Therefore, in this thesis, "cognitive test performance" or "results on cognitive tests" are used to describe test results, while self-reported symptoms, or postconcussion symptoms, are used to describe symptoms reported by the participants on questionnaires or in interviews.

1.2.1. Cognitive Test Performance

Cognitive test performance after MTBI has been studies extensively. From 1996 to 2013, at least 11 meta-analyses or systematic reviews were published (18–28), and in 2014, a systematic review of these meta-analyses was conducted (29). This review identified effect sizes (Cohen's *d*, or *g*) ranging between 0.07 and 0.61 (i.e., minimal to moderate effect sizes) when patients with MTBI were compared to controls without MTBI. Differences were greatest in the acute phase after the injury, and by 3 months, group differences were in most cases no longer detectable. There was a profound variability between studies and meta-analyses regarding which cognitive domain (i.e., memory, executive functioning, visuospatial ability) was reported as most affected. Later empirical studies have not reported findings casting doubt on the 2014 systematic review

conclusion. For example, in 2016, Losoi et al., found no significant differences between patients with MTBI and patients with orthopedic injuries 1 month after the injury (30). In 2017, Dikmen et al. reported differences between patients with MTBI and trauma controls on some measures of cognitive test performance 1 month after injury, but no differences at 12 months (31). It is important to note that the interpretation of studies examining cognitive test performance lies in the eye of the beholder. For example, in 2017, McInnes et al. published a scoping review where they concluded that about half of the patients with MTBI suffered from long-term cognitive dysfunction (32). This review was later heavily criticized for using a cognitive impairment cutoff that would classify most healthy individuals as cognitively impaired (33).

In sum, most evidence suggests that reduced cognitive test performance is common within the first few days and weeks after injury; while after 3 months, there are usually no group differences between patients with and without MTBI. However, the absence of statistically significant group differences between patients with MTBI and controls does not necessarily mean that *all* patients with MTBI are free from prolonged MTBI-related cognitive deficits. The research the last decade has to a large extent been focusing on subgroups of patients with MTBI, who are possibly experiencing prolonged cognitive deficits. An almost endless number of subgroups can be examined, such as injury-based subgroups (e.g., comparing patients with and without LOC, PTA and intracranial findings) and demographically-based subgroups (e.g., comparing women and men, young and old patients, etc.). Much of this research has been driven by the quite consistent observation that a substantial minority of patients with MTBI continue to *self-report* a diverse set of symptoms after MTBI.

1.2.2. Self-Reported Postconcussion Symptoms

Self-reported symptoms after MTBI are commonly referred to as postconcussion symptoms (PCS). These are usually assessed via clinical interview or questionnaires, such as the Rivermead Post Concussion Symptoms Questionnaire (RPQ) (34) and the British Colombia Postconcussion Symptom Inventory (BC-PSI) (35). Both these questionnaires contain a diverse set of symptoms. RPQ is probably the most used PCS questionnaire in the world and includes 16 symptoms, on which the participant is asked to rate the severity of each symptom during the last 24 hours

compared to before the injury. The symptoms rated are: headaches; feelings of dizziness; nausea and/or vomiting; noise sensitivity, easily upset by loud noise; sleep disturbance; fatigue, tiring more easily; being irritable, easily angered; feeling depressed or tearful; feeling frustrated or impatient; forgetfulness, poor memory; poor concentration; taking longer to think; blurred vision; light sensitivity, easily upset by bright light; double vision; and restlessness (34). It is common for patients with MTBI to experience one or several of these symptoms the first days after the injury, but as with cognitive test performance, improvement is usually seen within the first weeks or months (36,37). However, a consistent finding is that some patients with MTBI continue to report symptoms beyond 3 months (36–38).

When postconcussion symptoms of a certain magnitude persist over time, commonly more than 3 months, the patients experiencing them are often said to have postconcussion *syndrome* (38). No universally accepted definition for postconcussion syndrome exists, and therefore, the prevalence of the syndrome vary depending on the definition used in specific studies (38). By some, postconcussion syndrome is defined as reporting 3 or more symptoms of at least a moderate severity on a questionnaire, such as the RPQ (36), while others use the diagnostic criteria from the International Classification of Diseases, 10th edition (ICD-10) (39). In the ICD-10 definition of postconcussional syndrome (the term used in ICD-10), patients must report symptoms from at least 3 different symptom categories: (a) headaches, dizziness, malaise, fatigue, or noise intolerance, (b) irritability, emotional liability, depression, or anxiety, (c) concentration or memory difficulties, (d) insomnia, (e) reduced tolerance to alcohol, and (f) preoccupation with these symptoms or fear of brain damage. The prevalence of ICD-10 postconcussional syndrome varies considerably between studies, with a recent systematic review identifying a range of 6 to 64% at 6 months after injury (38). It should be noted that the abbreviation “PCS” is ambiguous because the “S” can refer to both “symptoms” and “syndrome”. It is debated among researcher whether people experiencing postconcussion symptoms are best described as having a *syndrome*. However, also researchers who avoid the term *syndrome*, commonly dichotomize patients into either experiencing, or not experiencing, postconcussion symptoms, based on a certain cut-off. In this thesis, the abbreviation PCS refers to postconcussion symptoms, and where needed, it is specified whether PCS were analyzed as a continuous or dichotomized variable.

1.2.3. Associations Between Cognitive Test Performance and PCS

It would not be surprising if patients reporting PCS, also had poorer cognitive test performance than patients without PCS. However, the relationship between overall PCS burden and cognitive test performance is poorly understood, and findings are mixed regarding whether there is an association between PCS and cognitive test performance (30,40–43). PCS are notably heterogeneous (i.e., includes both cognitive, emotional and somatic symptoms) and this could possibly contribute to the mixed findings on their association with cognitive performance. Intuitively, it seems reasonable that self-reported *cognitive* symptoms would show stronger associations with *cognitive* test performance than other domains of PCS, such as emotional or somatic symptoms. However, although some studies report statistically significant associations between cognitive test performances and self-reported cognitive symptoms (44–46), these associations are often weak or negligible in terms of effect sizes (45,47,48).

Studies on cognitive test performance and PCS are complicated by the fact that neither poor cognitive test performance, nor PCS, are specific for MTBI. It has consistently been shown that cognitive test performance varies considerably among people in general, and that one or several low test results are common in otherwise healthy adults (49–51). Similarly, PCS are not specific for head injury, rather, they are core features of many psychiatric and pain disorders, and are also commonly reported by healthy individuals (35,36,52). Referring to these symptoms as PCS in individuals without head injury might be confusing, and the term postconcussion-like symptoms is sometimes used about these symptoms in the absence of a TBI (35). The non-specificity of PCS, and the profound preinjury variability, may be particularly challenging in studies investigating the association between cognitive test performance and PCS. For example, a patient with MTBI who perform above average on cognitive testing, but reports several symptoms, would “weaken” a hypothesized correlation between poor test performance and PCS. However, it might be that this patient had excellent cognitive test performance before the injury, and that the performance postinjury actually represents reduced cognitive performance, had the patient been compared to his or her preinjury status. Unfortunately, preinjury cognitive functioning is seldom known, neither in research, nor in clinical practice. Longitudinal studies, however, enable *within-person* analyses and such analyses could investigate whether *change* in PCS is accompanied by *change* in test performance, with the advantage that participants serve as their own controls, thereby making

preinjury variability less important (53,54). However, the vast majority of studies on the association between PCS and test performance is cross-sectional (44–48). Utilizing the power of longitudinal designs could contribute to a better understanding of cognitive test performance and PCS in MTBI research.

1.3. Neuroimaging and Outcome

1.3.1. MTBI Pathology

MTBI-related brain pathology varies from patient to patient. In some cases, brain pathology is visible on Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). CT is part of the acute clinical routine in patients with suspected TBI. It is fast and sensitive for identifying fractures, contusions, hemorrhages, and brain swelling. Thus, pathology associated with an immediate need for neurosurgical intervention can be revealed on CT (55). However, while not part of the clinical routine in MTBI, MRI is more sensitive than CT due to superior spatial resolution and less artifacts at the interface between bone and brain (55). Traumatic axonal injury (TAI) and non-hemorrhagic contusions are examples of pathology that can be revealed on MRI, but rarely on CT (56,57).

The brain pathology visible on CT or MRI includes hematomas (epidural, subdural, subarachnoid, or intracerebral), contusions (coup or countercoup), and TAI (shown as microbleeds on susceptibility weighed imaging, Figure 1). These primary injuries represent direct consequences of the physical impact associated with the trauma. Secondary injuries are delayed responses not directly caused by the impact, including edema (cytotoxic or vasogenic), and increased intracranial pressure (58). Secondary injuries also occur on the cellular and molecular level, and even if a TBI is a sudden, single event, it initiates pathophysiological processes that in some cases may have degenerative consequences (59,60). MTBI, in most cases, is not associated with pathology visible on CT or conventional MRI, and secondary pathophysiological processes are believed to be central for the understanding of MTBI pathology (59). As with TBI in general, MTBI (i.e., the impact) is associated with acceleration and deceleration forces to the brain that initiate neurochemical and neurometabolic events in cells and axons. The mechanical disruption of cell membranes results in

depolarization, excitatory neurotransmitter release, efflux of potassium and an overload of intracellular calcium (59). To restore ionic balance, activity is increased in ionic pumps, eventually leading to depleted glucose stores. In MTBI, it is believed that these events are largely reversible (59).

In axons, the mechanical forces cause axonal stretching and deformation of axonal cell membranes. While some axonal loss may be a direct consequence of the impact (i.e., primary axotomy), most axonal damage is now considered to be caused by secondary pathophysiological processes (i.e., secondary axotomy) (61). The disruption of axonal membranes causes calcium influx, neurofilament compaction, and microtubule disassembly. This leads to impaired axonal transportation, axonal swelling and possibly secondary axotomy (59). TAI is believed to be the primary form of damage associated with MTBI (57). CT and *conventional, clinical* MRI are not sensitive for the *microstructural* axonal injuries assumed to characterize MTBI (i.e., CT and conventional MRI can reveal *macrostructural* pathology) (57). However, Diffusion Tensor Imaging (DTI), in detail described later, is a promising *advanced* MRI technique for detecting *microscopic* axonal injury.

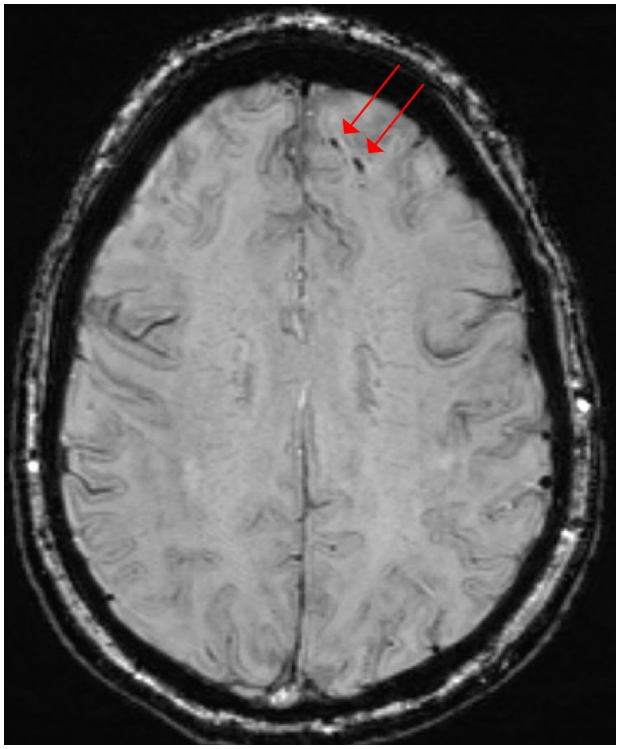


Figure 1. Transversal susceptibility weighted imaging (SWI) scan. The arrows show traumatic axonal injury in the left frontal lobe.

1.3.2. Macrostructural Pathology and Outcome

MTBI is commonly divided in complicated and uncomplicated MTBI, where patients with complicated MTBI have intracranial findings on CT or MRI (i.e., macrostructural brain pathology). This is a broad classification, not accounting for the magnitude or location of brain pathology, only whether it is visible or not. The proportion of uncomplicated and complicated MTBI varies considerably between study samples and depends largely on how the patients with MTBI are recruited. For example, a higher proportion of complicated MTBI is expected if recruitment takes place exclusively from level 1 emergency departments. In the Trondheim MTBI follow-up study, 12% of the patients had intracranial findings on MRI and around 7% had findings on CT (all those with visible findings on CT also had visible findings on MRI, when MRI was performed). The most common intracranial findings were contusions (identified in 57% of the patients with findings), followed by traumatic axonal injury (TAI, identified in 48% of the patients with findings), epidural hematoma (identified in 17 % of the patients with findings), subdural hematoma (identified in 13% of the patients with findings), and traumatic subarachnoid hemorrhage (identified in 13% of the patients with the findings) (62).

In a summary of the literature, patients with complicated MTBI had somewhat poorer cognitive test performance than patients with uncomplicated MTBI, but the differences were small. The same study found no clear support in the literature for greater PCS reporting, or poorer functional outcome, in patients with complicated MTBI (63). Because MRI is more sensitive than CT (i.e. more injuries are detected with MRI), it seems important to consider whether the classification was based on CT or MRI when groups with complicated and uncomplicated MTBI are compared. However, there is no clear evidence for a stronger or weaker association between intracranial findings and outcome in studies using CT or MRI (63). Rather, findings are strikingly heterogeneous between studies. It is common that studies report worse outcome in patients with complicated MTBI, but only on one of several measures. For example, Dikmen et al. reported poorer cognitive test performance and functional outcome (measured with Glasgow Outcome Scale) in patients with complicated MTBI (assessed with CT), but not greater PCS reporting (31). Similarly, Hughes et al. also found differences in cognitive test performance between patients with complicated and uncomplicated MTBI (assessed with MRI), but no differences on PCS reporting or return to work status (i.e., a functional outcome) (64). In contrast, Iverson et al found no

differences between patients with complicated and uncomplicated MTBI (assessed with MRI) on cognitive test performance and PCS reporting, but patients with complicated MTBI had longer return to work (65). Similar findings were seen in a study by de Haan et al. who found poorer functional outcome in patients with complicated MTBI, but no differences in symptom reporting (66). In sum, complicated MTBI has not been consistently associated with poorer outcome after MTBI and findings are surprisingly heterogeneous.

1.3.3. Microstructural Integrity - Diffusion Tensor and Kurtosis Imaging

Evidence suggests that MTBI, in many patients, is characterized by *microscopic* injuries in the white matter of the brain (57), and that these abnormalities in most cases are not visible on clinical MRI sequences. DTI is an advanced MRI technique shown to be sensitive to this pathophysiology (61,67,68). The basis in DTI is diffusion-weighted imaging (DWI) and DTI can be considered a specific modeling of the DWI data. To calculate the DTI-metrics (described below) at least 1 scan with little or no diffusion weighting, and at least 6 scans in different non-collinear diffusion encoding directions are needed (69). Depending on the brain tissue (e.g., white matter, gray matter, or cerebrospinal fluid), the diffusion of water molecules differs. For example, in cerebrospinal fluid, the diffusion of water molecules is relatively unrestricted, leading to great diffusion in all directions (isotropic diffusion). In white matter, the diffusion is restricted in the direction of the axon (anisotropic diffusion) (69). In DTI, the rate and direction of diffusion, in each brain voxel, is calculated, making it possible to visualize and quantify the integrity of the white matter. For example, it is expected that anisotropic diffusion is high in white matter tracts, and if this is not the case, white matter injury (e.g., TAI) can be suspected. Because both the magnitude and the direction of diffusion is of importance, several DTI metrics are usually calculated. Mean diffusivity (MD) represents the mean diffusion in all directions. Axial diffusivity (AD) represents the diffusion along the direction of primary movement (e.g., along the axon in a healthy brain). Radial diffusivity represents the mean movement in the other two directions (i.e., excluding the direction of the primary movement). Fractional anisotropy (FA) represents the directional restriction of movement (i.e., the amount of anisotropic diffusion, and not the magnitude of diffusion) (69). A FA value of 1 represents diffusion exclusively in one direction.

Diffusion kurtosis imaging (DKI) is a DTI-related technique, but in contrast to DTI, DKI does not assume a Gaussian distribution of diffusion. Due to the complexity of brain tissue, deviations from a normal distribution of diffusion are expected, and DKI has been proposed to be more sensitive than DTI in identifying microstructural abnormalities in brain tissue with high heterogeneity (70,71). The metrics derived from DKI indicate the kurtosis in different diffusion directions (i.e., mean kurtosis, Kmean, axial kurtosis, AK, and radial kurtosis, RK). Thus, values closer to zero indicate a diffusion of water molecules that is less restricted, approaching a Gaussian distribution (71), indicating lower tissue heterogeneity (72). Kurtosis fractional anisotropy (KFA) resembles FA in that it indicates the anisotropy of diffusion (70).

DTI data can be studied by a region of interests approach (ROI) or in a voxel-by-voxel manner. ROI analyses involves extraction of DTI and/or DKI metrics (e.g., FA, KFA) from a priory defined areas or white matter tracts. Tract Based Spatial Statistics (TBSS) is a common voxel-by-voxel approach where diffusion metrics in the whole white matter skeleton is investigated (73). The end product in TBSS studies is commonly an image of the white matter skeleton where significant voxels (e.g., voxels where FA is significantly lower in an MTBI group compared to a control group) are colored. Figure 2 shows the white matter skeleton used in TBSS analyses.

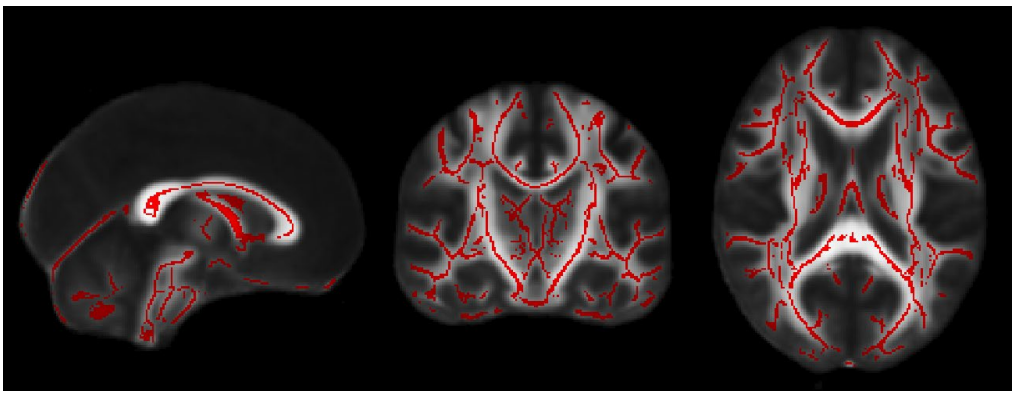


Figure 2. The white matter skeleton (in red) overlaid on a fractional anisotropy (FA) image (white areas equal higher FA).

1.3.4. Microstructural Integrity and PCS

Several meta-analyses and systematic reviews on DTI have concluded with diffusion alterations in white matter following MTBI (74–78). However, findings are inconsistent: many individual studies do not report diffusion differences between patients with MTBI and control groups; in studies reporting differences, the localization of the abnormalities differs; and longitudinal studies have not demonstrated consistent changes in diffusion metrics (78).

Although most research suggest that diffusion metrics are altered following MTBI, findings on the associations between diffusion metrics and PCS are more mixed. Khong et al. found support for PCS being associated with decreased FA and increased MD and RD in their systematic review, but the brain regions with alternations differed between studies (77). In the vast majority of previous studies, DTI has been conducted in the subacute (e.g., around or beyond 2 weeks) or chronic (beyond 3 months) phase after the MTBI and differences in DTI metrics between patients with and without PCS have been demonstrated in many of these studies (79–85), but not all (42,86–89). From a clinical perspective, it is important to identify patients at risk of poor outcome early after the injury, and acute DTI could potentially serve as a biomarker for poor long-term outcome. However, there is a paucity of studies examining whether acute (i.e., within 72 hours after the injury) DTI predicts later PCS.

DKI is a relatively new technique and has so far been much less used than DTI, but differences in DKI metrics between patients with MTBI and controls, in both white and gray matter, have been reported (72,90–95). Few studies have examined DKI alternations across the whole white matter skeleton, and findings on the association between DKI metrics and PCS are inconclusive (88,93,95).

The mixed findings on the associations between DTI and DKI metrics and PCS probably have several causes. First, the MTBI definition is wide. Patients having LOC between 0-30 minutes, and PTA between 0-24 hours, can all be diagnosed with MTBI. However, the most salient example of the wide definition might be the inclusion of patients both with and without CT-identified brain pathology. Second, patients with PCS differ from patients without PCS on several preinjury factors (see section 1.4), and in other fields of research, many of these factors have been associated with deviations in diffusion metrics (96–101). Thus, together with the small sample sizes characterizing most previous DTI and DKI studies (especially those conducted acutely), differences between samples in injury severity and preinjury factors most likely contribute to the heterogeneous results from past studies.

1.4. Preinjury Factors and Outcome

By definition, the variability in brain pathology in MTBI is in practice restricted by its lower (i.e., no or minimal head injury) and upper (i.e., moderate TBI) limits. Nonetheless, outcome after MTBI is heterogeneous. Further, even in the studies showing the greatest associations between brain pathology and outcome, most of the variance in outcome remains unexplained. This suggests that other factors, in addition to brain pathology, need to be considered in order to understand outcome after MTBI (38,102). Preinjury factors, in this thesis, refer to an individual's status, or characteristics, before the injury. These can be both biological (e.g., sex, age) and psychosocial (e.g., education, employment, personality).

1.4.1. Preinjury Factors in Multivariate Prognostic Models

Several studies have investigated the role of preinjury factors on outcome after MTBI. However, the factors examined vary between studies, and consequently, so do the factors reported as predictive for poor outcome. In 2015, Silverberg et al. conducted a systematic review of multivariable prognostic models for MTBI. Most of the identified studies used PCS as outcome, and poor preinjury mental health and female sex were the most robust preinjury predictors for poor outcome (103). In a systematic review on functional outcome after sports-related concussion, preinjury mental health problems was also identified as a predictor of slower return to normal activities. Teenage years and being women also increased the risk of slower return (104). In the multicenter UPFRONT study, poor preinjury mental health, lower education, and female sex were associated with lower GOSE scores 6 months after the injury (i.e., poorer functional recovery). Being 65 or older was associated with greater odds for complete recovery. However, age and sex were no longer significant predictors when emotional distress and coping style were controlled for, indicating that the effect age and sex might be mediated by other factors (105). In the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Study, PCS at 6 months was most strongly associated with fewer years of education, preinjury psychiatric problems, and previous MTBI, but also older age, female sex, and preinjury headache were associated with PCS in a multivariate model (106). The TRACK-TBI study has also identified preinjury unemployment as a risk factor for PCS and poor functional outcome (107).

Even if most would agree that preinjury factors contribute to outcome after MTBI, findings are mixed concerning the relative importance of different factors. A limited number of preinjury factors are usually assessed in each study, and there is variability between studies in which preinjury factors are assessed or included in analyses. As noted in the UPFRONT study (105), when additional variables (e.g., coping style) are included in multivariate prognostic models, the effect of others (e.g., sex) might be reduced. This suggests that the effect of some preinjury variables on outcome are mediated by others, possibly contributing to some of the conflicting findings in the literature (e.g., the effect of age on outcome). Including a broad range of preinjury variables in prognostic models could enhance the understanding of outcome after MTBI.

1.4.2. Cognitive Reserve

The theory of cognitive reserve aims to explain why outcome differs between patients in cases where the magnitude of brain pathology is similar (108,109). Research on cognitive reserve has traditionally focused on degenerative diseases (110–112) and it has been demonstrated that people with high cognitive reserve have better clinical outcome than people with low cognitive reserve, given the same amount of Alzheimer's brain pathology (110,113,114).

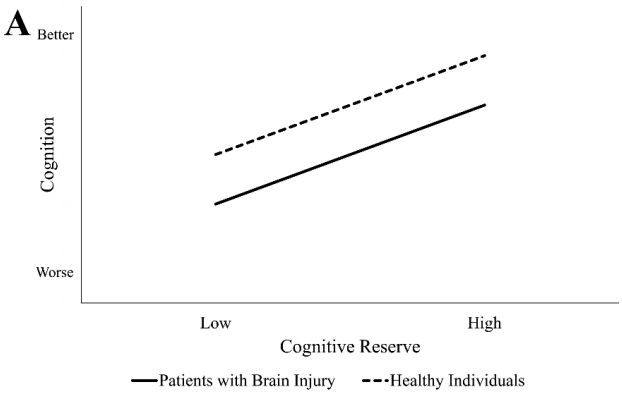
Cognitive reserve is a theoretical construct, to some extent used differently between studies, making the concept somewhat confusing. In some studies, cognitive reserve is used to describe the differences between predicted and observed outcome. When defining cognitive reserve like this, people with good cognitive outcome (when the magnitude of brain pathology is controlled for) have, by definition, high cognitive reserve (113). In statistical terms, cognitive reserve is the residual from a regression model where outcome is the dependent variable and the magnitude of brain pathology is the predictor. Used like this, cognitive reserve does not explain *why* outcome differs between patients, rather it is indistinguishable from outcome.

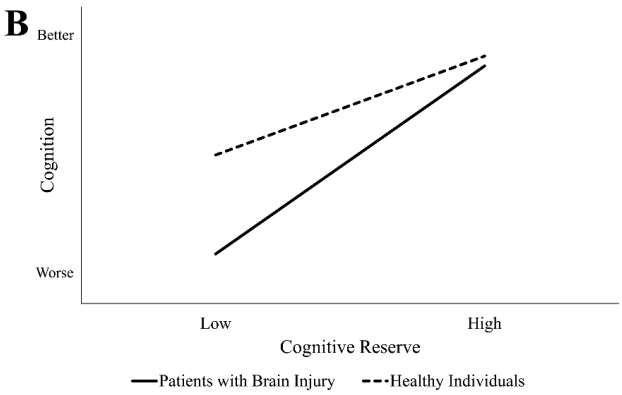
However, often, and especially in the context of acquired brain injury, cognitive reserve is conceptualized as a predictor of outcome (115). In this context, cognitive reserve cannot be directly measured, but is estimated through proxies, such as premorbid intelligence, level of education, and occupational attainment (i.e., factors shown to be associated with cognitive outcome when the magnitude of brain pathology is controlled for) (109). In this line of research, the question is *whether* and *how* proxies of cognitive reserve contribute to outcome.

Figure 3A and B illustrate two ways cognitive reserve could contribute to outcome, and how it can be assessed after acquired brain injuries using a control group of non-injured persons. In Figure 3A, patients with brain injuries are equally affected by the injury, regardless of their level of cognitive reserve. The difference in cognition between patients and controls is constant and does not vary as a function of cognitive reserve. However, higher cognitive reserve is associated with better cognition in this example, but this is true for the patients with brain injury as well as for the healthy controls. To demonstrate an effect like this, all needed is a positive correlation between a proxy of cognitive reserve and an outcome. Estimated premorbid intelligence and level of

education are common proxies for cognitive reserve (116) and cognitive test performance is a common outcome measure. Few researchers would argue against the existence of a positive association between intelligence, education, and cognitive test performance. In MTBI, this association has been demonstrated consistently (115,117–119). However, if intelligence is defined as general mental ability (120), these findings do not add much knowledge beyond that preinjury cognition is positively correlated with postinjury cognition, which is true, but maybe not very informative.

Figure 3B illustrates a quite different scenario where cognitive reserve moderates differences in cognition between patients and controls. In this scenario, the effect of the brain injury depends on whether the patient has high or low cognitive reserve. In patients with moderate and severe TBI, Sumowski et al. demonstrated an effect like this (121). They used educational attainment as a proxy of cognitive reserve and found that the effect of education on cognitive test performance was larger in patients with TBI than in healthy individuals. Thus, differences in cognitive test performance between patients and controls were most pronounced among participants with less education. Figure 3C illustrates a longitudinal design where the recovery rate between two time points depends on cognitive reserve. In this example, patients with high cognitive reserve have a faster recovery.





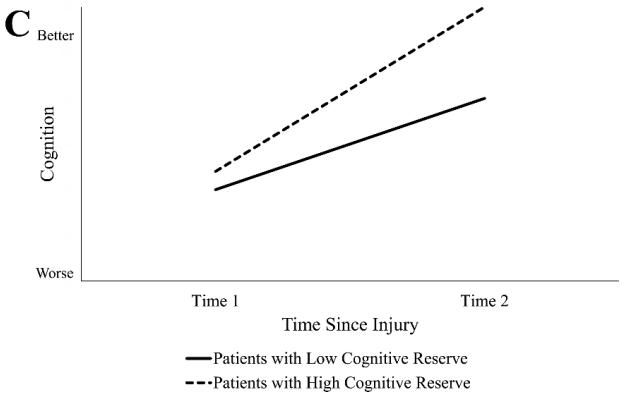


Figure 3. Cognitive reserve and outcome. Figure 3A illustrates a hypothetical scenario in which the effect of the brain injury is unrelated to the level of cognitive reserve. Patients with low and high cognitive reserve are equally affected by the injury, but cognitive reserve and cognition are positively correlated. In Figure 3B, the effect of the injury depends on the level of cognitive reserve (i.e., patients with low cognitive reserve are more affected). Thus, cognitive reserve moderates group differences in cognition. In a longitudinal design illustrated in Figure 3C, cognitive reserve moderates the recovery rate between two assessments. Patients with high cognitive reserve have a faster recovery.

Yaakow Stern, one of the key figures behind the concept of cognitive reserve, stresses that the core feature of cognitive reserve is that it is assumed to moderate the relationship between the status of the brain (e.g., TBI versus no TBI) and clinical status (e.g. cognitive test performance) (109). As such, evidence for the effect of cognitive reserve requires that a moderating effect of cognitive reserve is demonstrated (illustrated in Figure 3B and C), it is not enough with a correlation between a proxy of cognitive reserve and outcome (illustrated in Figure 3A).

Few studies have examined the role of cognitive reserve after MTBI. This is somewhat surprising considering the heterogeneity in outcome seen in this patient group and that the effect of preinjury variables have been consistently demonstrated. In a meta-analysis, Dougan et al. found that differences in cognition between patients with MTBI and controls were largest in the studies where participants had lowest education. Investigating the role of cognitive reserve was not an aim in the individual studies included in the meta-analysis, but the effect of education was seen when the study samples were examined (18). Steward et al. did not find that the effect of estimated premorbid intelligence was larger in patients with MTBI than in healthy controls 1 month after injury (117). However, this was a small study where 24 patients with and 28 without intracranial abnormalities were analyzed separately, leading to quite low statistical power in the interaction analyses. In sum, cognitive reserve could potentially increase the understanding of the variability in outcome after MTBI, but few studies have been designed for this specific purpose.

2. Aim of the Thesis

The overall aim of this thesis is to investigate the role of neuroimaging findings and preinjury factors on outcome after MTBI. The three specific aims are:

- To investigate the association between cognitive test performance and self-reported PCS.
    - Paper 1 examined associations between different domains of PCS (as continuous variables) and cognitive test performance. Paper 4 examined differences in cognitive test performance between patients with PCS and without PCS (i.e., a dichotomized variable).
- To investigate whether macrostructural brain pathology and microstructural integrity are associated with PCS.
    - Paper 2 (CT findings) and paper 3 (MRI findings) reported associations between macrostructural brain pathology and PCS. Paper 3 examined whether microstructural white matter integrity (assessed with DTI and DKI) was associated with PCS.
- To investigate which preinjury factors are associated with outcome.
    - Paper 2 examined which preinjury factors were associated with PCS. Paper 3 and 4 reported associations between PCS and estimated intelligence. Paper 4 examined whether cognitive reserve moderated cognitive test performance after MTBI.

3. Materials and Methods

3.1. Study Population

All studies in the thesis used data from the Trondheim MTBI follow-up study (122). From April 1st 2014 to December 5th 2015, the aim was to identify all patients 16.0 to 59.9 years old seeking medical care for MTBI in Trondheim, Norway, and four neighboring municipal entities. Recruitment took place at 2 emergency departments: a level 1 trauma center in Trondheim; and at the Trondheim Municipal Emergency clinic, a general practitioner-run, out-patient clinic. TBI was defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force (3), which was operationalized as: (1) the patient had experienced a physical trauma towards the head or high energy trauma, (2) followed by either (a) witnessed LOC or confusion and/or (b) self-reported amnesia for the event or the time period after the event, and/or (c) a traumatic brain lesion on CT. The TBI was further defined as mild per the criteria recommended by the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury: GCS-score of 13-15 at presentation in the emergency department, LOC <30 minutes, and PTA <24 hours (11). A total of 732 patients with MTBI were identified during the inclusion period. Of these, 378 patients were included in the Trondheim MTBI follow-up study (122).

Exclusion criteria in the Trondheim MTBI follow-up study were late presentation or presence of comorbidities or circumstances that would make it difficult to follow patients, or where outcome could not be reliably assessed: (a) non-fluency in the Norwegian language; (b) pre-existing severe psychiatric or somatic disease or drug abuse that could complicate follow-up; (c) a prior history of a complicated mild, moderate or severe TBI or other severe neurological conditions; (d) presentation more than 48 hours after the trauma; and (e) other concurrent major trauma.

Of the 378 patients, 199 were scheduled for extended follow-up including MRI and assessments of cognitive test performance. Whether or not a patient was asked to participate in the extended follow-up was dependent on: consent to MRI, no MRI contraindications, that MRI scanning could be performed within 72 hours (available MRI slot), and that they lived within a one-hour drive from the study hospital.

A sample of 82 age- and sex-matched patients with orthopedic injuries, free from polytrauma, trauma affecting the head, neck, or the dominant upper extremity was included as a control group (i.e., trauma controls). In addition, a sample of 83 age-, sex-, and education-matched community controls was recruited. The same exclusion criteria were applied for the control groups as for the MTBI group. In addition, the community control group were not to receive treatment for a severe psychiatric disorder, even if they might have been able to comply with follow-up. The control groups underwent the same outcome assessment as the MTBI group, but the trauma controls did not undergo MRI. The trauma controls were recruited from the same emergency departments as the MTBI group. The community controls were recruited among hospital- and university staff, students, and acquaintances of staff and patients.

In this thesis, all participants in the Trondheim MTBI follow-up study were included in paper 2, while the participants in the extended follow-up (including assessment of cognitive test performance and MRI) were included in paper 1, 3, and 4 (Figure 4). Demographics and clinical characteristics of the participants included in the Trondheim MTBI follow-up study are shown in Table 1.

The Trondheim MTBI follow-up study was approved by the regional committee for research ethics (REK 2013/754). All participants, and parents of participants younger than 18 years, gave informed consent.

Table 1. Demographic- and injury-characteristics of the MTBI group, the trauma control group, and the community control group in the Trondheim MTBI follow-up study.

Variables	MTBI n=378	Trauma Controls n=82	Community Controls n=83	*P*
Age, years				
M (SD)	31.2 (13.0)	32.6 (13.0)	33.1 (13.0)	
Mdn (IQR)	25.1 (20.8-40.9)	28.0 (21.8-45.6)	27.8 (23.1-43.8)	0.211
Sex, female, *n* (%)	131 (34.7)	31 (37.8)	33 (39.8)	0.631
Education years, *Mdn* (*IQR*)	13 (12-16)	14 (12-16)	13 (12-16)	0.063
CT Findings, *n* (%)				
Yes	22 (5.8)			
No	277 (73.3)			
Not performed	79 (20.9)			
LOC, *n* (%)				
Yes, witnessed	173 (17.7)			
No	67 (45.8)			
Unknown	138 (36.5)			
GCS-score, *n* (%)				
13	5 (1.3)			
14	57 (15.1)			
15	277 (73.3)			
Unknown	39 (10.3			
PTA long (1-24h), *n* (%)	107 (28.3)			
Cause of Injury, *n* (%)				
Fall	135 (35.7)	26 (31.7)		
Violence	65 (17.2)	1 (1.2)		
Bicycle	58 (15.3)	7 (8.5)		
Sports accident	54 (14.3)	30 (36.6)		
Motor vehicle accident	43 (11.4)	3 (3.7)		
Struck object	17 (4.5)	6 (7.3)		
Other /unknown	6 (1.6)	9 (11.0)		
Level of care				
Admitted neurosurg. dep.	39 (10.3)			
Admitted other dep.	18 (4.8)	11 (13.4)		
Observed < 24 hours	61 (16.1)			
Not admitted	260 (68.8)	71 (86.6)		

P-values from Kruskal-Wallis tests and Chi-Square test. CT = Computed Tomography; GCS = Glasgow Coma Scale; LOC = Loss of Consciousness; MTBI = Mild Traumatic Brain Injury; PTA = Post-Traumatic Amnesia

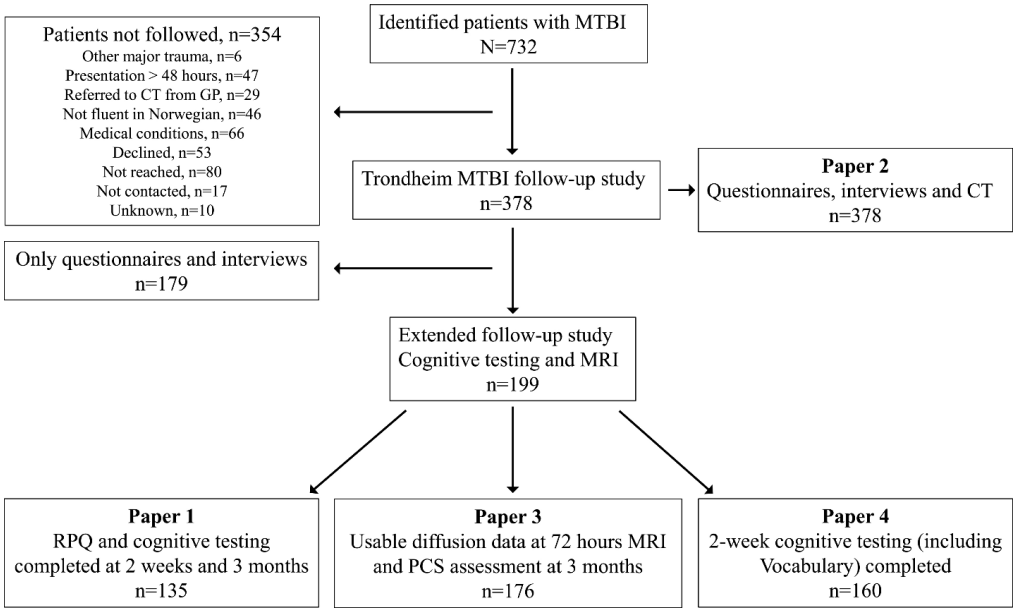


Figure 4. Flowchart Trondheim MTBI follow-up study. GP = General Practitioner; MRI = Magnetic Resonance Imaging; MTBI = Mild Traumatic Brain Injury; PCS = Postconcussion Symptoms; RPQ = Rivermead Post Concussion Symptoms Questionnaire

3.2. Procedures

Study personnel screened all head CT referrals and patient lists at the municipal ED daily and contacted the neurosurgical residents on call. If needed, the potential participant's medical record was evaluated for inclusion and exclusion criteria. Study personnel were present at the hospital all weekdays (8–12 hours each day) and were called in as required on weekends. Patients with a possible MTBI were contacted either in the hospital ward, the emergency department, or contacted by phone if they had left the emergency department. Subsequently, study personnel interviewed potential participants and evaluated their eligibility for the study. Recruiters were PhD candidates and medical students. Compliance with study protocol was ensured by training and participation in Good Clinical Practice courses. Recruiters had access to supervision by consultants during their shifts.

Information on GCS-score, LOC and PTA came from patient interviews and medical records. The GCS-score was observed by the study personnel or retrieved from the medical record. If the GCS-score was lacking in the medical record, the history and clinical descriptions were used to estimate a score. LOC was considered present if witnessed. Duration of PTA was defined as the time after injury for which the patient had no continuous memory. It was dichotomized to < 1 h or 1–24 h. Head CT findings were recorded according to the radiology report.

Outcomes were assessed and MRI was performed at several time points. The assessments relevant for the present thesis were:

- Within 72 hours: MRI
- Within the first days: Interview comprising injury-related variables and preinjury status and functioning.
- 2 weeks: Questionnaires on preinjury functioning and outcome (including RPQ). Administration of cognitive tests.
- 3 months: Interview (including BC-PSI) and questionnaires (including RPQ). Administration of cognitive tests.

3.3. Preinjury Factors

Several preinjury (referred to as "personal factors" in paper 2) variables were collected through interview or questionnaires. Information on age, sex, years of completed education, school marks, reading difficulties, work status, previous MTBI, pain, psychiatric problems, and substance use, were obtained through interview. Preinjury headache was assessed through a questionnaire similar to the one developed for The Trøndelag Health Study (HUNT), alcohol use was assessed with the Alcohol Use Disorders Identification Test (AUDIT) (123), sleep quality with the Insomnia Severity Index (ISI) (124), ADHD (Attention Deficit Hyperactivity Disorder) symptoms with the Adult ADHD Self-Report Scale version 1.1 (ASRS) (125), personality traits with the Big Five Inventory (BFI-44) (126), life orientation (optimism/pessimism) with the Life Orientation Test-Revised (LOT-R) (127), threatening events with the List of Threatening Events Questionnaire (LTE-Q) (128), and resilience with the Resilience Scale for Adults (RSA) (129).

3.4. Magnetic Resonance Imaging

Patients with MTBI underwent MRI on a 3T Siemens Skyra system with a 32-channel head coil, the majority (91%) within 72 hours after injury. Patients with intracranial abnormalities visible on clinical MRI sequences were defined as having complicated MTBI, and those without as having uncomplicated MTBI. A neuroradiologist and a resident in radiology read and reported the following MRI sequences: (1) three dimensional (3D) T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE); (2) two dimensional (2D) diffusion-weighted imaging (DWI) (3) 3D T2 space; (4) 3D T2-weighted fluid-attenuated inversion recovery (FLAIR); (5) 3D T2-weighted susceptibility-weighted imaging (SWI) (62).

The DTI/DKI sequence was a single-shot balanced-echo EPI sequence acquired in 30 non-collinear directions with 3 b-values (b=0; b=1000; and b=2000 s/mm2). The parameters used were: TR 8800 ms; TE 95 ms; FOV 240 × 240 mm; slice thickness 2.5 mm; acquisition matrix 96 × 96. Transversal slices (n=60) with no gaps were acquired, giving full brain coverage. Images without diffusion weighting (n=5) were obtained to increase signal-to-noise ratio. To correct for image distortion, two additional b0 images were obtained with opposite phase encoding polarity.

3.4.1. Diffusion Tensor and Kurtosis Imaging Processing

Image analyses were performed with the fMRIB Software Library (FSL: http://www.fmrib.ox.ac.uk/fsl) and Diffusion Kurtosis Estimator (DKE: https://medicine.musc.edu/departments/centers/cbi/dki/dki-data-processing). The Brain Extraction Tool (FSL) removed non-brain tissue. Artifacts caused by eddy currents and movements were adjusted with eddy (FSL). Topup (FSL) corrected susceptibility-induced off-resonance field artifacts. DKI and DTI model fitting was performed using DKE and parametric maps and were calculated for 8 metrics: Fractional Anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), kurtosis fractional anisotropy (KFA), mean kurtosis (Kmean), axial kurtosis (Kax), and radial kurtosis (Krad) (130).

Voxel-wise statistical analysis was performed with TBSS (73). All participants' FA data were aligned into a common space and a mean FA image was created from the FA images and thinned to create a skeletonized mean FA representing the centers of all tracts common to all the participants in the analysis. The mean FA skeleton was thresholded to FA < 0.2 to include major white matter tracts. Each participant's aligned FA data were then projected onto this skeleton. The skeletonization process was also applied to MD, AD, RD, KFA, Kmean, Kax and Krad.

3.5. Outcome Assessment

3.5.1. Self-Reported Symptoms

In paper 1, PCS were assessed with the RPQ. Participants are asked to rate the severity of each symptom during the last 24 hours compared to before the injury (0 = not experienced at all; 1 = no more of a problem; 2 = a mild problem; 3 = a moderate problem; 4 = a severe problem) (34). In addition to the total score, 3 symptom subscales were calculated for the RPQ: cognitive (range 0-12), emotional (range 0-16), and somatic symptoms (range 0-36) (131,132). In paper 1, the Brief Symptom Inventory 18 (BSI-18), which consists of 18 items, with 6 items belonging to each subscale: depression, anxiety, and somatization, was also included (133). On a five-point Likert-type scale, participants reported how much a given problem bothered them during the past week.

The items for each subscale are summed to calculate a score (range: 0-24), where higher scores correspond to more psychological symptoms.

In the first studies published on the Trondheim MTBI follow-up study (including paper 4 in the thesis), the International Classification of Diseases-10th Edition (ICD-10) postconcussional syndrome (the term used in ICD-10) classification was used. BC-PSI was specifically developed for the purpose of assessing postconcussional syndrome according to ICD-10 (35). BC-PSI consists of 13 core symptoms, distributed over 4 symptom categories (i.e., somatic; emotional; cognitive; sleep disturbance), and 3 life problems, distributed over 2 additional symptom categories (i.e., reduced tolerance to alcohol; preoccupation with the symptoms and fear of permanent brain damage). The frequency and severity of each core symptom is rated (range 0-5) and these scores are then combined into an item score representing both the frequency and severity of that symptom (range 0-4). Postconcussional syndrome was defined as having at least one core symptom/life problem rated as moderate (item score $\geq$ 3) in 3 of the 6 different symptom categories, consistent with the ICD-10 criteria of PCS (39).

In the later studies published on the Trondheim MTBI follow-up study (including paper 2 and 3 in the thesis), we used slightly modified criteria to also include patients who reported several (i.e., more than 3) symptoms, but not necessarily of a moderate severity/frequency. The 13 core symptoms were used to calculate the total score. PCS was defined as having at least 3 core symptoms rated as at least moderate (score $\geq$ 3), or a total score $\geq$13.

3.5.2. Cognitive Test Performance

Patients with MTBI and trauma controls underwent cognitive assessments 2 weeks and 3 months after injury. The community controls were assessed 3 months apart. Traditional, well-established, pencil-and-paper tests as well as tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were administered. In total, 15 tests (each including several potential outcome measures) were administered. To analyze the results from each of these tests, in every study using data from Trondheim MTBI follow-up study, is not feasible, and increases the risk of false positive findings. In this thesis, only the traditional, well-established, pencil-and-paper tests were used as

outcome measures. These have all been recommended as common data elements in TBI research (134). The usefulness and psychometric properties of the CANTAB tests have been evaluated in separate papers, not part of this thesis. The general findings from these studies are that the CANTAB tests are not more sensitive to cognitive dysfunction after MTBI than pencil-and-paper tests, and the test-retest reliability is quite low (135–138)

How to best analyze cognitive test results is widely debated. In the thesis, both individual tests corresponding to cognitive domains (paper 1) and a composite score (paper 4) have been used. In paper 1, the Rey Auditory Verbal Learning (RAVLT) measured verbal learning and memory (139), the Trail Making Test Part B (TMT-B) measured executive functioning (140), letter fluency (also called Controlled Oral Word Association Test (COWAT)) measured verbal fluency and executive functioning (141), and the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) Coding subtest measured processing speed (142,143).

In paper 4, a cognitive composite was used. A cognitive composite score combine several test results into a summary score. If a condition or trauma (such as MTBI) is associated with a deficit in one specific cognitive domain, it could be argued that this deficit will be washed out in a composite that includes measures of several domains. However, there is substantial variability between studies regarding which cognitive domains are most affected after MTBI (29), suggesting heterogeneity in deficits between patients (e.g., some patients have executive deficits, while others have memory problems). Under these circumstances, deficits might be non-detectable when analyzes are performed test by test (with appropriate correction for multiple comparisons), while a cognitive composite score might be well suited for identifying reduced cognitive functioning at the group level. In paper 4, a cognitive composite score calculated according to Miller and Rohling (144) was used as the main outcome measure. This composite score is commonly used and considered to be a reliable measure of cognition (145,146). The scores are converted to a common metric (T-scores: mean = 50, standard deviation = 10, in the normative group) using published norms and the composite score is then calculated by averaging the T-scores from the individual test scores. Measures of processing speed (the Coding and Symbol Search subtests from the WAIS-IV), memory and learning (RAVLT), and executive functioning (the letter and semantic trail of a verbal fluency test, were included in the composite score.

3.6. Preinjury Intelligence and Cognitive Reserve

The Vocabulary subtest from Wechsler Abbreviated Scale of Intelligence (147,148) administered at the 2-week assessment, was used as an estimate of preinjury intelligence, and a proxy of cognitive reserve, which is a commonly used procedure in TBI research (116). The Vocabulary subtest is considered an estimate of general mental ability (17) and test performance has been shown to be unaffected by cognitive impairment following MTBI (149,150). Of note, in paper 3, the results on the Vocabulary subtest is referred to as an estimate of preinjury intelligence, while in paper 4, as an estimate of cognitive reserve. This is related to the purpose of including vocabulary scores in the papers, and the different ways they were handled in the statistical models. In paper 4, it was investigated whether vocabulary scores moderated the effect of the MTBI (i.e., in line with the cognitive reserve research framework), while in paper 3, vocabulary scores were included simply as a covariate (i.e., the main effect of vocabulary scores was controlled for).

3.7. Statistical Analyses

3.7.1. Paper 1

Associations between cognitive test performance and PCS were examined and most of the analyses relied on *nonparametric* methods. It is expected, and this was also the case in the present sample, that the distribution of self-reported symptoms has a zero-inflation (i.e., a large number of the participants do not report any symptoms). Consequently, the distributions were not normal and traditional parametric methods not suitable (e.g., Pearson's *r*, Student's t-test). Furthermore, a distribution of self-reported symptoms commonly includes values that would be characterized as outliers in traditional parametric methods (i.e., some individuals report many symptoms) and these observations could have an unproportionally large impact on the results. For this reason, Spearman's rank correlations (*rho*), which rely on ranked data, were used to investigate the associations between self-report measures and cognitive test performance. To investigate whether change in self-reported symptoms from 2 weeks to 3 months was associated with change in cognitive test performance, change scores were calculated. For each participant, self-reported symptom scores at 2 weeks were subtracted from scores at 3 months (i.e., a negative score means reduced symptom severity at the 3-month assessment). Similarly, cognitive test scores at 2 weeks

were subtracted from scores at 3 months (i.e., a positive score means better performance at 3 months). The associations between these change scores were then investigated with Spearman's rank correlations. Because change scores are correlated with the scores at the first assessment, a phenomenon known as regression to the mean (151,152), analyses accounting for this potential effect were also presented. The residuals were saved from a regression model where the change score was the dependent variable and the 2-week score was the independent variable. These residuals were analyzed in place of the raw change scores for this analysis.

3.7.2. Paper 2

Whether personal and injury-related factors predicted PCS in patients with MTBI, was evaluated with *logistic regression* models. First, univariable analyses for each variable of interest were conducted. Odds-ratios (OR) with 95% confidence interval were reported. Second, models were fitted by penalized logistic regression with *lasso* (least absolute shrinkage and selection operator) as implemented in the Stata command lasso logit (153). This is a useful method when the effect of many predictors are examined. Lasso shrinks the coefficients to less extreme values, and thereby improves the external validity of the model. For variables with low predictive value, the coefficients could be shrunk (set) to zero (thus, left out of the final model). The degree of shrinkage was determined by 10-fold cross-validation. In effect, lasso performs coefficient estimation and variable selection simultaneously and provides estimates of overall fit rather than statistical significance of each predictor. The uncertainty of the coefficients was assessed by repeating the penalized regression procedure in 1000 bootstrap samples.

Bootstrapping is a nonparametric technique used to estimate the uncertainty of a statistic or a coefficient. It is particularly useful when the underlying distribution (i.e., the distribution that the specific sample came from) is unknown and possibly non-normal (154). In a traditional t-test or linear regression model, the standard errors are based on the standard deviation (and the sample size) in the sample. When bootstrapping, a large number of samples is drawn from the original sample (i.e., resampling with replacement) and the statistic of interest (such as the mean, or a coefficient) is calculated in each of these bootstrap samples. The standard error (and confidence interval) can then be derived directly from the standard deviation in this bootstrap distribution. In

the lasso model, the uncertainty for each of the predictors was assessed by the proportion of the 1000 bootstrap samples when its coefficient was set to zero. The lower proportion, the higher is the probability that a variable is important for outcome prediction. The area under the curve (AUC) of the receiver operating characteristics curves was used to assess performance of the models. Optimism-corrected AUCs with 95% confidence intervals were obtained from bootstrapping with 1000 replications. In this *internal validation procedure*, the model is estimated in the bootstrap samples and then tested in the original sample. The mean difference between the AUCs obtained in the bootstrap samples and the original sample is referred to as the "optimism", which is subtracted from the AUC obtained in the original model (155).

3.7.3. Paper 3

Differences in diffusion metrics between patients with PCS, patients without PCS, and the control group (i.e. 3 comparisons) were analyzed with the *Randomise* tool in FSL, which is a non-parametric, permutation-based method using threshold-free cluster enhancement (TFCE) with a correction for multiple comparisons (156). Basically, Randomise performs analyses on every voxel in the white matter skeleton, but the TFCE option enhances voxels close in space, thereby increasing the statistical power and making it more likely to find clusters of voxels that differ between the groups examined. A corrected p-value of <0.05 was considered statistically significant. Age, age^2, sex, and scanner upgrade (due to scanner upgrade during the inclusion period) were controlled for in all analyses. All analyses were performed with the patients with complicated MTBI both included (i.e., the total sample) and excluded (i.e., the uncomplicated sample). Further, analyses were also performed with estimated intelligence (i.e., vocabulary scores) included as an additional covariate to investigate whether differences in estimated intelligence between the groups affected the results.

3.7.4. Paper 4

A *linear mixed effects model* was fitted to examine whether cognitive reserve (i.e., vocabulary scores) moderated differences in cognitive test performance between groups (MTBI, trauma controls, community controls) at 2 weeks and 3 months after injury. Mixed effects models are

suitable when observations are nested (i.e., not independent) (157). Observations can be nested in several ways, for example, nested within countries or hospitals, but in longitudinal designs, observations are typically nested within individuals (i.e., the same individual is assessed 2 or more times). Simplified, observations can be considered nested when one value can be predicted based on another (e.g., in longitudinal designs, for a specific individual, it is more likely to correctly guess the score on the second assessment if the score on the first assessment is known). This independence needs to be accounted for when model parameters are calculated. A mixed effect model is superior to a mixed ANOVA (which also accounts for dependence between observations) when some observations are missing, which they usually are in longitudinal studies. In a typical mixed ANOVA, only complete cases are analyzed (i.e., an individual needs to have complete data to be included in the analysis), while a mixed effect model can utilize data from an individual even if data from some of the assessments is missing (that is, if the dependent variable is missing. Mixed models cannot handle missing independent variables).

In linear mixed effects models, both random and fixed effects are fitted. For fixed effects, just like in traditional linear regression models, coefficients are calculated and these are interpreted as they would be in a linear regression (i.e., the coefficients represent the change in the dependent variable associated with a one-unit increase in the independent variable). For random effects, coefficients are not calculated. Instead, it is calculated how much of the variance in the dependent variable is at level 1 (typically observations in longitudinal designs) and how much is at level 2 (typically individuals in longitudinal designs) (158). In longitudinal designs, the variance is often larger at level 2 than at level 1, meaning that there is more variability *between* people than *within* people (i.e., if cognitive test performance is the outcome variable, there is great variability between persons on this variable, but less variability within a person that is repeatedly assessed).

In the mixed model in paper 4, subjects were fitted as random effects and the within-subject correlation was modeled by a random, subject-specific intercept. Group, time of assessment (2-week/3-month), vocabulary scores, age, and sex were entered as fixed effects. The 3-way interaction vocabulary*time*group and the 2-way interactions time*group, vocabulary*group, and vocabulary*time, were examined. A 3-way interaction term can be hard to digest, but a few examples can clarify how these effects should be interpreted, starting with the 2-way interactions.

A significant time*group interaction suggests that the effect of time differs depending on group. For example, the effect of time could be greater in the MTBI group with the consequence that improvement from 2-weeks to 3-months was greatest in the MTBI group. A significant vocabulary*group interaction suggests that the effect of vocabulary differs depending on group. For example, the effect of vocabulary could be greater in the MTBI group with the consequence that group differences (MTBI/trauma controls/community controls) in cognitive test performance were greatest among participants with lower vocabulary scores. A significant vocabulary*time interaction suggests that the effect of vocabulary differs depending on time. For example, the effect of vocabulary scores could be greater at the 3-month assessment with the consequence that improvement from 2 weeks to 3 months was greatest among participants with higher vocabulary scores. A significant vocabulary*time*group *3-way* interaction indicates that the effect of vocabulary differs depending on *both* time and group. For example, the effect of vocabulary could be greatest in patients with MTBI at the 3 month assessment, with the consequence that improvement in cognitive test performance from 2 weeks to 3 months was greatest among the patients with MTBI who had higher vocabulary scores. A similar linear mixed effects model was used to explore differences in the cognitive composite score between patients with and without PCS. Group (PCS+, PCS-), time, vocabulary scores, age, and sex were entered as fixed effects. The 3-way interaction group*time*vocabulary and all 2-way interactions were examined, also in this model. Group differences in the cognitive composite score between patients with and without PCS were also reported with vocabulary scores excluded from the model (i.e., unadjusted model).

4. Summary of Results

4.1. Paper 1

Change in self-reported cognitive symptoms after mild traumatic brain injury is associated with changes in emotional and somatic symptoms and not changes in cognitive performance.

Background: Previous findings on the association between self-reported PCS and cognitive test performance are mixed. However, there is a lack of studies longitudinally investigating whether change in PCS is associated with change in cognitive test performance. The aims of this paper were to investigate (1) whether self-reported cognitive symptoms after MTBI were associated with cognitive test performance at 2 weeks and 3 months after the injury, and (2) whether improvement in self-reported cognitive symptoms from 2 weeks to 3 months was associated with improvement in cognitive test performance.

Method: Patients with MTBI (*n*=135) completed the RPQ, the Brief Symptom Inventory 18, and cognitive tests (i.e., Controlled Oral Word Association, Coding, Rey Auditory Verbal Learning, and Trail Making test) at 2 weeks and 3 months after MTBI. Using Spearman's rank correlations (*rho*), associations were examined between self-report measures and cognitive test performance at each time point and between change scores (i.e., 3-month score minus 2-week score) on each outcome.

Results: At 3 months, 27% reported cognitive symptoms to some extent. At both assessments, greater severity of RPQ cognitive symptoms was very weakly associated with worse cognitive test performance (2-week *rho* range: -0.19 to -0.01; 3-month *rho* range: -0.20 to -0.10). RPQ cognitive symptoms were, however, strongly related to greater somatic and emotional symptoms. Change in self-reported cognitive symptoms from 2 weeks to 3 months was not associated with change in cognitive test performance. In contrast, change in self-reported cognitive symptoms was strongly associated with change in emotional (*rho*=0.58) and somatic symptoms (*rho*=0.57).

Conclusions: These findings indicate that improvements in subjective cognitive symptoms after MTBI co-occur with improvements on other subjective metrics, but are not related to improvements in objectively measured cognitive functioning.

4.2. Paper 2

Personal factors associated with postconcussion symptoms three months after mild traumatic brain injury

Background: Personal (i.e. preinjury) factors have consistently been associated with PCS. However, previous studies have examined only a limited number of personal factors. The aims of this study were (1) to describe several personal factors in patients with MTBI, in trauma controls, and in community controls, and (2) to explore how such factors were associated with PCS.

Method: Patients with MTBI (n=378), trauma controls (n=82), and community controls (n=81) were included. Data on preinjury health and work status, personality, resilience, attention/hyperactivity and substance use were collected using interviews and questionnaires. CT findings and posttraumatic amnesia were recorded. Symptoms were assessed in all groups at 3 months with the British Columbia Postconcussion Symptom Inventory. PCS was defined as reporting at least 3 symptoms of at least a moderate severity, and/or having a total score ≥ 13. Predictive models were fitted with penalized logistic regression using the least absolute shrinkage and selection operator in the MTBI group, and model fit was assessed with optimism-corrected area under the receiver operating curve.

Results: There were few differences in personal factors between the MTBI group and the trauma controls and community controls. Rates of PCS were 20.8% in the MTBI group, 8.0% in trauma controls, and 1.3% in community controls. In the MTBI group, there were differences between the PCS+ and PCS- group on most personal factors and injury-related variables in univariable comparisons. In the penalized multivariable regression models, the optimism-corrected area under the curve for the full model was 0.79, 0.73 for the model only including personal factors, and 0.63 for the model only including injury variables. Working less than full time before injury, having preinjury pain, poor sleep quality, and being female were among the selected predictors, but also resilience and some personality traits contributed in the model. Intracranial abnormalities on CT were also a risk factor for PCS.

Conclusions: Personal factors convey important prognostic information in patients with MTBI. A vulnerable work status and preinjury health problems might indicate a need for follow-up and targeted interventions.

4.3. Paper 3

Acute diffusion tensor and kurtosis imaging and outcome following mild traumatic brain injury

Background: There is a paucity of studies examining whether findings from acute DTI and DKI metrics are associated with later PCS. Further, the wide definition of MTBI and preinjury differences between patients with and without PCS hampers the understanding of DTI and DKI findings in MTBI. The aim of this study was to investigate associations between acute DTI and DKI metrics and PCS at 3 months following MTBI.

Methods: Patients with MTBI (*n*=176) underwent MRI within 72 hours after the injury, and assessment of PCS 3 months after the injury. Preinjury intelligence was estimated with the Vocabulary subtest. Healthy community controls (*n*=78) also underwent MRI. Differences in 8 DTI and DKI metrics between patients with PCS, patients without PCS, and controls were examined with tract-based spatial statistics. All analyses were performed in the total sample, in patients without intracranial findings on clinical MRI sequences (i.e., uncomplicated MTBI), and with estimated intelligence both included and excluded from the statistical models.

Results: The prevalence of PCS was higher in patients with complicated MTBI (44%) than in patients with uncomplicated MTBI (17%). Patients with PCS had lower fractional anisotropy and kurtosis fractional anisotropy, and higher radial diffusivity, than patients without PCS. In the uncomplicated MTBI sample, significant differences in FA between patients with and without PCS remained. Compared to healthy controls, patients with PCS had widespread differences in all 8 DTI and DKI metrics examined. When including estimated preinjury intelligence in the statistical models, no significant differences in DTI or DKI metrics between patients with and without PCS were present in the total sample or in the uncomplicated MTBI sample, but patients with PCS still had significantly higher mean, radial, and axial diffusivity than controls.

Conclusions: Acutely after the injury, patients with PCS had poorer white matter microstructural integrity than patients without PCS and healthy controls. However, these differences became less pronounced when estimated preinjury intelligence was controlled for, suggesting that preinjury differences, and not only the MTBI, accounted for some of the observed differences in white matter integrity.

4.4. Paper 4

Cognitive reserve moderates cognitive outcome after mild traumatic brain injury

Background: The cognitive reserve hypothesis postulates that the effect of a brain injury depends on a patient's cognitive reserve. Cognitive reserve has been thoroughly studied in neurodegenerative diseases, and to some extent in moderate and severe TBI. Few studies have, however, examined the role of cognitive reserve in MTBI. The aims of this paper were (1) to investigate whether cognitive reserve moderates differences in cognitive test performance between patients with MTBI and controls, and (2) to examine whether patients with PCS have lower cognitive test performance than patients without, at 2 weeks and 3 months after injury.

Method: Patients with MTBI (n=160), trauma controls (n=71), community controls (n=79) were included. A cognitive composite score was used as outcome measure. The Vocabulary subtest was used as a proxy of cognitive reserve. PCS was assessed at 3 months with the British Columbia Postconcussion Symptom Inventory.

Results: Linear mixed models demonstrated that the effect of vocabulary scores on the cognitive composite scores was larger in patients with MTBI than in community controls at 2 weeks and at 3 months after injury (p=0.001). Thus, group differences in the cognitive composite score varied as a function of vocabulary scores, with the biggest differences seen among participants with lower vocabulary scores. There were no significant differences in the cognitive composite score between patients with and without PCS, but patients with PCS had lower vocabulary scores.

Conclusions: Cognitive reserve, but not PCS, was associated with cognitive test performance after MTBI. This supports the cognitive reserve hypothesis in the MTBI context and suggests that persons with low cognitive reserve are more vulnerable to reduced cognitive functioning if they sustain an MTBI.

5. General Discussion

5.1. Main Findings

The overall aim of this thesis was to investigate the role of neuroimaging findings and preinjury factors on outcome after MTBI. First, associations between cognitive test performance and self-reported PCS were weak. Thus, whether a patient presents with good or poor outcome after MTBI, partly depends on the assessment conducted. Second, macrostructural brain pathology, as measured by CT and MRI, was associated with PCS 3 months after the injury. Microstructural white matter integrity, as measured by DTI and DKI, was also associated with PCS. However, poor microstructural white matter integrity in patients with PCS was not necessarily exclusively caused by the injury. Third, a range of preinjury factors were associated with PCS at 3 months, including employment status, sex, preinjury health, personality, resilience, and intelligence. Further, cognitive reserve moderated differences in cognitive test performance between patients with MTBI, trauma controls, and community controls, suggesting that persons with low cognitive reserve are more vulnerable to reduced cognitive functioning if they sustain an MTBI. Importantly, although this thesis has demonstrated the importance of preinjury factors on outcome after MTBI, preinjury factors alone do not seem to be responsible for symptoms and poor cognitive test performance. Rather, the *combined* or *synergistic* effects of an MTBI and certain preinjury factors make people vulnerable to symptoms and poorer cognitive test performance.

5.2. Appraisal of the Findings

5.2.1. Associations Between Cognitive Test Performance and PCS

At 2 weeks and 3 months after the injury, the associations between cognitive test performance and PCS were weak. In paper 1, self-reported symptoms were analyzed as continuous variables. In paper 4, self-reported symptoms were dichotomized (i.e., PCS or not PCS), but the finding of weak associations with cognitive test performance was the same. Further, the associations remained weak when self-reported *cognitive* symptoms were analyzed separately. As such, we confirmed findings from many previous cross-sectional studies (45,47,48,159,160). Unlike previous studies, we also examined whether *changes* in cognitive test performance were associated with *changes* in self-reported cognitive symptoms from 2 weeks to 3 months following MTBI. In these analyses,

every participant served as their own control, and the possibly confounding effect of preinjury variability in cognitive test performance and self-reported cognitive symptoms was minimized. These longitudinal analyses showed that association between *change* in cognitive test performance and *change* in self-reported cognitive symptoms were absent or weak. As such, these results extend previous findings from cross-sectional studies (45,47,48,159,160).

In many aspects, these results are perplexing. If a patient reports great improvement in cognitive symptoms, intuitively, it could be expected that this improvement would be evident also on cognitive test results. However, it was not. The reasons for weak associations between cognitive test performance and self-reported cognitive symptoms can be (at least) 3: (1) they measure different aspects of functioning; (2) people are bad at reporting their own symptoms; (3) cognitive tests lack reliability and/or validity. Probably, all of these potential reasons are true to some extent. Regarding (1), cognitive tests and self-report measures are *supposed* to measure different aspects of functioning. There would be no need for cognitive tests if they were perfectly correlated with questionnaires, and there would certainly be no need to include both as outcomes in TBI research, which is recommended (134). Regarding (2), studies show that people often are inconsistent in their symptoms reporting, especially when asked to evaluate how symptoms have changed over time (which they do on the RPQ). Research on the "good-old-days" bias suggests that people may underestimate their preinjury symptoms (161), and their perception of their preinjury symptoms change over time (162). Regarding (3), cognitive tests are not error free measures. Different tests designed to measure the same underlying cognitive function often show only modest correlations (163,164), and test-retest correlations vary between tests, but are commonly around 0.7 (165). Even though a test-retest coefficient of 0.7 can be considered "adequate" (139), it means that only around 50% of the variance in test scores at one occasion is explained by the variance at another occasion. Without doubt, a cognitive test score is associated with uncertainty. Regardless of the reason behind weak associations between cognitive test performance and PCS, this needs to be considered in both MTBI research and clinical practice, because results may vary, depending on the outcome measure analyzed.

Interestingly, while the associations between cognitive test performance and self-reported cognitive symptoms were weak, associations between self-reported cognitive, emotional and

somatic symptoms were considerably stronger. This was true in both cross-sectional and longitudinal analyses. This suggests that different domains of PCS are partly dependent, and that change in one domain can be expected to be accompanied by changes in others.

5.2.2. Effect of Macrostructural Brain Pathology and Microstructural Integrity on PCS

In paper 2, macrostructural brain abnormalities were assessed with CT. CT findings were significantly associated with PCS in both univariate and multivariate analyses. Results showed that 58% of those with findings on CT had PCS, while 21% of those without CT findings had PCS (or 19%, if also those without CT assessment, due to good clinical presentation, were included in the group without CT findings). In paper 3, macrostructural brain abnormalities were assessed with MRI and 44% of those with MRI findings had PCS, while 17% of those without MRI findings had PCS. Together, these results suggest that macrostructural findings increase the risk of PCS. These results are in contrast to some previous studies not finding associations between macrostructural pathology and PCS in patients with MTBI (31,64–66). However, our findings align with recent publications from two large-scale multicenter studies, the Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) and the TRACK-TBI study, who both found poorer functional outcome (measured with the Glasgow Outcome Scale – Extended, GOSE) in patients with macrostructural pathology (assessed with CT) (166,167). The Trondheim MTBI follow-up study, the CENTER-TBI study, and the TRACK-TBI study are all considerably larger than most previous studies examining associations between macrostructural pathology and outcome, and the positive findings in these studies suggest that differences in statistical power between studies could explain some of the mixed findings in the literature. For example, in the TRACK-TBI study, the difference in prevalence of functional impairment between patients with macrostructural pathology (61%) and patients without pathology (49%) was quite modest (although surprisingly high in both groups), but the large sample size (n=1453) drove these differences to statistical significance. In a smaller study, a difference of this magnitude would not have been statistically significant, and the authors might have concluded differently.

Although macrostructural pathology was associated with PCS, it is important to note that among patients with PCS, most did not have findings on CT (84%). Similarly, most of the patients with

PCS did not have findings on MRI (77%). This is related to the fact that CT and MRI findings are uncommon among patients with MTBI (i.e., around 6% of the patients had CT abnormalities in the Trondheim MTBI study, and around 10% had MRI findings). Thus, in isolation, and in clinical practice, macrostructural brain pathology (i.e., complicated MTBI), and especially the absence of it, is difficult to use for outcome prediction.

In paper 3, microstructural white matter integrity was assessed with DTI and DKI in the acute phase after the injury. Poorer white matter integrity was associated with PCS at 3 months. This was evident by (1) differences in diffusion metrics between patients with and without PCS and (2) more pronounced differences between patients with PCS and community controls than between patients without PCS and community controls. This finding of differences in acute diffusion metrics between patients with and without PCS extends findings of previous studies reporting differences in diffusion metrics between these groups in the subacute and chronic phase after the injury (79–85). However, differences in diffusion metrics between patients with and without PCS were reduced when estimated preinjury intelligence was adjusted for. Importantly, this suggests that preinjury differences, and not exclusively the MTBI, might account for some of the observed differences between these groups. Estimated intelligence was unfortunately not assessed in all participants, increasing the uncertainty in this finding. However, paper 2 (discussed below) clearly demonstrated that patients with PCS differed from patients without PCS on a range of preinjury factors. Several of these preinjury factors have been associated with poorer white matter integrity outside the MTBI research context, for example headache (168), depression (96), ADHD (97), and poor sleep quality (169). Considering this fact, it would be unexpected if patients with PCS *did not* differ from patients without PCS in preinjury white matter microstructural integrity. Thus, the present findings together with previous research show that preinjury differences are of importance in DTI studies on PCS. We chose to adjust for preinjury intelligence because it has been shown to be associated with white matter integrity (98–101). However, several preinjury factors most likely affect diffusion metrics in patients with PCS, and intelligence should be considered as *one* example, rather than the most important one.

Interestingly, if patients who develop PCS after MTBI have poorer *preinjury* white matter integrity, this is an example of how low *brain reserve* can contribute to outcome after MTBI. Brain

reserve, or brain resilience, refers to preinjury individual differences in structural characteristics that might be protective against brain pathology (109). While *cognitive* reserve can be described as preinjury software differences, brain reserve can be considered preinjury hardware differences, such as differences in intracranial volume, brain volume, cortical thickness, and white matter integrity (109).

5.2.3. Effect of Preinjury Factors on Outcome

Unlike previous studies, we examined the associations between a broad range of preinjury factors and PCS in paper 2. Female sex, not working or studying full time, pain, a psychiatric history, poor sleep quality, higher neuroticism, and lower resilience, were all preinjury factors significantly associated with PCS in univariate models. Not working or studying full time was a particularly strong predictor for PCS in both the univariate analysis and in the multivariate lasso model. Although unemployment has been shown to predict PCS in previous studies (107,170), our results extend these findings by showing the importance of this variable also when potential confounders were controlled for (e.g., preinjury pain and psychiatric history). Similarly, female sex was one of the variables most often included in the lasso model. Previous findings on the role of sex on outcome after MTBI are mixed (171,172), but our results suggest that sex is of importance even when controlling for a range of possible confounders. In addition to the preinjury factors included in paper 2, paper 4 showed that patients with PCS had lower estimated intelligence than patients without PCS, in line with some previous research (41).

Injury-related variables, such as CT findings and longer PTA were also related to PCS, but all together, the preinjury factors had higher discriminative ability than the injury-related factors. Importantly, the MTBI group, the trauma control group, and the community control group, did not differ significantly on the preinjury factors that predicted PCS. Nonetheless, the prevalence of PCS (or "postconcussion-like symptoms", as they more correctly should be referred to in people who have not had an MTBI) was much higher in the MTBI group (21%), than in the trauma control group (8%) and the community control group (1%). This suggests that PCS cannot be ascribed to preinjury factors alone, and the MTBI in itself is of importance. If the MTBI was of none, or minor, importance, we would expect a similar rate of PCS in the MTBI group as in the two control groups,

considering that these 3 groups were similar on the preinjury factors predicting PCS. Consequently, these findings are in line with a biopsychosocial understanding of outcome after MTBI (102), where biological, psychological, and social factors all contribute to outcome in an additive or interactive way.

Cognitive reserve, estimated through preinjury intelligence, was found to moderate differences in cognitive test performance between the MTBI group, the trauma control group, and the community control group (paper 4). Thus, differences in cognitive test performance between the MTBI group, the trauma control group, and the community control group, were greatest among participants with lower cognitive reserve, and no differences between these groups were evident among participants with higher cognitive reserve. Relating this finding to the different ways cognitive reserve can contribute to outcome illustrated in Figure 3 (page 23), we found that the effect of the MTBI differed depending on the level of cognitive reserve (Figure 3B). Cognitive reserve has previously been found to moderate outcome in neurodegenerative diseases, and to some extent in moderate to severe TBI (121,173). Our results extend these findings and suggest that cognitive reserve contributes to outcome also in MTBI. However, cognitive reserve was not found to moderate the rate of improvement in cognitive test performance between 2 weeks and 3 months (such a hypothetical effect is illustrated in Figure 3C). One possible explanation for this is that the vast majority of people with high cognitive reserve had fully recovered already at 2 weeks. To demonstrate that cognitive reserve moderates recovery rate between 2 assessments, requires that patients with high cognitive reserve have measurable cognitive deficits at the first assessment, which possibly was not the case in this sample of mostly non-hospitalized patients with MTBI who had their first assessment 2-3 weeks after the injury. Support for this notion comes from a recent study on a sample of predominantly *moderate and severe* TBI. Fraser et al. (173) demonstrated faster recovery between 2 assessments in patients with high cognitive reserve. Patients were assessed around 1 month postinjury and again around 3-4 years later. Cognitive reserve was estimated with the National Adult Reading Test (a measure of preinjury intelligence) and patients with higher cognitive reserve had a greater improvement in cognitive test performance between the 2 assessments.

Educational attainment is, beside intelligence, considered a proxy of cognitive reserve (109). In paper 2, we did not find that years of education predicted PCS at 3 months. This is in contrast to previous studies which have shown that fewer years of education is associated with poorer functional outcome and PCS (105,106). However, the median age of the MTBI sample in the Trondheim MTBI follow-up study was 25, meaning that many participants were still *in* education (either high school or university) and years of education is therefore a poor proxy for cognitive reserve in this sample. Occupational attainment is also considered a proxy of cognitive reserve (109), but as with educational attainment, this proxy is less useful in a young sample. However, a variable related to occupational attainment, namely unemployment (i.e., working or studying less than 80%), was the most important predictor of PCS in the multivariate model in paper 2, and it had a strong effect in the univariate analyses. Altogether, our findings suggest that cognitive reserve is important for outcome after MTBI.

5.3. Clinical Implications

This thesis examined the associations between neuroimaging findings, preinjury factors, and outcome after MTBI. Formulated differently; the thesis sought to increase the understanding on why outcome is poor in some individuals. Understanding *why* some patients are at risk for poor outcome is an important step towards better outcome prediction, more precise psychoeducation, more directed follow-ups, and more effective interventions.

Paper 1 demonstrated a weak association between cognitive test performance and PCS. Clinicians should be aware of this and not expect that patients reporting a lot of symptoms will perform poorly on cognitive tests. Similarly, improvement in symptom reporting was not associated with improvement in cognitive test performance. Thus, clinicians following patients over time cannot expect that improvement in symptom reporting will be mirrored by improvement in cognitive test performance (beyond practice effects). Further, it was shown that different clusters of symptoms (i.e., cognitive, emotional, and somatic) were highly intercorrelated, and that improvement in one cluster (e.g., cognitive symptoms) was strongly related to improvement in others (e.g., somatic symptoms). This finding is promising for treatment as interventions can be directed toward one cluster with the expectation that improvement in other clusters will follow.

In Norway, CT is part of the clinical routine when a patient with suspected TBI seeks medical care, with the purpose of detecting fractures, contusions, and hemorrhages that could lead to deterioration. Our findings suggest that the CT examination also is important for outcome prediction. However, clinicians should be aware that PCS is more common than intracranial findings. Thus, when meeting a patient with PCS, the chance that this patient did not have intracranial findings is greater than that intracranial findings were present. DTI and DKI are not part of the clinical routine per today. Implementing DTI and DKI in the clinic would be extremely resource demanding. Thus, from a cost-benefit perspective, they would need to show very good discriminative abilities between patients with and without MTBI, or between patients with good and poor outcome. This seems not to be the case. Rather, poor microstructural integrity identified with DTI or DKI should be considered as one of many factors associated with poor outcome after MTBI.

Several preinjury factors seem to be critical in the development of PCS and some of them could be targets for interventions. For example, resilience, is suggested to be more modifiable than typical personality traits, making it a possible target for interventions (174). Further, it is important to note that the risk factors identified will be overrepresented in patients seeking medical care for prolonged symptoms after MTBI. Thus, even if an intervention is not directly targeting a specific risk factor, the interventions offered need to be effective for people having these preinjury characteristics. Across clinical disorders, treatment efficacy varies between patients (175) and to identify which treatment works for whom is a central part of personalized medicine. For example, higher baseline neuroticism (identified as a risk factor for PCS in paper 2) has been associated with poorer outcome after cognitive behavioral therapy and acceptance and commitment therapy in anxiety disorders (176).

5.4. Methodological Considerations and Limitations

5.4.1. Validity and Reliability

External validity refers to the generalizability of the findings (177) and is highly dependent on whether the participants in the Trondheim MTBI follow-up study (and the participants in paper 1 to 4, in particularly) are representative for patients with MTBI. The Trondheim MTBI study is a population-based study that aimed to identify all patients with MTBI aged 16 to 59 in the catchment area during the inclusion period. Unlike many other studies, inclusion took place not only at a level 1 emergency clinic, but also at a municipal emergency clinic (a general practitioner-run, out-patient clinic). As such, the Trondheim MTBI study could identify many of the milder, as well as the more severe, forms of MTBI, and the sample can therefore be considered to be representative for patients with MTBI. However, it is assumed that a great portion of people with MTBI do not seek acute medical care (16), and these could, naturally, not be identified and included. Thus, the sample in the Trondheim MTBI study can be said to be representative for patients with MTBI seeking medical care, but not necessarily for the total population of persons with MTBI. Further, Norway is a high-income country, and Trondheim a university city. Thus, the findings are not necessarily generalizable to low-income countries. Also, it is important to remember that patients with MTBI are not representative of the general population. Young men are overrepresented (16), which also was the case in the Trondheim MTBI study (122).

Internal validity, and more specifically selection bias, refers to the way participants are included into the study (177). In the Trondheim MTBI study, all patients identified with MTBI (N=732) were not included in the follow-up study (n=378), and all patients in the follow-up study were not included in the *extended* follow-up study, including cognitive testing and MRI (n=199). This constitutes a threat to internal validity, if there was a bias in who were included in the follow-up study, and who were included in the extended follow-up study. As expected, not all patients wished to participate in the follow-up study, a considerable portion met one of the exclusion criteria (e.g., not fluent in Norwegian), and practical reasons (e.g., available MRI slots) made it impossible to follow all patients. However, differences between enrolled and not enrolled patients were, in general, small (122), and although patients included in the *extended* follow-up study were somewhat older than the rest of the patients in the follow-up study, differences were mostly small

and non-significant (62). The decision to include more patients in a *simple* follow-up (i.e., all 378 patients) than in the *extended* follow-up had some, potentially confusing, consequences for this thesis. For example, the Vocabulary test, an essential measure in paper 3 and 4, was not included as a predictor in paper 2, because it was administered only to the patients in the *extended* follow-up.

In the Trondheim MTBI follow-up study, patients with intracranial findings on CT were included. Some researchers consider complicated MTBI to be a special case of MTBI, and that findings from patients with complicated MTBI are not necessarily valid for patients with uncomplicated MTBI. This view can, however, become increasingly problematic with the continuous development of more sensitive imaging techniques (i.e., the proportion of "complicated" MTBI will increase). Nevertheless, in the paper 2, 3, and 4 in the present study, most of the analyses were conducted with the complicated cases both included and excluded, and findings were largely similar. This is of importance, maybe especially, for the findings in paper 4, because these could potentially be biased had the patients with low cognitive reserve had more severe injuries (i.e., more brain pathology). However, when patients with complicated MTBI were excluded, the effect of cognitive reserve was similar in those with uncomplicated MTBI and in the whole MTBI group.

Reliability relates to the consistency of measures (178). The validity of study findings depends on the reliability of the tools used to measure different variables. In the Trondheim MTBI follow-up study, many core variables relied on self-report (e.g., some injury severity variables, preinjury factors, PCS), which is natural, since the patient's own experience was often the only source of information available. One exception is LOC, which had to be witnessed in order to be classified as present. Length of PTA was, however, self-reported. This could be problematic as some evidence suggests that patients with TBI tend to overestimate their PTA duration, especially patients with cognitive deficits (10). PTA is commonly used as a measure of injury severity, but PTA could also be considered to be an ultra-early outcome. Also, longer PTA has been associated with fewer years of education (8), further complicating the use of PTA as a "pure" measure of injury severity.

We did not administer any formal symptom validity test in the Trondheim MTBI follow-up study, which is common in studies from the US, and especially when cognitive test performance is evaluated. This constitutes a limitation of the study as patients may exaggerate symptoms and/or underperform on cognitive testing for the purpose of attaining benefits (179,180). However, because the results from the Trondheim MTBI follow-up study were solely part of a research repository and not available to future medico-legal assessments, the lack of symptom validity testing is less critical. Further, the process, and importance, of litigation issues, differ substantially between the US and the Scandinavian countries. In paper 4, however, we did perform a validity check by examining the results on the Coding and the Symbol Search tests, which have been suggested as embedded validity indicators (181,182), and we found no indications of invalid results.

The cognitive tests used in the present thesis are well-established in TBI research and have a long tradition in neuropsychological practice (17,134). Nonetheless, neither reliability (e.g., test-retest reliability), nor validity (e.g. concurrent validity), of cognitive tests are perfect (163–165) and test results are associated with several sources of errors and biases, such as the internal consistency of the test and measurement error related to time and situational variables (183). While some cognitive functions can be measured precisely, such as a person's ability to read single words, other cognitive abilities, such as memory and executive functioning, are usually more difficult to measure reliably (165). In general, cognitive composite scores have higher test-retest reliability than individual test scores (136), and this is one of the reasons why a composite score was used as a single outcome measure in paper 4. Further, the complexity of the statistical analyses (i.e., mixed effect models with a 3-way interaction term) made a composite score particularly suited for this paper.

The Vocabulary subtest was used as a measure of preinjury intelligence and cognitive reserve. Using a single test to measure intelligence lowers the reliability of the results. Intelligence is preferably measured with a battery of tests, such as the WAIS-IV. However, in studies on brain injury, it is of importance that results on tests of intelligence are not affected by the injury (i.e., that they measure *preinjury* functioning). Therefore, single tests known to be largely insensitive to brain pathology are usually used to estimate intelligence in brain injury studies, and among them

is the Vocabulary subtest (116). Tests of preinjury intelligence are often language-based and measure vocabulary knowledge or word reading in different varieties (116,184). There are some tests which have been developed with the specific purpose of measuring preinjury intelligence, such as the Wechsler Test of Adult Reading (WTAR) and the National Adult Reading Test (NART). However, these tests are not formally validated in Norwegian and were not administered in the Trondheim MTBI follow-up study. Importantly, the Vocabulary subtest has been shown to be the subtest in WAIS-IV with strongest correlations to WTAR and NART (both r=0.75) (184). Further, in a structural equation modelling of cognitive reserve, the Vocabulary subtest was the indicator (among 9 others, such as matrix reasoning, socioeconomic status, and cognitive-, physical-, and social activity) with the strongest loading on the latent variable cognitive reserve, in a one-factor model (standardized path coefficient = 0.88) (116).

PCS have been assessed with the RPQ (paper 1) and the BC-PSI (paper 2, 3 and 4). There is no consensus in the literature regarding when postconcussion *symptoms* should be classified as postconcussion *syndrome*, but in all definitions, the core of postconcussion syndrome is postconcussion symptoms of a certain magnitude (185). In the present thesis, the abbreviation PCS has been used for postconcussion symptoms, and in paper 1, these were analyzed as a continuous variable, while in paper 2, 3, and 4, as a dichotomized variable (i.e., what some people would call postconcussion *syndrome*). The symptoms assessed with RPQ and BC-PSI have a considerable overlap and both questionnaires have been used frequently in MTBI research (42,134,186). The most profound difference between these instruments is that on BC-PSI, respondents are asked to rate the frequency and severity of each symptom during the last 2 weeks, without reference to whether or not these symptoms were already present before the injury. On RPQ, however, respondents are asked to rate the severity of each symptom, during the last 24 hours, with reference to the status before the injury (e.g., if the symptom is present, but not more severe than before the injury, respondents should rate this symptoms as "1"). Intuitively, it can be assumed that RPQ has higher specificity for MTBI-induced symptoms because respondents are asked to compare their current status with their preinjury status. However, it has been shown that it is surprisingly difficult for people to compare their current status with a previous status (161,162), and as such, BC-PSI may provide a more pure reflection of a patient's current situation. Further, RPQ is not straightforward to administer to people without an injury (e.g., the community controls) because

they have no preinjury status to compare their current status with. Therefore, BC-PSI was defined as the primary PCS measure in the Trondheim MTBI follow-up study and it was administered as an interview, while RPQ was administered as a questionnaire that should be returned by post. Probably related to the different modes of administration, fewer participants responded to RPQ than BC-PSI. BC-PSI was therefore the preferred instrument in this thesis. However, BC-PSI was not administered at 2 weeks along with the assessment of cognitive test performance (the first BC-PSI assessment was at 3 months) and RPQ was therefore used in paper 1.

DTI, and especially DKI, are relatively new advanced MRI techniques, and the metrics derived from them are associated with uncertainty. Importantly, DTI and DKI do not measure the microstructural integrity directly, rather, they measure the diffusion of water molecules. The direction and magnitude of diffusion are then used to conclude on the integrity of the white matter. Even if experimental designs have demonstrated the relation between brain injury, diffusion changes, and axonal damage (61,68), the pathophysiological underpinnings of deviations in diffusion metrics are debated, and partly unknown. Further, the reduction of complex data that DTI and DKI offer (i.e., the output is a single value of each brain voxel) is a strength of the methods and enables the statistical comparisons made. However, the brain is complex and a single voxel can contain different types of tissue (causing partial volume effects) and white matter fibers running in different directions (i.e., crossing fibers) and this can distort the diffusion values obtained (187).

5.4.2. General Considerations

Cognitive tests were administered 2 weeks and 3 months after the injury. When the entire MTBI group was compared to the control groups, differences in cognitive test performance were minimal to small at 2 weeks, as evident in paper 4 and in other papers published on this sample (135,137). A priory, 2 weeks after the injury is an interesting time point to assess cognitive test performance because (1) most previous studies have assessed cognition either before (i.e. acute) or after (i.e., chronic) 2 weeks; (2) in the previous studies performed around 2 weeks, findings are mixed on whether cognitive test performance is reduced at this time point (188–191); (3) the CENTER-TBI study assessed patients at 2 weeks, making it possible to validate findings in the Trondheim MTBI

follow-up study in CENTER-TBI, and vice versa. In retrospect, knowing that the differences in cognitive test performance between the MTBI group and the control groups were small at 2 weeks, the 3 months assessment becomes somewhat redundant. An assessment in the acute phase (i.e., within the first few days) could have enriched the findings in this thesis. For example, regarding paper 4, it might be that cognitive reserve had been shown to moderate the recovery rate from the acute phase to 2 weeks. Further, it might be that the associations between cognitive test performance and PCS would have been stronger in an acute assessment. However, it is important to note that even though differences at 2 weeks were non-significant, the MTBI group performed worse than the community control group on every single test, and worse than the trauma control group on 4/5 tests (paper 4). Results like this open the theoretical possibility that a subgroup of MTBI patients actually has profound cognitive deficits, while the large majority of patients with MTBI is cognitively unaffected. Findings from paper 4 suggest that patients with low cognitive reserve might constitute such a subgroup. However, it is likely that this subgroup of patients with reduced cognitive performance after MTBI (assuming it exists), in reality, is more complex. Low cognitive reserve is probably only one of several (e.g., low resilience, poor microstructural integrity in white matter, etc.) defining characteristics for this subgroup.

Functional outcome (e.g., return to work and other activities) was not analyzed in the papers constituting this thesis. GOSE is the most commonly used instrument for assessing functional outcome after MTBI. However, functional outcome can be difficult to separate from PCS reporting on the GOSE. A score of 7 (where a score of 8 equals complete recovery) is given to participants who report “any other current problems relating to the injury which affects daily life”, and examples given are headaches, dizziness, sensitivity to noise or light, slowness, memory failure and concentration problems (i.e., typical PCS) (192). Further, the results from paper 2 illustrate problems that can arise when using functional outcomes in MTBI research. The strongest predictor for PCS was unemployment *before* the injury. Thus, unemployment is overrepresented in patients with PCS, and consequently, many patients with PCS do not have a work to return to. Functional outcome, such as return to work, is difficult to consistently assess in these patients.

Paper 2 identified several preinjury factors as predictive for PCS. However, interaction terms were not included in the statistical models. In paper 4, the interaction term group*vocabulary was

significant, meaning that the effect of vocabulary on the outcome (cognitive test performance) was greater in the MTBI group. This could have been investigated for the predictors included in paper 2, as well. For example, a group*resilience interaction term could have been included to investigate whether the effect of resilience on PCS was the same in the MTBI group as in the control groups. Because PCS are non-specific for MTBI (35,36,193), this is a highly relevant question. However, because the prevalence of PCS was low in the control groups (i.e., 6 trauma controls and 1 community control fulfilled the PCS criteria), it was not possible to reliably assess predictors of PCS in these groups. Thus, per today, we do not know if the predictors of PCS identified in paper 2 also predict postconcussion-like symptoms in persons without MTBI.

In paper 3, TBSS was used to examine differences in diffusion metrics. The advantage of TBSS is that the whole white matter skeleton is examined (i.e., there is no need to a priory define regions of interests) and the threshold-free cluster enhancement increases the chance of finding voxel clusters that differ between groups. However, it is difficult to estimate the size of the observed effects when using TBSS and the output from TBSS alone gives few clues to the discriminative abilities of diffusion metrics (e.g., between two groups). Also, there is no straightforward way to transfer results from TBSS into multivariate prognostic models (e.g., the model in paper 2). To do this, other approaches, such as calculating the number of abnormal regions of interest and then include this variable in multivariable models (81), are often used. However, also these methods have limitations, among them the requirement of a predefined threshold for what constitutes "abnormal" diffusion values. Further, penalized regression cannot be implemented easily in TBSS. In paper 3, preinjury intelligence was included as a covariate, but ideally, all the preinjury variables of importance identified in paper 2 should have been included for a more comprehensive examination of the role of preinjury factors on diffusion metrics.

Cognitive tests, DTI and DKI have been important measures in this thesis. One of the most appealing aspects with these methods is the fine-graded quantification of respectively cognition and microstructural brain integrity that they offer. However, while the fine-graded quantification probably has contributed to the widespread use of these techniques, it also constitutes a limitation of these methods. Cognitive test performance and DTI- and DKI metrics are all subject to considerable preinjury variability. For example, both processing speed and FA vary considerably

in the general population. Thus, for an individual patient, it is very difficult to determine whether a T-score of 35 on a cognitive test, or a FA value of 0.7, represents preinjury functioning or an MTBI-related reduction. There is no universal threshold for a low test score, or a low FA value. In contrast, few would argue against an observed subdural hematoma on a clinical MRI sequence being caused by the MTBI 24 hours earlier (even though there are exceptions when injuries are small). Because very few patients with MTBI are assessed with cognitive tests or MRI before the injury, this limitation is unavoidable in most cases. In the Trondheim MTBI follow-up study, none of the patients were assessed before the injury. Nonetheless, preinjury variability has been a central theme in all the papers included in the present thesis, and different methods have been used to account for it. In paper 1, within-patients analyses were conducted to control for the effect of preinjury variability in cognitive test performance and PCS. In paper 2, the effect of self-reported preinjury factors on PCS was the main focus. In paper 3, estimated preinjury intelligence was controlled for in analyses comparing diffusion metrics in patients with and without PCS. In paper 4, the role of cognitive reserve (i.e., a preinjury variable) on cognitive test performance was explored.

6. Future Perspectives

Future studies should carefully consider preinjury differences between patients with good and poor outcome after MTBI. Many research groups are searching for, not only an "objective" biomarker for MTBI "per se", but also a biomarker for poor outcome after MTBI. Advanced MRI and blood biomarkers (194) are among the key biomarker candidates. However, especially for studies on advanced MRI, such as DTI or DKI, preinjury variability in these metrics is often neglected. Many of the personal factors identified as predictive of PCS in paper 3 are related to poor white matter integrity (e.g., lower FA). Thus, poor white matter integrity might be predictive for PCS, without being related to the injury. Low FA could, potentially, be considered as both a preinjury risk factor, and an injury-related biomarker, and this should be examined in future studies.

The effects of structural brain pathology and preinjury factors on outcome after MTBI are without doubt complex. Evidence suggests that outcome is affected by biological, psychological, and social factors. How these factors interact is, however, understudied. In the cognitive reserve research framework, cognitive reserve is considered a moderator of outcome: it is postulated that cognitive reserve moderates the relationship between brain pathology and outcome. MTBI research in general would capitalize on applying this framework also when variables other than cognitive reserve are studied. Future studies should examine how different preinjury variables moderate the effects of each other. For example, it might be that poor preinjury sleep problems is associated with poor outcome after MTBI, but especially so among participants with low resilience. A similar approach can be applied to biological factors, and the role of brain reserve on outcome should be examined. For example, it might be that low FA is associated with poor outcome after MTBI, but that this effect is evident only among patients with small volumes of certain brain structures (an example of low brain reserve). Further, if preinjury MRI data is available, it could be assessed whether reduced FA is particularly critical among patients with lower preinjury FA. Also relevant are interactions across biological and psychological factors. Hypothetically, low FA may be a particularly strong predictor for poor outcome among participants with preinjury health problems. In practice, including interactions terms in statistical models means including more variables, and more variables require larger sample sizes. Because MTBI has been studied extensively during the last decades, larger sample sizes do not necessarily mean that new data collections are needed. Rather, by combining available data, large datasets can be obtained. Several initiatives aiming to

pool worldwide TBI-data exists, such as the ENIGMA (Enhancing NeuroImaging Genetics through Meta Analysis)- project (195), and these approaches have the potential to substantially increase the understanding of outcome after MTBI.

Brain pathology has been assessed with neuroimaging methods in this thesis. It should be noted that neuroimaging is one of several methods for assessing pathology after MTBI. The association between neuroinflammation, commonly assessed by inflammatory blood biomarkers, and outcome has gained research interest the last decade (196). Thus, to better understand the role of brain pathology on outcome, future research should combine different methods for assessing MTBI-related pathology.

Longitudinal designs have many advantages over pure cross-sectional designs. Even if longitudinal studies are becoming more common in MTBI research, the power associated with these designs is not always utilized. For example, longitudinal designs, where both predictors and outcomes are repeatedly assessed, enable both between- and within-person analyses (53,54). Separating between-persons effects from within-person effects can be particularly informative if it is suspected that preinjury variability in a predictor, or an outcome, confounds the results. For example, consider a DTI study where FA and cognitive test performance are assessed at two time points. Hypothetically, between-person analyses could show that people with lower FA have lower cognitive test performance, while within-person analyses could show that increased FA from time 1 to time 2 is unrelated to changes in cognitive test performance. Studying both between-person and within-person effects increases the understanding of how two variables are related. Unfortunately, between- and within-subjects effects are seldom separately reported in MTBI studies. One possible reason for this is that between- and within-person effects typically are combined into a single coefficient in the statistical output from mixed effects models (158). However, methods exist to separate these effects (53,54) and future research should consider doing this more frequently than today.

7. Conclusions

This thesis has demonstrated the importance of both neuroimaging findings and preinjury factors on outcome after MTBI. First, outcome after MTBI is multidimensional and patients can present with good cognitive test performance, but still self-report several symptoms. Second, both macrostructural brain pathology, identified with CT and MRI, and poor microstructural integrity in white matter, identified with DTI and DKI, seem to be risk factors for later PCS. However, macrostructural brain pathology is uncommon in MTBI and it is important to remember that most patients with PCS will not have intracranial findings on either CT or MRI. Further, the results suggest that microstructural integrity might be affected by preinjury differences between patients with and without PCS, and not only the MTBI. Third, preinjury factors such as unemployment and physical and mental health seem to be of particular importance in the development of PCS after MTBI. Finally, low cognitive reserve seems to be a risk factor for reduced cognitive test performance.

Notably, even if this thesis has demonstrated the importance of preinjury factors on outcome after MTBI, it must be stressed that preinjury factors alone do not seem to cause symptoms and low cognitive test performance. This was evident by a much higher prevalence of PCS in patients with MTBI than in trauma and community controls, despite these groups being similar on the preinjury factors that predicted PCS. Further, the *synergistic* effect of MTBI and low cognitive reserve seemed to be associated with lower cognitive test performance, over and above the effects of MTBI and cognitive reserve alone. In sum, several preinjury factors increase the risk of poor outcome following MTBI. Patients having these risk factors may profit from a more comprehensive follow-up, and interventions can be designed to target, not only the symptoms experienced, but also some of the preinjury risk factors.

8. References

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9. Individual Papers

PAPER 1

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Change in Self-Reported Cognitive Symptoms After Mild Traumatic Brain Injury Is Associated With Changes in Emotional and Somatic Symptoms and Not Changes in Cognitive Performance

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Objective: To investigate (a) whether self-reported cognitive symptoms after mild traumatic brain injury (MTBI) are associated with cognitive test performances, and (b) whether improvement in self-reported symptoms from 2 weeks to 3 months after MTBI is associated with improvement in cognitive test performances. ***Method:*** Patients with MTBI (n = 135), aged 16–59, who initially presented to the emergency department, completed the Rivermead Post Concussion Symptoms Questionnaire (RPQ), the Brief Symptom Inventory 18, and cognitive tests (i.e., Controlled Oral Word Association, Coding, Rey Auditory Verbal Learning, and Trail Making test) at 2 weeks and 3 months after MTBI. Using Spearman's rank correlations (ρ), associations were examined between self-report measures and cognitive test performances at each time point and between change scores (i.e., 3-month score minus 2-week score) on each outcome. ***Results:*** At 3 months, 27% reported cognitive symptoms to some extent. At both assessments, greater severity of RPQ cognitive symptoms was very weakly associated with worse cognitive test performances (2-week ρ range = −0.19 to −0.01; 3-month ρ range = −0.20 to −0.10). RPQ cognitive symptoms were, however, strongly related to greater somatic and emotional symptoms. Change in self-reported cognitive symptoms from 2 weeks to 3 months was not associated with change in cognitive test performance. In contrast, change in self-reported cognitive symptoms was strongly associated with change in emotional (ρ = 0.58) and somatic symptoms (ρ = 0.57). ***Conclusions:*** These

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findings indicate that improvements in subjective cognitive symptoms after MTBI co-occur with improvements on other subjective metrics, but are not related to improvements in objectively measured cognitive functioning.

Key Points

Question: After a mild traumatic brain injury (MTBI), many individuals have subjective cognitive concerns, and this study examined how changes in these concerns related to changes in cognitive test performances and emotional and physical symptoms from 2 weeks to 3 months after MTBI. ***Findings:*** A reduction in cognitive concerns was unrelated to improvements in cognitive test performances but was related to reductions in emotional and physical symptoms. ***Importance:*** These findings can be informative for clinical practice, where treatment of emotional or physical symptoms may result in perceived improvement in cognitive functioning. ***Next Steps:*** Future researchers should continue to examine the relationships between *changes* in different outcomes typically evaluated after MTBI (e.g., cognitive concerns, cognitive test performances, and emotional and physical symptoms) rather than continuing to explore these associations at a single point in time.

Keywords: neuropsychology, brain concussion, cognition

Cognitive test performances and self-reported cognitive, emotional, and somatic symptoms are routinely evaluated after traumatic brain injury (TBI). In mild TBI (MTBI), which is the most common severity of brain injury (Nguyen et al., 2016), the majority of evidence suggests that reduced cognitive test performances are common within the first few days and weeks of injury; while after 3 months, there are often no group differences between patients with and without MTBI (Carroll et al., 2014; Karr, Areshenkoff, & Garcia-Barrera, 2014). Postconcussion symptoms, commonly assessed via clinical interview or self-report questionnaires, follow a similar trajectory as cognitive test performance, in that symptoms often arise and subside within the first months after injury. However, a subgroup of patients with MTBI continue to report persistent cognitive, emotional, and/or somatic symptoms more than 3 months after MTBI (Cassidy et al., 2014; Polinder et al., 2018; Williams, Potter, & Ryland, 2010). The relationship between overall postconcussion symptom burden and cognitive test performance is poorly understood, and findings are mixed regarding whether patients who report more symptoms also have lower cognitive test performances (Lange et al., 2015; Losoi et al., 2016; Oldenburg, Lundin, Edman, Nygren-de Boussard, & Bartfai, 2016; Stenberg et al., 2020; Sterr, Herron, Hayward, & Montaldi, 2006).

Postconcussion symptoms are notably heterogeneous, which could possibly explain the mixed findings on their association with cognitive performances. It seems intuitive that self-reported *cognitive* symptoms would show stronger associations with *cognitive* performance than other domains of postconcussion symptoms. However, although some previous research has found statistically significant associations between cognitive test performances and self-reported cognitive symptoms (French, Lange, & Brickell, 2014; Jamora, Young, & Ruff, 2012; Ngwenya et al., 2018; Stillman, Madigan, Torres, Swan, & Alexander, 2019), these associations are often weak or negligible in terms of effect sizes (French et al., 2014; Karr et al., 2019; Spencer, Drag, Walker, & Bieliauskas, 2010; Stillman et al., 2019; Stulemeijer, Vos, Bleijenberg, & van der Werf, 2007). The relationship between self-reported cognitive symptoms and cognitive test performance may be further complicated by premorbid characteristics that differ between patients who report and who do not report cognitive symptoms, such as level of education and psychiatric history (Ngwenya et al., 2018; Stillman et al., 2019; Stulemeijer et al., 2007). In addition, prior studies use multiple different definitions for MTBI (Kristman et al., 2014), possibly contributing to mixed findings in the field.

The vast majority of studies on the association between self-reported symptoms and test performances compare individuals by examining correlations between self-reported symptoms and performances at a single time point rather than change in both outcomes within individuals over time (French et al., 2014; Jamora et al., 2012; Ngwenya et al., 2018; Spencer et al., 2010; Stillman et al., 2019; Stulemeijer et al., 2007). Longitudinal data, where both self-reported symptoms and test performances are repeatedly assessed, enables within-person analyses. Such analyses could investigate whether *change* in self-reported symptoms is accompanied by *change* in test performances, with the advantage that participants serve as their own controls, thereby reducing the potential effect of confounding variables (Curran & Bauer, 2011; van de Pol & Wright, 2009). This study design aligns with neuropsychological practice. Patients are assessed to investigate whether a condition, such as MTBI, has induced a change in test performance, or to assess the rate of cognitive recovery in an individual. Studying both differences between persons, and changes within persons, in the context of self-reported symptoms and cognitive test performances, could contribute to the understanding of these commonly reported outcomes in TBI research. In this study, participants with MTBI completed self-report symptom scales and cognitive tests at 2 weeks and 3 months after MTBI, with the aims of (a) examining the relationship between self-reported symptoms (e.g., cognitive, emotional, and somatic) and cognitive test performances at both measurement occasions, and (b) investigating whether changes in self-reported cognitive symptoms from 2 weeks to 3 months after MTBI were associated with changes in cognitive test performances or changes in other symptom domains.

Method

Participants

Patients between the ages of 16 and 59 were recruited from April 2014 to December 2015 as part of the Trondheim MTBI follow-up study ($N = 378$; Skandsen et al., 2018). They had experienced a physical trauma toward the head or high energy trauma followed by either (a) witnessed loss of consciousness (LOC) or confusion, (b) self-reported amnesia for the event or the time period after the event (PTA), and/or (c) traumatic brain lesions on computed tomography (CT). The TBI was further defined as mild per the criteria recommended by the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury: Glasgow Coma Scale (GCS) score of 13–15 at presentation to the emergency department, LOC <30 min, and PTA <24 hr (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004). Exclusion criteria were nonfluency in the Norwegian language; pre-existing severe neurological (e.g., stroke, multiple sclerosis), psychiatric, somatic, or substance use disorders, determined to be severe enough to likely interfere with follow-up; a prior history of a complicated mild, moderate, or severe TBI; or other concurrent major trauma. The research collaborators (a medical doctor or a medical student under supervision) conducted a structured interview to identify pre-existing conditions.

Recruitment took place at two emergency departments: a Level 1 trauma center in Trondheim, Norway, and the Trondheim Municipal Emergency clinic, an outpatient clinic run by general practitioners. Of the enrolled patients, 199 participated in an extended follow-up study including neuropsychological assessment and magnetic resonance imaging (MRI). Intracranial traumatic findings were obtained from acute head CT and MRI, performed within 72 hr (Einarsen et al., 2019). The study was approved by the regional committee for research ethics (REK 2013/754) and was conducted in accordance with the Helsinki declaration. All participants, and caregivers of participants younger than 18 years old, gave informed consent.

Neuropsychological Testing

Participants with MTBI underwent neuropsychological testing approximately 2 weeks ($M = 16.5$ days, $SD = 3.0$ days) and 3 months ($M = 95.0$ days, $SD = 6.3$ days) after injury. A licensed psychologist or student in psychology or neuroscience with at least a bachelor's degree (supervised by a licensed psychologist) performed the testing. The testing involved a larger battery, with only a selection of tests corresponding to specific cognitive domains analyzed in the current study: the Rey Auditory Verbal Learning Test (RAVLT, verbal learning and memory), the Trail Making Test Part B (TMT-B, executive functioning), the Controlled Oral Word Association Test (COWAT, verbal fluency), and the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) Coding subtest (processing speed). These tests have all been recommended as common data elements outcome measures after MTBI (Hicks et al., 2013). The same tests were administered at both time points.

The RAVLT is a widely used test of verbal learning and memory (Strauss, Sherman, & Spreen, 2006). The examiner reads a list of 15 words aloud, and the participant is asked to orally recall as many words as possible. The test includes five trials during which the full word list is read. Then, a distractor list is read and participants are asked to recall the words from the distractor list. Thereafter, they are asked to recall the words from the original list immediately after the distractor list and again after 20 min. The total number of words remembered across the five trials and the delayed recall score were used as outcome measures. A higher number of words recalled are indicative of a better performance. Different word lists were administered for the 2-week and the 3-month assessments. The TMT-B measures cognitive set shifting (i.e., an executive function), visual attention, and processing speed (Strauss et al., 2006). The participant is asked to draw a line alternating between numbers and letters (e.g., 1 – A – 2 – B – 3 – C). The outcome measure used was time-to-completion, with a faster time indicative of a better performance. The COWAT is a measure of verbal fluency, which is a construct related to language and executive function (Strauss et al., 2006; Tombaugh, Kozak, & Rees, 1999). The task is to generate as many words as possible beginning with a specific letter (i.e., F, A, and S) in 1 min. The total number of words produced across all three trials was used as the outcome measure, with a greater number of words indicative of a better performance. In the WAIS-IV Coding subtest (Wechsler, 2008, 2011), the participant is presented with a series of numbers and a coding key, which provides an abstract symbol that corresponds to each number. The participant must match as many symbols as possible to their corresponding number within 2 min. The total correct items completed within the time limit were used as the outcome measure, with a higher score indicative of better performance. For all tests, published norms (Mitrushina, Boone, Razani, & D'Elia, 2005; Schmidt, 1996; Tombaugh et al., 1999; Wechsler, 2011) were used to calculate age-adjusted T scores ($M = 50$, $SD = 10$, higher scores equal better performances on all tests), which were used in the analyses.

Self-Reported Symptom Assessment

The Rivermead Post Concussion Symptoms Questionnaire (RPQ) is recommended for the assessment of postconcussion symptoms after MTBI (Hicks et al., 2013) and was administered at the same time points as the cognitive tests. The RPQ includes 16 symptoms, on which the participant is asked to rate the severity of each symptom during the last 24 hr compared with before the injury (0 = *not experienced at all*, 1 = *no more of a problem*, 2 = *a mild problem*, 3 = *a moderate problem*, 4 = *a severe problem*). Consistent with previous studies on the RPQ (Eyres, Carey, Gilworth, Neumann, & Tennant, 2005; King, Crawford, Wenden, Moss, & Wade, 1995), all ratings of 1 (i.e., no more of a problem) were converted to zeros before the scores were combined. Three symptom subscales were calculated for the RPQ, with the items included summed for each subscale listed in parentheses: cognitive (i.e., forgetfulness, poor memory; poor concentration; and taking longer to think), emotional (i.e., being irritable, easily angered; feeling depressed or tearful; feeling frustrated or impatient; and restlessness), and somatic symptoms (i.e., headaches; feelings of dizziness; nausea and/or vomiting; noise sensitivity, easily upset by loud noise; sleep disturbance; fatigue, tiring more easily; blurred vision; light sensitivity, easily upset by bright light; and double vision; Potter, Leigh, Wade, & Fleminger, 2006; Smith-Seemiller, Fow, Kant, & Franzen, 2003). Participants also com-

pleted the Brief Symptom Inventory-18 (BSI-18), which consists of 18 items, with six items belonging to each subscale: depression, anxiety, and somatization (Derogatis, 2000). On a 5-point Likert-type scale, participants reported how much a given problem bothered them during the past week. The items for each subscale are summed to calculate a score (range = 0–24), where higher scores correspond to more psychological symptoms.

Statistical Analyses

Spearman's rank correlations (ρ) were used to investigate the associations between self-report measures and cognitive test performances. Participants who had one missing item on the RPQ ($n = 1$) or BSI-18 ($n = 2$) had the missing value replaced with the mean of their answers to the completed items on that subscale. Differences in self-reported symptom severity and cognitive test performances between the 2-week and 3-month assessments were analyzed with Wilcoxon signed-ranks test and r is reported as the effect size (the z-statistic associated with the Wilcoxon signed-ranks test divided by the squared root of the sample size; Fritz, Morris, & Richler, 2012; Pallant, 2007), interpreted as: 0.1 = a small effect, 0.3 = a medium effect, 0.5 = a large effect (Cohen, 1988). To investigate whether change in self-reported symptoms from 2 weeks to 3 months was associated with change in cognitive test performances, change scores were calculated. For each participant, self-reported symptom scores at 2 weeks were subtracted from scores at 3 months (i.e., a negative score means reduced symptom severity at the 3-month assessment). Similarly, cognitive test scores at 2 weeks were subtracted from scores at 3 months (i.e., a positive score means better performance at 3 months). The associations between these change scores were then investigated with Spearman's rank correlations. Because change scores are correlated with the scores at the first assessment, a phenomenon known as regression to the mean (Barnett, van der Pols, & Dobson, 2005; Clifton & Clifton, 2019), we also present analyses accounting for this potential effect. The residuals were saved from a regression model where the change score was the dependent variable and the 2-week score was the independent variable. These residuals were analyzed in place of the raw change scores for this analysis. Spearman's rank correlations and Mann–Whitney U tests, with r reported as effect sizes (the z-statistic associated with the Mann–Whitney U tests divided by the squared root of the sample size), were used to investigate the association between demographic and injury-related variables and change in self-reported cognitive symptoms. All analyses were conducted in Stata v. 15.1 (StataCorp, 2017).

Results

Participant Characteristics

Among the 199 participants with MTBI taking part in the extended follow-up, 178 completed the 2-week cognitive assessment, of which 135 (76%) completed the 3-month cognitive assessment and the two RPQ assessments. Demographic and clinical information is presented in Table 1. The mean age of the participants was 33.7 years and 34.8% were women (n = 47). The most common cause of injury was a fall. LOC was witnessed in 47.4% of participants, 25.2% had PTA exceeding 1 hr, and intracranial findings on CT or MRI were found in 11.1% of participants. Participants in the extended follow-up who did not complete one or both of the assessments ($n = 64$) were younger ($M = 29.2$ years old, $p = .015$) and had a higher frequency of PTA exceeding 1 hr (43.8%, $p = .008$), but the frequency of women ($p = .427$), LOC ($p = .986$), and intracranial findings ($p = .370$) did not differ.

Table 1
Characteristics of Participants With Mild Traumatic Brain Injury

Variable	Value
Age, years	
Median (IQR)	30.2 (22.2–46.6)
Mean (*SD*)	33.7 (13.2)
Sex, women, *n* (%)	47 (34.8)
Education, years	
Median (IQR)	13.0 (12–16)
Mean (*SD*)	14.2 (2.7)
Cause of injury (%)	
Fall	39.3
Bicycle	21.5
Sports accidents	14.8
Violence	9.6
Motor vehicle accidents	7.4
Hit by object	6.7
Unknown	0.7
Loss of consciousness	
(% witnessed/no/unknown-not witnessed)	47.4/17.0/35.6
Glasgow Coma Scale score	
(% 13/14/15/unknown)	2.2/12.6/77.8/7.4
Posttraumatic amnesia (%)	
(% 1–24 hr/<1 hr)	25.2/74.8
Intracranial findings (on CT or MRI)	
(% yes/no)	11.1/88.9
Level of care (%)	
Not admitted	71.9
Observed <24 hr	15.6
Admitted to neurosurgery department	8.9
Admitted to other department	3.7

Note. CT = computed tomography; IQR = interquartile range; MRI = magnetic resonance imaging.

Associations Between Self-Reported Symptoms and Cognitive Test Performances

Descriptive statistics for self-reported symptoms and cognitive test performances are presented in Table 2. On the cognitive tests, the mean group level performances were within the normal range at both the 2-week and the 3-month assessment (i.e., all mean scores were within ±5 T scores of the norm group mean of T score 50; Table 2). At the 2-week and the 3-month assessments, a greater severity of RPQ cognitive symptoms was significantly associated with worse performance on the delayed trial of the RAVLT (ρ = −0.19 and −0.20, respectively), but not with the other cognitive tests, and the effect sizes were uniformly small and similar across assessments (2-week ρ range = −0.19 to −0.01, 3-month ρ range = −0.20 to −0.10; Table 3). The RPQ emotional symptoms were significantly associated with the delayed trial of the RAVLT at the 2-week assessment (ρ = −0.18), but not with the other cognitive tests. The RPQ somatic symptoms were not significantly associated with any of the cognitive tests. For BSI-18,

Table 2
Self-Reported Symptoms and Cognitive Test Performances at 2 Weeks and 3 Months

Variable	2-Week assessment				3-Month assessment					
	Mean	*SD*	Median	IQR	Mean	*SD*	Median	IQR	*p*-value[a]	*r*
RAVLT-1 to 5	46.6	11.3	47.7	40.8–54.5	48.4	11.7	49.0	39.7–56.1	0.104	0.10
RAVLT-Delayed	49.3	10.6	50.3	42.5–56.8	48.9	10.9	49.6	40.8–56.8	0.189	0.08
TMT Part B	48.9	12.5	52.2	43.6–56.7	51.5	12.7	54.6	46.8–57.9	<.001	0.27
COWAT	47.3	12.5	47.3	38.9–55.2	50.8	14.3	49.9	40.3–60.2	<.001	0.31
Coding	50.9	8.9	50.0	43.4–56.7	54.9	10.2	53.3	46.7–60.0	<.001	0.45
RPQ-Cognitive	2.4	3.1	0	0–5	1.4	2.7	0	0–2	0.002	0.19
RPQ-Emotional	1.6	2.8	0	0–2	1.1	2.5	0	0–2	0.271	0.07
RPQ-Somatic	6.0	6.6	4	0–10	3.3	5.2	0	0–5	<.001	0.30
RPQ-Total Score	10.0	10.9	6	0–16	5.9	9.1	2	0–9	<.001	0.26
BSI-18-Depression	2.1	3.2	1	0–3	1.9	3.3	0	0–2	0.238	0.07
BSI-18-Anxiety	2.0	3.1	1	0–3	1.6	3.0	0	0–2	0.010	0.16
BSI-18-Somatic	3.4	3.3	2	1–5	2.0	2.8	1	0–3	<.001	0.32

Note. RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Test; RPQ = Rivermead Post Concussion Symptoms Questionnaire; BSI-18 = Brief Symptom Inventory-18. Neuropsychological test scores are presented as *T*-scores ($M = 50$, $SD = 10$). One participant had six missing items on BSI-18 at the 3-month assessment and was excluded from these analyses. r = The effect size (0.1 = small, 0.3 = medium, 0.5 = large). A positive effect size indicates improvement.
[a] Wilcoxon signed-rank tests.

the depression and anxiety subscales were not significantly associated with any of the cognitive tests. The BSI-18 somatization scale showed significant associations with 2-week performance on the COWAT ($\rho = -0.17$) and 3-month performance on the WAIS-IV Coding subtest ($\rho = -0.19$), but not with the other cognitive tests. Associations between different types of self-reported symptoms (i.e., the cognitive, emotional, and somatic symptoms on the RPQ, and the depression, anxiety, and somatization scales on BSI-18) were considerably stronger (ρ range = 0.23–0.67; Table 3).

Table 3
Spearman Correlations Between Self-Report Measures and Cognitive Test Scores at 2 Weeks and 3 Months After Injury

Variable	1	2	3	4	5	6	7	8	9	10	11
2 Weeks											
1. RAVLT-Trials 1 to 5	1										
2. RAVLT-Delayed	.712**	1									
3. TMT Part B	.299**	.310**	1								
4. COWAT	.327**	.266**	.308**	1							
5. Coding	.383**	.445**	.515**	.346**	1						
6. RPQ-Cognitive	−.129	−.185*	−.005	−.117	−.033	1					
7. RPQ-Emotional	−.121	−.176*	−.053	−.134	−.089	.610**	1				
8. RPQ-Somatic	−.009	−.072	.132	−.067	−.022	.602**	.501**	1			
9. RPQ-Total Score	−.057	−.134	.069	−.116	−.050	.803**	.695**	.928**	1		
10. BSI-18-Depression	−.058	−.072	−.061	−.111	−.018	.413**	.487**	.335**	.434**	1	
11. BSI-18-Anxiety	.002	−.044	−.123	−.064	.036	.396**	.471**	.282**	.382**	.547**	1
12. BSI-18-Somatization	.099	.006	.005	−.172*	.012	.499**	.458**	.599**	.630**	.460**	.448**
3 Months											
1. RAVLT-Trials 1 to 5	1										
2. RAVLT-Delayed	.776**	1									
3. TMT Part B	.275**	.237**	1								
4. COWAT	.459**	.324**	.389**	1							
5. Coding	.456**	.398**	.452**	.271**	1						
6. RPQ-Cognitive	−.129	−.195*	−.125	−.144	−.096	1					
7. RPQ-Emotional	−.111	−.076	−.003	.000	−.011	.625**	1				
8. RPQ-Somatic	−.116	−.078	−.055	−.053	.027	.668**	.571**	1			
9. RPQ-Total Score	−.157	−.115	−.083	−.066	−.037	.777**	.735**	.924**	1		
10. BSI-18-Depression	−.001	.068	−.013	.080	−.028	.308**	.422**	.226**	.312**	1	
11. BSI-18-Anxiety	.004	−.038	−.040	.136	.031	.339**	.406**	.252**	.299**	.577**	1
12. BSI-18-Somatization	−.152	−.149	−.122	−.116	−.188*	.411**	.447**	.379**	.437**	.498**	.504**

Note. RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Test; RPQ = Rivermead Post Concussion Symptoms Questionnaire; BSI-18 = Brief Symptom Inventory-18.
* $p < .05$. ** $p < .01$.

Associations Between Change in Cognitive Symptoms and Test Performances

The RPQ cognitive symptom severity was significantly higher at the 2-week assessment compared with the 3-month assessment (see Table 2). At 2 weeks after MTBI, 55% ($n = 74$) of the participants had a score of 0 on the RPQ cognitive items (i.e., endorsed no cognitive symptoms as worse compared with before their injury), 10% ($n = 14$) had a score of 2 on the cognitive items (i.e., reported a minor problem on one of the items), and 35% ($n = 47$) had a score between 3 and 12. At 3 months after MTBI, 73% ($n = 99$) had a score of 0 on the RPQ cognitive symptoms, 5% ($n = 7$) had a score of 2, and 22% ($n = 29$) had a score between 3 and 12. Significantly more RPQ somatic symptoms and BSI-18 anxiety and somatization symptoms were also reported on the 2-week compared with the 3-month assessment. Participants performed better on all cognitive tests at 3 months after injury compared with 2 weeks, except on the RAVLT, on which the scores did not differ statistically at the two time points (see Table 2). Change in self-reported cognitive symptoms from 2 weeks to 3 months was not significantly associated with change in cognitive test performances (ρ range = −0.11 to 0.05). Thus, improvement in self-reported cognitive symptoms was not related to improvement in test performance. In contrast, improvement in RPQ cognitive symptoms was strongly associated with improvement in RPQ emotional symptoms and RPQ somatic symptoms; and also, but to a lesser extent, with improvement in depression, anxiety, and somatization symptoms as measured with the BSI-18 (see Table 4). Reanalysis of these data controlling for the potential regression to the mean effect produced the same results (see Table 4).

Variables Associated With Change in Self-Reported Cognitive Symptoms

Age (ρ = 0.01, $p = .924$) and years of education (ρ = −0.07, $p = .431$) were not associated with improvement (i.e., change) in self-reported cognitive symptoms from 2 weeks to 3 months. There was a nonsignificant trend that women had a greater improvement in self-reported cognitive symptoms than men ($U = 1703.5$, $p = 0.070$, $r = .16$). Among the injury-related variables, there were no differences in the improvement of self-reported cognitive symptoms between patients with and without LOC ($U = 659$, $p = .416$, $r = .09$), between patients with GCS 15 versus GCS 13–14 ($U = 1037.5$, $p = .928$, $r = .01$), between patients with long versus short PTA ($U = 1422$, $p = .108$, $r = .14$), or between patients with and without traumatic intracranial findings ($U = 792.5$, $p = .418$, $r = .07$).

Table 4
Correlations Between Change in RPQ Cognitive Symptoms and Change in Other Self-Report Measures and Cognitive Tests

Variable	RPQ-cognitive change scores (raw)		RPQ-cognitive change scores (residual)[a]	
	Spearman's ρ	*p*-value	Spearman's ρ	*p*-value
RAVLT-Trials 1 to 5	−0.029	0.738	−0.032	0.710
RAVLT-Delayed	−0.114	0.189	−0.141	0.103
TMT Part B	0.043	0.618	−0.029	0.738
COWAT	0.051	0.558	0.080	0.356
Coding	−0.055	0.523	−0.089	0.306
RPQ-Emotional	0.576	<.001	0.611	<.001
RPQ-Somatic	0.568	<.001	0.616	<.001
BSI-18-Depression	0.251	0.003	0.256	0.003
BSI-18-Anxiety	0.228	0.008	0.287	<.001
BSI-18-Somatization	0.268	0.002	0.301	<.001

Note. RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Test; RPQ = Rivermead Post Concussion Symptoms Questionnaire; BSI-18 = Brief Symptom Inventory-18.
[a] The residuals from a regression model where the change score is the dependent variable, and the 2-week score is the independent variable, were analyzed instead of the raw change scores.

Discussion

This study focused on the association between subjectively experienced and objectively measured cognitive functioning at 2 weeks and 3 months after MTBI. Consistent with previous research, weak and mostly nonsignificant associations were observed between self-reported cognitive symptoms and cognitive test performances at both time points, whereas the associations between self-reported cognitive, somatic, depressive, and anxiety-related symptoms were considerably stronger (French et al., 2014; Karr et al., 2019; Spencer et al., 2010; Stillman et al., 2019; Stulemeijer et al., 2007). Similarly, *change* in cognitive symptom severity from 2 weeks to 3 months was unrelated to change in cognitive test performance, whereas *change* in cognitive symptoms was strongly associated with change in depression, anxiety, and somatic symptoms over this same time period.

The longitudinal design of the present study allowed us to evaluate how change in one variable is related to changes in other variables. Our results extend previous findings from cross-sectional studies (French et al., 2014; Jamora et al., 2012; Ngwenya et al., 2018; Spencer et al., 2010; Stillman et al., 2019; Stulemeijer et al., 2007) by showing that that the association between change in self-reported cognitive symptoms and change cognitive test performance was as weak, or even weaker, than the association between self-reported cognitive symptoms and test performance at a single time point. As a group, the patients with MTBI improved significantly in self-reported cognitive symptom severity from 2 weeks to 3 months. These same patients showed, on average, improvement on most objective cognitive outcomes from 2 weeks to 3 months as well. However, the negligible associations between change in self-reported cognitive symptoms and change in test performances suggest a discrepancy in recovery trajectories between these two outcomes. This finding adds to previous research suggesting different recovery pace for different outcome domains (Losoi et al., 2016), in that cognitive performances and symptoms will not necessarily improve in tandem. The limited relationship between objective and subjective cognition and the prominent relationship between different symptom domains can be informative for clinical practice. For instance, a patient who reports cognitive symptoms will not necessarily show reduced cognitive performances; and improvement in these cognitive symptoms could occur with reductions in emotional and somatic symptoms, but may not correspond with any change in objectively measured cognitive functioning.

Demographic characteristics suggested to be associated with outcome after MTBI, such as age (van der Naalt et al., 2017), gender (Merritt, Padgett, & Jak, 2019), and education (van der

Naalt et al., 2017), could possibly affect the association between self-reported and performance-based cognition; but, the nonparametric methods used in the present study did not allow us to control for these variables. However, for the within-person analyses, in which the association between change in self-reported cognitive symptoms and performance-based cognition was examined, by design, participants served as their own controls, and the possible effects of confounding variables were minimized. We did, however, examine whether improvement in self-reported cognitive symptoms was related to demographic and injury-related factors and found only a weak and nonsignificant tendency of greater improvement in women.

We did not find any significant associations between depressive and anxiety symptoms reported on the BSI-18 and cognitive test performance. These correlations were in fact weaker than the correlations between self-reported cognitive symptoms and cognitive test performance. These findings are in contrast to some previous studies linking depression to poorer cognitive test performance after MTBI (Barker-Collo et al., 2015; Levin et al., 2001; Rapoport, McCullagh, Shammi, & Feinstein, 2005; Terry, Brassil, Iverson, Panenka, & Silverberg, 2019). However, unlike many previous studies, the present study did not include patients who sought health care because of persistent symptoms, but rather recruited patients from the emergency department and followed them prospectively. Although this approach yields a representative sample of patients with MTBI, the symptom severity is likely less pronounced than in many other studies. Further, we did not examine if patients' symptoms met a threshold typical of a depression diagnosis or whether these symptoms caused sufficient impairment to rationalize a diagnosis. Our findings may have differed if we focused solely on patients meeting criteria for Major Depressive Disorder after MTBI, and these differences in study design could contribute to the differences in results between the present study and some previous findings.

The present study had several limitations that are important to consider when interpreting the findings. The RPQ is worded so that individuals rate their symptoms in relation to their perceived preinjury baseline. The reliance on a perceived baseline has inherent issues, in that patients may underestimate their preinjury symptoms (Lange, Iverson, & Rose, 2010) and their perception of their preinjury symptoms may change over time (Yang et al., 2014). Further, a substantial proportion of the sample may have recovered at the time of the first assessment at 2 weeks (Carroll et al., 2014; Cassidy et al., 2014; Karr et al., 2014). This is exemplified by the majority of participants reporting no cognitive symptoms, and the mean *T* scores for every cognitive test falling broadly within the average range at both assessments. Stronger associations between change in self-reported symptoms and change in test performances may have been observed if the first assessment was conducted more proximal to injury. A final limitation was that improvement in cognitive test performances from 2 weeks to 3 months is partly because of practice effects rather than recovery (Stenberg et al., 2020). Of note, the only test on which participants did not improve at retest was the RAVLT, for which an alternative form was used to reduce the impact of practice. However, it is unlikely that this practice effect confounded the main analyses of our study (i.e., the associations between self-reported cognitive symptoms and test performances), which examined *variability* in improvement between patients rather than group mean improvement.

Self-reported cognitive symptoms and cognitive test performances appear to be unique outcomes after MTBI, with cognitive symptom severity being more closely related to emotional and somatic symptom severity than objective cognitive functioning. Being commonly used outcomes in MTBI research, neuropsychological test performance and self-reported cognitive symptoms are not redundant, and both have a role in a comprehensive assessment of outcome after MTBI. The present findings may be useful for guiding interventions among patients who experience persistent cognitive complaints after MTBI. The correspondence between change in mental health symptoms and cognitive symptoms over the course of recovery suggests that patients with persistent subjective cognitive symptoms may benefit from an evidence-based mental health intervention.

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PAPER 2

Running Head: **Personal Factors and PCS**

Personal Factors Associated with Postconcussion Symptoms Three Months after Mild Traumatic Brain Injury

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Competing interests

Grant Iverson, Ph.D. has been reimbursed by the government, professional scientific bodies, and commercial organizations for discussing or presenting research relating to mild TBI and sport-related concussion at meetings, scientific conferences, and symposiums. He has a clinical and consulting practice in forensic neuropsychology, including expert testimony, involving individuals who have sustained mild TBIs. He has received research funding from several test publishing companies, including ImPACT Applications, Inc., CNS Vital Signs, and Psychological Assessment Resources (PAR, Inc.). He receives royalties from one neuropsychological test (WCST-64). He acknowledges unrestricted philanthropic support from ImPACT Applications, Inc., the Heinz Family Foundation, the Mooney-Reed Charitable Foundation, and the Spaulding Research Institute. The other authors report no competing interest.

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Abstract

Objective: To describe personal factors in patients with mild traumatic brain injury (MTBI) and two control groups, and to explore how such factors were associated with postconcussion symptoms (PCS).

Design: Prospective cohort study

Setting: Level 1 trauma center and outpatient clinic.

Participants: Patients with MTBI (n=378), trauma controls (n=82), community controls (n=81).

Main Measures: Data on preinjury health and work status, personality, resilience, attention deficit/hyperactivity, and substance use. Computed Tomography (CT) findings and posttraumatic amnesia were recorded. Symptoms were assessed at 3 months with the British Columbia Postconcussion Symptom Inventory and labelled as PCS+ if ≥3 symptoms were reported, or the total score was ≥13. Predictive models were fitted with penalized logistic regression using the least absolute shrinkage and selection operator (lasso) in the MTBI group, and model fit was assessed with optimism-corrected Area Under the Receiver Operating Curve (AUC).

Results: There were few differences in personal factors between the MTBI group and the two control groups. Rates of PCS+ were 20.8% for the MTBI group, 8.0% for trauma controls, and 1.3% for community controls. In the MTBI group, there were differences between the PCS+ and PCS- group on most personal factors and injury-related variables in univariable comparisons. In the lasso models, the optimism-corrected AUC for the full model was 0.79, 0.73 for the model only including personal factors, and 0.63 for the model only including injury variables. Working less than full time before injury, having preinjury pain and poor sleep quality, and being female were among the selected predictors, but also resilience and some personality traits contributed in the model. Intracranial abnormalities on CT were also a risk factor for PCS.

Conclusion: Personal factors convey important prognostic information in patients with MTBI. A vulnerable work status and preinjury health problems might indicate a need for follow-up and targeted interventions.

Keywords: preinjury factors; brain concussion; post-concussion syndrome

Abbreviations: ASRS = Adult ADHD (Attention Deficit Hyperactivity Disorder) Self-Report Scale; AUC = The area under the curve of the receiver operating characteristics curves; AUDIT = Alcohol Use Disorders Identification Test; BC-PSI = British Columbia Postconcussion Symptom Inventory; BFI = Big Five Inventory; CC = Community Control; CI = Confidence Interval; CT = Computed Tomography; GCS = Glasgow Coma Scale; ISI = Insomnia Severity Index; IQR = Interquartile Range; LOT-R = Life Orientation Test-Revised; LTE-Q = List of Threatening Events Questionnaire; LOC = Loss Of Consciousness; MTBI = Mild Traumatic Brain Injury; OR = Odds Ratio; PCS = Postconcussion Symptoms; PTA; Post-Traumatic Amnesia; RSA = Resilience Scale for Adults; TC = Trauma Control

Introduction

After mild traumatic brain injury (MTBI), a significant minority experiences a range of persistent somatic, cognitive, and emotional symptoms over months or even years; a condition here referred to as postconcussion symptoms (PCS).[1] PCS is associated with considerable functional limitations and reduced quality of life,[2, 3] but only weak association has been found between MTBI severity and outcome,[4, 5] and the disability some people experience can therefore seem out of proportion to a TBI that is categorized as mild. The heterogeneity in MTBI outcome, together with the inconsistent findings on the role of injury severity and neuroimaging findings on outcome, suggest that the biopsychosocial model may serve as a framework to understand and treat PCS.[1, 6, 7] A biopsychosocial treatment approach is likely most effective if initiated early after injury;[8] thus identification of patients at risk is important. Personal factors, as conceptualized in the International Classification of Function (ICF),[9] like personality and preinjury mental and physical health, have all been associated with PCS.[10, 11] Female sex has been found to be a risk factor in some, but not all studies.[12-14] However, more research is needed to explore which personal factors should be included in future prognostic models.[15, 16] In the Trondheim MTBI follow-up study, we acquired comprehensive information in patients and control participants about a range of personal factors such as personality, resilience, optimism, and preinjury somatic and psychological health as well as experienced life events and substance use, in addition to measures of injury severity. Our aims were to describe these in patients with MTBI and two control groups, and to explore whether such factors were associated with MTBI and PCS. We built prediction models and explored which of the personal factors were most consistently associated with PCS after MTBI, and to what degree the injury-related variables added to model performance.

Methods

Participants

The patients with MTBI were part of the Trondheim MTBI follow-up study (*n*=378), a study consisting of patients 16-59 years presenting from April 2014 to December 2015 at two emergency departments: at St. Olavs Hospital, Trondheim University Hospital, a level 1 trauma center; and at the Trondheim Municipal Emergency clinic, a general practitioner-run, out-patient clinic.[17] In this cohort, around 60% of all eligible patients were enrolled, and the cohort has been shown to be representative of all young adult and middle-aged patients with MTBI in the catchment area.[17] Inclusion criteria were having sustained a TBI,[18] categorized as mild according to the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury criteria. All had Glasgow Coma Scale scores (GCS) of 13-15 at presentation in the emergency room and either witnessed loss of consciousness (LOC) < 30 minutes, confusion, or post-traumatic amnesia (PTA) < 24 hours. Patients that met these criteria and had traumatic lesions on CT scans were included in the study, if the intracranial lesion did not require surgery.[19] Exclusion criteria were (1) non-fluency in the Norwegian language; (2) pre-existing severe neurological disorder (e.g., stroke, multiple sclerosis), or a prior history of a complicated mild, moderate, or severe TBI; or (3) ongoing psychiatric (e.g., psychotic or bipolar disorder), health (e.g., cancer), or substance abuse problems, determined by the researcher responsible for inclusion and considered to be severe enough to likely interfere with follow up.[17]

The control groups were: (1) trauma controls (TC); 82 patients with minor orthopedic injuries, matched on the group level, on age and sex, using a procedure ensuring similar numbers of men and women in each 5-year age interval, and (2) community controls (CC); 81 persons recruited among staff, family and acquaintances of patients and staff, matched on age, sex, and

education, using a procedure also ensuring similar years of education in each 5-year age interval. The exclusion criteria applied to the MTBI group were used for the controls, but in addition, the TCs did not have trauma affecting the head, neck, or dominant arm, and the CCs were not receiving treatment for psychiatric disorders.

The regional committee for research ethics approved the study. Participants, and parents of participants younger than 18 years, in the cohort study, gave informed consent.

Study Procedures

Patients were consecutively identified based on lists of ED visits and CT referrals and approached and enrolled as previously described.[17] Data on preinjury characteristics (personal factors) was collected during the first week after injury, considering the situation as it was before their injury. Both a structured interview and questionnaires were used. At 3 months after injury, the patients underwent an outcome evaluation by a telephone interview.

Study Variables

Posttraumatic amnesia (PTA) was defined as the self-reported time after injury for which the patient had no memory. From a pilot study, we knew that many participants would not be able to provide a valid estimate in minutes; therefore, a predefined option was to record PTA as either <1 hour or 1-24 hours. Intracranial traumatic findings were obtained from the radiology report of the acute head CT, here recorded as yes/no. Fractures of the cranium, face, or other bones were obtained from the radiology report and recorded as yes/no.

Personal factors assessed were all preinjury: age, sex, education, school marks, reading difficulties, work status, previous MTBI, headache, other pain, psychiatric problems, substance use, alcohol use, sleep quality, ADHD symptoms (Attention Deficit Hyperactivity Disorder),

personality traits, life orientation (optimism/pessimism), threatening events, and resilience. Measures, definitions, and cut-off criteria are shown in Table 1.

Outcome was assessed at three months after injury with the British Columbia Postconcussion Symptom Inventory (BC-PSI).[20] BC-PSI consists of 13 core symptoms, distributed over four symptom categories and three life problems. In the current study, the 13 core symptoms were used to calculate the total score. PCS was defined as having at least three core symptoms rated as at least moderate (score ≥ 3), or a total score ≥13. PCS was assessed both in the MTBI and control groups and refers to a high level of postconcussion/postconcussion-like symptoms. The MTBI group was accordingly divided into a PCS+ and a PCS- group.

Statistical analyses

Missing values on single questionnaire items were replaced by that individual's mean of the answered questions on the scale/questionnaire. The proportion of missing items across questionnaires ranged from 0.12-0.44%. Very few participants had more than one item missing on a returned questionnaire: Adult ADHD Self-Report Scale, respondents with ≥1 missing items 3.10% and respondents with two missing items 0.48%; the Alcohol Use Disorders Identification Test, respondents with 1 missing item 1.17% and none had 2 or more missing items; the Big Five Inventory, respondents with ≥1 missing items 10.88% and respondents with ≥2 missing items 3.98%; Life Orientation Test-Revised, respondents with 1 missing item 1.64% and none had 2 or more missing items; List of Threatening Events Questionnaire, respondents with ≥1 missing item 2.36% and respondents with 2 missing items 0.23%; the Resilience Scale for Adults, respondents with ≥1 missing items 4.00% and respondents with ≥2 missing items 0.24%.

Group differences between the MTBI group, the TC group, and the CC group were evaluated with Kruskal-Wallis tests and Chi-squared tests. Whether personal and injury-related

factors predicted PCS in patients with MTBI, was evaluated with logistic regression models. First, univariable analyses for each variable of interest were conducted. To reduce the number of comparisons, we only analyzed one measure from most questionnaires (e.g., from the ASRS, only the total score was analyzed). Odds-ratios (OR) with 95% confidence interval are reported. For the group comparisons and the univariable analyses, *p*-values uncorrected for multiple comparisons are reported, as well as differences that remained statistically significant after Bonferroni correction. Second, models were fitted by penalized logistic regression using the lasso (least absolute shrinkage and selection operator) as implemented in the Stata command lasso logit. To account for many predictors, lasso shrinks the values of the coefficients to less extreme values, thereby improving the external validity of the model. For variables with low predictive value, the coefficients could be shrunk (set) to zero and be left out of the final model. The degree of shrinkage was determined by 10-fold cross-validation. In effect, the method performs estimation of the coefficients and variable selection simultaneously and provides estimates of overall fit rather than statistical significance of the individual predictors. Stata handles factor variables by including all dummy variables (ie., none is initially left out as reference category), and the lasso procedure then shrinks one or more of the dummy variables to zero. The uncertainty of the coefficients from the lasso was assessed by repeating the penalized regression procedure in 1000 bootstrap samples. The uncertainty for each of the variables was assessed by the proportion of the 1000 bootstrap samples when its coefficient was set to zero. The lower proportion, the higher is the probability that a variable contributes to outcome prediction. The area under the curve (AUC) of the receiver operating characteristics curves was used to assess performance of the models. Optimism-corrected AUCs with 95% confidence intervals were obtained from bootstrapping with 1000 replications. In this internal validation

procedure, the model is estimated in the bootstrap samples and then tested in the original sample. The mean difference between the AUCs obtained in the bootstrap samples and the original sample is referred to as the "optimism", which is subtracted from the AUC obtained in the original model.[21] In the univariable analyses, we allowed for a different number of observations between analyses (i.e., all available data was used), while in the lasso models only complete cases were included.

Results

Overall characteristics of the MTBI group and the control groups

There were small and mostly statistically non-significant differences between the MTBI group, TC, and CC (Table 2). More people in the MTBI group reported prior MTBI, reading difficulties, and a psychiatric history, and the higher frequency of prior MTBI remained statistically significant after Bonferroni correction.

There were 70 (20.8%) patients in the MTBI group with PCS (the PCS+ group) three months after injury. In the control groups, 6 (8%) of the TCs and 1 (1.3%) of the CCs met PCS criteria.

Correlations between personal factors

A bivariate correlation matrix illustrating associations between the preinjury personal characteristics is presented in Figure 1. There were very small correlations for many of the variables, such as age, previous MTBI, pain, headache, alcohol use, and experienced life events. Resilience correlated positively with extroversion, agreeableness, and conscientiousness, and negatively with pessimism, ADHD symptoms, and neuroticism. School marks correlated positively with education, psychiatric history correlated with reduced employment, ADHD

symptoms correlated positively with neuroticism and negatively with conscientiousness, and female sex correlated positively with neuroticism.

Comparison of the PCS+ and PCS- groups in univariable analyses

More individuals in the PCS+ group had intracranial lesions on CT and long PTA duration. Regarding the personal factors, many statistically significant differences were revealed. In the PCS + group, there were more women, more worked less than full time before the injury, and more reported preinjury pain, psychiatric problems, poor sleep quality, and headache. They had higher scores on the measure of ADHD symptoms and neuroticism, and they had lower scores on extroversion. The PCS+ group also reported lower resilience, higher pessimism, and more threatening life events (Table 3).

Prediction of PCS in multivariable analyses

Table 4 shows the predictors selected, and their penalized coefficients, from the full lasso model. The AUC for the selected model was 0.864 (optimism-corrected: 0.790, 95% CI 0.724-0.857). In the 1000 bootstrap samples, working less than full time, preinjury pain, CT findings, not being triaged to CT, female sex, preinjury headache, poor preinjury sleep quality, openness, long PTA, and total resilience were the ten predictors most often not set to 0 (i.e., the most important variables in predicting PCS. Figure 2).

In a model excluding the injury-related variables, female sex, working less than full time, preinjury pain, poor sleep quality, headache, ADHD symptoms, higher neuroticism, and openness, and lower extroversion and resilience were selected as predictive of PCS, and the AUC was 0.805 (optimism-corrected: 0.734, 95% CI 0.657-0.814). In a model that only included the injury-related variables, selected predictors for PCS were intracranial lesions on CT, not

being triaged to CT, and longer PTA duration, and the AUC was lower, 0.661 (optimism-corrected: 0.631, 95% CI 0.551-0.700).

In a subgroup of patients without intracranial lesions on CT, female sex, working less than full time, preinjury pain, poor sleep quality, headache, ADHD symptoms, openness, and resilience were predictors, and the AUC was 0.818 (optimism-corrected: 0.734, 95% CI 0.647-0.814).

Discussion

This study illustrates that a diverse range of personal factors are associated with having persistent symptoms three months following an MTBI. Women were more likely than men to have persistent symptoms and being unemployed or working less than full time before the injury was a predictor for having persistent symptoms, as were preinjury health problems and personality characteristics. Having intracranial traumatic lesions on head CT was also associated with PCS but was less important than the personal factors in the multivariable model.

Female sex was one of the factors most often included in the multivariable PCS prediction model. Thus, sex was a predictor for PCS, even when some possibly confounding variables were controlled for. Previous reviews have concluded that the literature is inconclusive when it comes to female sex being a risk factor for PCS,[12, 13] and called for further research. We consider our study to add important evidence in this respect, given that we were able to control for a broad range of personal factors which could otherwise confound the association between sex and PCS.

Importantly, we found that reduced employment was a strong and unique predictor of PCS, even when possibly confounding variables were controlled for in the multivariable lasso model (e.g., poor sleep quality and psychiatric history, which correlated moderately with reduced

employment). Unemployment has previously been found to predict PCS after MTBI[22, 23] and poor functional outcome after moderate to severe TBI.[24] Reduced employment might be a vulnerability factor or full-time employment might be a protective factor. For example, having a structured daily activity to return to after MTBI may be motivating and colleagues at the workplace may provide vital support. Efforts to promote an effective and durable return to work are likely important during the early rehabilitation following MTBI.

Preinjury health factors, such as having a psychiatric history, symptoms of ADHD, headaches, and sleep problems, were all significant predictors. Having preinjury bodily pain emerged as a particularly strong predictor. Preinjury health problems as a risk factor for PCS have also been reported in other studies,[25, 26] and there is emerging evidence that people reporting PCS are more likely to endorse health complaints compatible with somatization.[27] It was expected that preinjury health factors would be associated with PCS. In fact, some of the preinjury factors assessed in the present study also constitute symptoms of PCS (e.g., headache). This illustrates the complexity of assessing PCS because the symptoms are non-specific for MTBI and they are common in the general population.[20, 28] Thus, it is challenging to separate symptoms related to preinjury health factors from MTBI-related symptoms. However, the prevalence of PCS was considerable higher in patients with MTBI than in trauma and community controls, despite very small differences in preinjury health factors between these groups (Table 2), suggesting that the *combined* effect of preinjury health factors and MTBI is associated with the development of PCS.

Personality characteristics were also related to persistent symptoms. Not surprisingly, neuroticism, a personality trait linked to an increased tendency of experiencing negative emotions and distress, was associated with PCS, in line with other studies of patients with

MTBI[23, 29, 30] and healthy people.[31] Further, low resilience was a risk factor for PCS, similar to in previous studies.[23, 32-35] Low resilience has previously been found to be associated with high neuroticism,[36] and these factors also were correlated also in the present study. A person's resilience is considered to be more modifiable than personality traits,[37, 38] possibly making it a target for interventions after MTBI.

A history of psychiatric problems is considered to be a risk factor for persistent symptoms following MTBI.[16, 23, 39] Interestingly, this was not one of the variables most often included in our lasso multivariable model. The reason for this might be that other correlated variables, such as low resilience, high neuroticism, and reduced employment, have greater explanatory power.

Some injury severity indicators were associated with outcome. In the present study, head CT had been performed in 79% of the sample, and, of those, only 6% had intracranial traumatic lesions (i.e., a complicated MTBI). Patients with complicated MTBI had higher risk for PCS, which is in line with one previous study[40], but in contrast to others.[28, 41, 42] PTA duration of greater than 1 hour was also associated with PCS, albeit weakly, and not in the uncomplicated MTBI group. Interestingly, *not being triaged for CT*, which probably can be considered a proxy for having fewer symptoms and an overall better clinical presentation in the ER, was associated with a *reduced* risk of PCS.

One aim of this study was to report the discriminative ability of different models using the AUC of the ROC, and to explore how a broad range of personal factors contributed to model performance. In the full model, we found an AUC value of 0.79 after optimism correction, which is high compared to other reported multivariable models in MTBI.[16] When injury-related variables were removed, the AUC was only modestly reduced to 0.73. In contrast, a model with

only injury severity variables performed poorly (AUC=0.63). In the subsample with uncomplicated MTBI, the full model also performed adequately (AUC=0.73), and interestingly, PTA duration was not selected in this model. Positive CT findings were clearly related to having persistent symptoms, but because it is uncommon to have an abnormal head CT following MTBI, combining this and other injury severity variables did not produce a useful prediction model.

Limitations

This study has several limitations. First, preinjury personal factors were all based on self-report, and they were all collected following the injury, making them susceptible to some degree of reporting bias or inaccuracy. This limitation is, for the most part, unavoidable. Second, there was a low rate of complicated MTBIs in this study, which reduces the statistical power of that variable for predicting persistent symptoms. Importantly, however, we consider that a natural consequence of recruiting a more representative cohort of people with MTBIs from both ambulatory clinics and the ED. Third, although our sample size was large (N=378), the prevalence of some potentially important preinjury predictor variables in the cohort was small and thus power was reduced in analyses of the influence of those predictors (e.g., reading difficulties, reduced employment, and possible ADHD). Fourth, the number of cases with PCS was modest, and a larger sample of people with PCS would have allowed for analyses on how prognostic factors moderate each other. Fifth, in the multivariable models, only complete cases were included. Using multiple imputation in lasso models is less straightforward than for ordinary regression models, because lasso performs variable selection. However, in the univariable analyses, we could use all data available (i.e., the number of observations differed between analyses), and the most important factors for predicting PCS in the lasso models were

also strongly associated with PCS in the univariable models, further supporting their role in the development of PCS. Sixth, the community control group was not population-based, and the rate of PCS in the community control group should be interpreted with caution. However, the groups were matched, not only on age and sex, but also on education, and there were only small differences between the MTBI group, the trauma control group, and the community control group on the factors that predicted PCS. Seventh, litigation is associated with PCS in other studies and countries, and we did not collect information on this variable.[43, 44] However, in our study, conducted in a country where health care is free, and people have access to sickness and disability benefits from the government, a litigation process is seldom initiated in the first few months, when our study was conducted. Also, results from this study were solely for research purposes, not available for anyone else, hence; no financial gain could be obtained through participation. Finally, the relative strength of risk factors may differ in other settings and in other countries, as illustrated in a study of moderate TBI in Norway and the Netherlands[45], and our findings need to be replicated.

Conclusions

We collected a wider range of personal factors than prior studies and found that several of these factors contributed in large, important, and unique ways to predicting persistent symptoms following MTBI. Particularly important *preinjury personal factors* relating to persistent symptoms were reduced employment, bodily pain, and headaches, and women were more likely than men to have persistent symptoms. Other important preinjury characteristics included poor sleep quality, symptoms of ADHD, a tendency toward neuroticism, and lower resilience. The common injury-related variables, CT abnormalities and longer duration of PTA, were also predictive of worse outcome, but much less so than a combination of personal factors.

The results of this study, illustrated in Figure 3, highlight the value of taking a broad approach and using the biopsychosocial model as a framework to understand and treat PCS.[1, 10, 11] The study represents an important step in the development of practical and feasible prognostic models for adults with MTBI, with the ultimate goal of using these models to identify at risk individuals and refer them for earlier evidence-informed treatment and rehabilitation.

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Table 1. Personal factors in the study describing preinjury status.

Variable	Measures and Categorization	Collection method and Measure Details
Age	Years	Medical records
Sex	Man or woman	Medical records
Education	Years of completed education. Starting from the first year of school, at six years of age.	Self-report, interview
School marks	Average high school marks on a 1-6 scale.	Self-report, interview
Reading difficulties	Recorded as "yes" if the person had been diagnosed with reading difficulties.	Self-report, interview
Reduced work	Recorded as "yes" if the person was working or studying < 80% (of a 37.5-hour week).	Self-report, interview
Previous MTBI	Recorded as "yes" if the person had sustained one or more head traumas likely to have fulfilled the same criteria for MTBI as applied in this study.	Self-report, interview
Preinjury Pain	Recorded as "yes" if the person had non-headache pain in any part of the body graded ≥3 on a 0-10 NRS	Pain map and NRS
Preinjury Headache	Recorded as "yes" or "no"	Item from self-report questionnaire. "Have you suffered from headache during the last year?"
Psychiatric history	Recorded "yes" if the person reported a history of psychiatric illness.	Self-report, interview
Substance use	Recorded "yes" if the person reported using drugs other than alcohol.	Self-report, interview
Poor preinjury sleep quality	Insomnia Severity Index (ISI),[46] the first three items: difficulties falling asleep, staying asleep, and waking up to early.	ISI is a questionnaire, but the three first questions were administered as an interview. Self-report questionnaire. A five-point Likert scale, Higher scores indicate greater sleep problems/poor sleep quality.
ADHD symptoms	Adult ADHD Self-Report Scale version 1.1 (ASRS).[47, 48] Individual scores for inattention, hyperactivity, and total symptom burden. The scores were calculated both for the screening part of the questionnaire (the first six items) and the full scale (all 18 items). The total score was calculated for each scale. A likely diagnosis of attention deficit hyperactivity disorder (ADHD) was defined as scoring at or above a threshold ("sometimes" on question 1-3 and "often" on question 4-6) on at least four of the first six items.[49]	Self-report questionnaire. Higher scores indicate more attention/hyperactivity problems. Two missing items were accepted.
Alcohol use	The Alcohol Use Disorders Identification Test (AUDIT)[50] The total score of the ten items, and "high use" if total scores ≥8.[50]	Self-report questionnaire. Higher scores indicate higher consumption. Two missing items were accepted.
Personality traits	Big Five Inventory (BFI-44),[51, 52] a short form of the BFI including 44 items. The mean score for each scale was calculated.	Self-report questionnaire yielding individual scores on extroversion, agreeableness, conscientiousness, neuroticism, and openness. Higher scores indicate higher levels of that personality trait. At least 50% of the items on each personality domain had to be answered for that scale to be calculated.

PERSONAL FACTORS AND PCS

Pessimism	Life Orientation Test-Revised (LOT-R)[53, 54]	Self-report questionnaire with ten items, six of them measuring optimism/pessimism, and four fillers (not scored items). Lower scores indicate higher optimism and the variable is therefore referred to as "pessimism" Two missing items were accepted.
Threatening Life events	List of Threatening Events Questionnaire (LTE-Q).[55, 56] The total number of events was calculated.	Self-report questionnaire measuring experience of environmental stressful events during the last year. The Norwegian version comprised 13 items. Two missing items were accepted on LTE-Q
Resilience	Resilience Scale for Adults (RSA).[36, 57, 58] The mean score was calculated for all dimensions separately and total resilience score was the mean of all item scores.	Self-report questionnaire with 33 items measuring six dimensions (perception of self, planned future, social competence, family cohesion, social resources and structured style) and a score of total resilience. Higher scores indicate higher resilience. Three missing items were accepted on RSA.

Table 2. Comparisons between the MTBI group, the trauma control group, and the community control group.

Variables	*n*	MTBI	*n*	Trauma Controls	*n*	Community Controls	*P*
Age	378		82		81		
M (SD)		31.23 (12.99)		32.60 (13.04)		33.23 (13.12)	
Mdn (IQR)		25.10 (20.80-40.95)		28.02 (21.85-45.58)		28.16 (22.90-44.21)	0.208
Sex, female, *n* (%)	378	131 (34.7)	82	31 (37.8)	81	31 (38.3)	0.752
CT Findings, yes/not performed *n* (%)	378	22 (5.8) / 79 (20.9)	-	-	-	-	-
PTA long, *n* (%)	378	107 (28.3)	-	-	-	-	-
Other injuries (fractures), yes, *n* (%)	378	58 (15.3)	82	48 (58.5)	-	-	-
Cause of Injury, *n* (%)	378		82		-	-	-
Fall		135 (35.7)		26 (31.7)	-	-	-
Violence		65 (17.2)		1 (1.2)	-	-	-
Bicycle		58 (15.3)		7 (8.5)	-	-	-
Sports accident		54 (14.3)		30 (36.6)	-	-	-
Motor vehicle accident		43 (11.4)		3 (3.7)	-	-	-
Struck object		17 (4.5)		6 (7.3)	-	-	-
Other /unknown		6 (1.6)		9 (11.0)	-	-	-
Education years, *Mdn* (*IQR*)	375	13.00 (12.00-16.00)	81	14.00 (12.00-16.00)	81	13.00 (12.00-16.00)	0.063
School marks, *Mdn* (*IQR*)	364	4.50 (3.50-4.50)	81	4.50 (4.50-5.50)	80	4.50 (3.50-5.50)	0.090
Reading difficulties, yes, *n* (%)	373	43 (11.5)	81	3 (3.7)	81	3 (3.7)	0.016
Reduced work	376	45 (12.0)	81	7 (8.6)	81	4 (4.9)	0.146
Part time not working, yes, *n* (%)†		22 (5.9)		5 (6.2)		1 (1.2)	-
Full time not working, yes, *n* (%)		23 (6.1)		2 (2.4)		3 (3.7)	-
Previous MTBI, yes, *n* (%)	374	82 (21.9)	81	6 (7.4)	81	8 (9.9)	**0.001***
Preinjury pain, yes, *n* (%)	372	71 (19.1)	81	9 (11.1)	74	14 (18.9)	0.228
Preinjury headache, yes, *n* (%)	272	83 (30.5)	76	21 (27.6)	76	29 (38.2)	0.331
Psychiatric history, yes, *n* (%)	376	61 (16.2)	81	9 (11.1)	81	5 (6.2)	0.044
Substance use, yes, *n* (%)	369	29 (7.9)	81	5 (6.2)	80	12 (15.0)	0.083
Poor preinjury sleep quality (ISI), *Mdn* (*IQR*)	370	0.00 (0.00-0.33)	81	0.00 (0.00-0.33)	81	0.00 (0.00-0.67)	0.538
ADHD symptoms (ASRS), *Mdn* (*IQR*)	264		80		76		
Screener inattention		5.00 (3.00-5.00)		5.00 (3.00-6.00)		5.00 (4.00-6.75)	0.315
Screener hyperactivity		3.00 (2.00-5.00)		3.00 (2.00-5.00)		3.00 (2.00-4.00)	0.726
Screener total		8.00 (6.00-10.00)		7.00 (5.00-10.00)		8.00 (6.00-10.75)	0.392
Full scale inattention		12.00 (9.00-14.00)		11.00 (8.25-14.75)		12.00 (9.25-15.00)	0.406
Full scale hyperactivity		10.00 (7.00-14.00)		9.00 (7.00-13.75)		11.00 (7.25-13.75)	0.425
Full scale		22.50 (17.00-27.75)		21.00 (16.00-26.00)		23.50 (18.25-28.00)	0.345
Probable ADHD diagnosis, *n* (%)		24 (9.1)		7 (8.8)		10 (13.2)	0.543
Alcohol use (AUDIT)	272		80		76		
Full scale, *Mdn* (*IQR*)		6.00 (3.00-10.00)		5.00 (4.00-8.00)		6.00 (4.00-9.00)	0.371
At or above 8, *n* (%)		107 (39.3)		24 (30.0)		26 (34.2)	0.277
Personality (BFI), *Mdn* (*IQR*)	271		80		76		
Extroversion		4.75 (4.00-5.38)		4.63 (3.88-5.25)		4.63 (4.00-5.25)	0.469
Agreeableness		5.33 (4.89-5.89)		5.44 (4.89-6.11)		5.39 (4.78-6.00)	0.722
Conscientiousness		5.00 (4.44-5.67)		5.11 (4.33-5.78)		5.06 (4.11-5.53)	0.389
Neuroticism		3.00 (2.38-3.75)		3.12 (2.13-3.75)		3.00 (2.41-3.63)	0.812
Openness		4.60 (4.00-5.30)		4.70 (4.03-5.20)		4.65 (4.03-5.30)	0.875
Pessimism (LOT-R), *Mdn* (*IQR*)	270	1.17 (0.83-1.67)	80	1.17 (0.83-1.83)	76	1.17 (0.80-1.67)	0.796
Threatening Life events (LTE-Q), *Mdn* (*IQR*)	269	1.00 (0.00-2.00)	79	1.00 (0.00-2.00)	76	1.00 (0.00-2.00)	0.355
Resilience (RSA), *Mdn* (*IQR*)	269		80		76		
Perception of self		5.33 (4.36-6.00)		5.50 (4.21-6.00)		5.33 (4.38-5.83)	0.907
Planned future		5.75 (4.37-6.00)		5.75 (4.75-6.25)		5.50 (4.83-6.33)	0.757
Social competence		5.33 (4.50-6.00)		5.33 (4.50-6.17)		5.50 (4.83-6.33)	0.215
Family Cohesion		5.67 (4.83-6.17)		5.83 (5.17-6.17)		5.67 (4.83-6.33)	0.822
Social Resources		6.14 (5.71-6.71)		6.28 (5.75-6.71)		6.07 (5.57-6.68)	0.464
Structured style		5.00 (4.25-5.75)		5.25 (4.50-6.00)		5.00 (4.06-5.75)	0.498
Total resilience		5.51 (5.00-5.94)		5.66 (5.08-5.96)		5.56 (4.89-6.06)	0.765

Note. *= The comparisons remained statistically significant after Bonferroni-correction for multiple comparisons (critical p-value=0.002). †= Not working or studying at the time of injury at all ("full time not working"), or working or studying to some extent, but less than 80% ("part time not working"). ASRS = Adult ADHD (Attention Deficit Hyperactivity Disorder) Self-Report Scale; AUDIT = Alcohol Use Disorders Identification Test; BFI = Big Five Inventory; CT = Computed Tomography; ISI = Mean of the first three items of Insomnia Severity Index; IQR = Interquartile Range; LOT-R = Life Orientation Test-Revised; LTE-Q = List of Threatening Events Questionnaire; Mdn = Median; MTBI = Mild Traumatic Brain Injury; PTA = Post-Traumatic Amnesia; RSA = Resilience Scale for Adult

Table 3. Associations between PCS and personal and injury-related factors at three months in patients with MTBI (univariate logistic analyses).

Variables	*n*	PCS+	*n*	PCS-	OR	CI 95%	P-value
Age, *Mdn* (*IQR*)	70	26.27 (20.83-42.47)	267	25.70 (21.06-42.51)	1.00	0.98-1.02	0.847
Sex, female, *n* (%)	70	38 (54.3)	267	76 (28.5)	**2.98**	1.74-5.12	**<0.001***
CT Findings	70		267				**<0.001***
Findings, yes, *n* (%)		11 (15.7)		8 (3.0)	**5.18**	1.98-13.54	0.001
Not performed, yes, n (%)		7 (10.0)		63 (23.6)	**0.42**	0.18-0.97	0.042
No findings, yes, *n* (%)		52 (74.3)		196 (73.4)	*Ref*		-
PTA long, *n* (%)	70	29 (41.4)	267	65 (24.3)	2.20	1.27-3.82	0.005
Other injuries (fractures), yes, *n* (%)	70	14 (20.0)	267	39 (14.6)	1.46	0.74-2.88	0.272
Education, years, *Mdn* (*IQR*)	70	12.00 (12.00-15.25)	264	13.00 (12.00-16.00)	0.89	0.80-1.00	0.054
School marks, *Mdn* (*IQR*)	66	4.50 (3.50-4.50)	257	4.50 (3.50-4.50)	0.66	0.48-0.92	0.013
Reading difficulties, yes, *n* (%)	69	11 (15.9)	263	25 (9.5)	1.81	0.84-3.88	0.130
Reduced work, yes, *n* (%)	70	23 (32.9)	265	16 (6.0)	**7.62**	3.74-15.49	**<0.001***
Previous MTBI, yes, *n* (%)	70	18 (25.7)	264	54 (20.5)	1.35	0.73-2.49	0.343
Preinjury pain, yes, *n* (%)	69	28 (40.6)	262	36 (13.7)	**4.29**	2.36-7.78	**<0.001***
Preinjury headache, yes, *n* (%)	49	23 (46.9)	211	58 (27.5)	2.33	1.23-4.41	0.009
Psychiatric history, yes, *n* (%)	70	23 (32.9)	265	33 (12.5)	**3.44**	1.85-6.38	**<0.001***
Substance use, yes, *n* (%)	68	4 (5.9)	261	20 (7.7)	0.75	0.25-2.28	0.616
Poor preinjury sleep quality (ISI), *Mdn* (*IQR*)	69	0.33 (0.0-1.0)	261	0.0 (0.0-0.33)	**2.15**	1.49-3.10	**<0.001***
ADHD symptoms (ASRS), *Mdn* (*IQR*)	48	23.65 (19.25-32.75)	204	22.00 (16.00-27.75)	1.04	1.01-1.08	0.016
Alcohol use (AUDIT), *Mdn* (*IQR*)	49	6.00 (3.00-10.50)	211	6.00 (4.00-10.00)	0.99	0.93-1.05	0.703
Personality (BFI), *Mdn* (*IQR*)	49		210				
Extroversion		4.38 (3.75-5.13)		4.88 (4.13-5.45)	0.67	0.48-0.93	0.019
Agreeableness		5.33 (4.83-6.00)		5.33 (4.89-5.89)	0.93	0.60-1.43	0.733
Conscientiousness		4.89 (4.28-5.61)		5.00 (4.44-5.69)	0.80	0.56-1.16	0.246
Neuroticism		3.63 (2.81-4.19)		2.88 (2.25-3.75)	**1.70**	1.25-2.31	**0.001***
Openness		4.80 (4.05-5.45)		4.60 (4.08-5.30)	1.16	0.81-1.64	0.415
Pessimism (LOT-R), *Mdn* (*IQR*)	49	1.50 (0.92-2.00)	209	1.17 (0.83-1.50)	1.81	1.17-2.81	0.008
Threatening Life events (LTE-Q), *Mdn* (*IQR*)	49	1.00 (0.00-3.00)	208	1.00 (0.00-2.00)	1.25	1.05-1.47	0.010
Resilience (RSA), *Mdn* (*IQR*)	49	5.27 (4.48-5.79)	208	5.57 (5.07-5.97)	**0.47**	0.31-0.71	**<0.001***

*Statistically significant after Bonferroni-correction for multiple comparisons (critical *p*-value=0.002). ASRS = Full scale of the Adult ADHD (Attention Deficit Hyperactivity Disorder) Self-Report Scale; AUDIT = Full scale of the Alcohol Use Disorders Identification Test; CI = Confidence Interval; CT = Computed Tomography; Extroversion, Agreeableness, Conscientiousness, Neuroticism, and Openness = Subscales from the Big Five Inventory (BFI); ISI = Mean of the three first items in Insomnia Severity Index; IQR = Interquartile Range; Mdn = Median; MTBI = Mild Traumatic Brain Injury; OR = Odds Ratio; PCS = Prolonged Postconcussion Symptoms; LOT-R = Full scale of the Life Orientation Test-Revised; PTA; Post-Traumatic Amnesia; LTE-Q = List of Threatening Events Questionnaire, total numbers of events; RSA = Full scale from the Resilience Scale for Adults.

Table 4. Penalized coefficients from a lasso model predicting PCS (complete case analysis: PCS+ n= 42; PCS- n=192).

Variables	Estimate	OR (95% CI)	Percentage Coefficient = 0
Age	0	1 (0.99-1.04)	56.4
Sex (female)*	0.38	**1.46** (1.00-4.28)	13.4
CT			
No findings	0	1 (1.00-1.00)	99.5
Findings*	1.53	**4.59** (1.00-33.45)	3.9
Not performed*	-0.85	**0.43** (0.05-1.00)	8.3
PTA (long)*	0.25	**1.28** (1.00-3.71)	27.6
Other injuries (fractures)	0	1 (0.50-2.72)	50.0
Education	0	1 (0.89-1.19)	64.7
School marks	0	1 (0.52-1.48)	53.4
Reading difficulties	0	1 (0.54-3.46)	58.9
Reduced work*	1.80	**6.07** (1.64-41.01)	0.8
Previous MTBI	0	1 (0.31-1.35)	55.7
Preinjury Pain*	0.88	**2.42** (1.00-10.78)	3.5
Preinjury Headache*	0.36	**1.43** (1.00-4.18)	21.0
Psychiatric history*	-0.00	**1.00** (0.11-1.29)	48.0
Substance use	0	1 (0.18-1.12)	60.9
Poor preinjury sleep quality (ISI)*	0.18	**1.12** (1.00-2.40)	21.9
ADHD symptoms (ASRS)*	0.01	**1.01** (1.00-1.07)	42.5
Alcohol use (AUDIT)	0	1 (0.92-1.01)	62.9
Personality (BFI)			
Extroversion*	-0.01	**0.99** (0.52-1.00)	47.7
Agreeableness	0	1 (0.70-2.06)	60.5
Conscientiousness	0	1 (0.50-1.00)	59.2
Neuroticism*	0.11	**1.12** (1.00-1.85)	34.5
Openness*	0.15	**1.16** (1.00-2.45)	24.5
Pessimism (LOT-R)	0	1 (0.80-2.19)	61.5
Threatening Life events (LTE-Q)	0	1 (0.95-1.33)	50.2
Resilience (RSA)*	-0.33	**0.72** (0.33-1.00)	28.7

*Variables selected by lasso. A coefficient of 0 means that the variable was not selected by lasso. 95% percentile confidence intervals and the proportion of times the variables were set to zero were obtained from bootstrapping with 1000 replications. CT-No Findings was not selected by lasso and is therefore reference category for this factor variable. ASRS = Full scale of the Adult ADHD (Attention Deficit Hyperactivity Disorder) Self-Report Scale; AUDIT = Full scale of the Alcohol Use Disorders Identification Test; CI = Confidence Interval; CT = Computed Tomography; Extroversion, Agreeableness, Conscientiousness, Neuroticism, and Openness = Subscales from the Big Five Inventory (BFI); ISI = Mean of the three first items in Insomnia Severity Index; LOT-R = Full scale of the Life Orientation Test-Revised; OR = Odds Ratio; PCS = Prolonged Postconcussion Symptoms; PTA = Post-Traumatic Amnesia; LTE-Q = List of Threatening Events Questionnaire, total numbers of events; Resilience = Full scale from the Resilience Scale for Adults

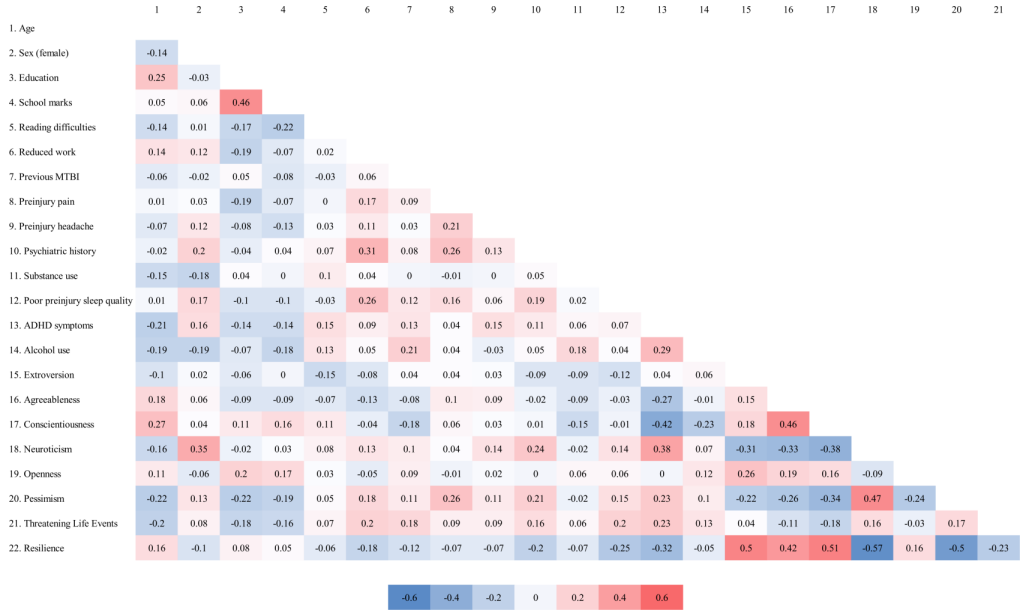

Figure 1. Spearman correlations (continuous-continuous associations), rank-biserial correlations (nominal-continuous associations), and phi coefficients (nominal-nominal associations) between the personal factors in the MTBI group.

Note: ADHD symptoms = Full scale of the Adult ADHD (Attention Deficit Hyperactivity Disorder) Self-Report Scale; Alcohol use = Full scale of the Alcohol Use Disorders Identification Test; Extroversion, Agreeableness, Conscientiousness, Neuroticism, and Openness = Subscales from the Big Five Inventory; Pessimism = Full scale of the Life Orientation Test-Revised; Poor preinjury sleep quality = Mean of the three first items in Insomnia Severity Index; Threatening Life Events = List of Threatening Events Questionnaire, total numbers of events; Resilience = Full scale from the Resilience Scale for Adults.

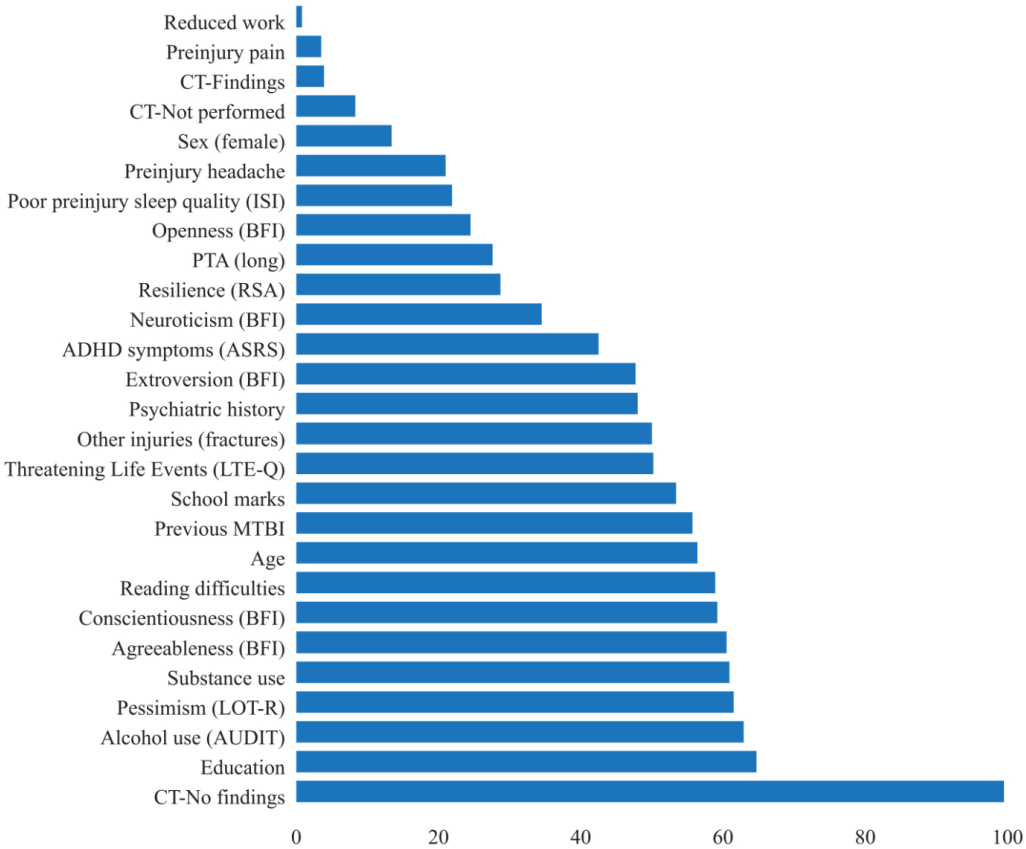

Figure 2. The factors most often set to zero.

Note: The histogram shows the percentage of the 1000 bootstrap samples that gave coefficients equal to zero for each variable. Proportions closer to zero indicate greater probability for the variable to be included in the model. ASRS = Full scale of the Adult ADHD (Attention Deficit Hyperactivity Disorder) Self-Report Scale; AUDIT = Full scale of the Alcohol Use Disorders Identification Test; CT = Computed Tomography; Extroversion, Agreeableness, Conscientiousness, Neuroticism, and Openness = Subscales from the Big Five Inventory (BFI); ISI = Mean of the three first items in Insomnia Severity Index; LOT-R = Full scale of the Life Orientation Test-Revised; PTA = Post-Traumatic Amnesia; LTE-Q = List of Threatening Events Questionnaire, total numbers of events; Resilience = Full scale from the Resilience Scale for Adults.

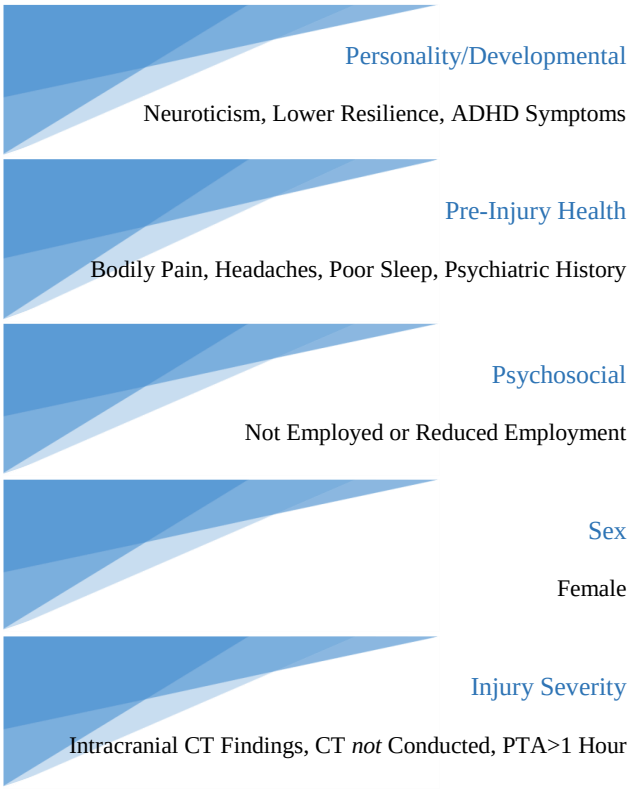

Figure 3. Biopsychosocial factors related to symptom reporting at three months following MTBI.
Note: PTA = Post-Traumatic Amnesia.

PAPER 3

Acute Diffusion Tensor and Kurtosis Imaging and Outcome Following Mild Traumatic Brain Injury

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Abstract

Objective: To investigate associations between acute diffusion tensor (DTI) and kurtosis (DKI) imaging metrics and postconcussion symptoms (PCS) 3 months after mild traumatic brain injury (MTBI).

Methods: Patients with MTBI (*n*=176) underwent MRI within 72 hours after the injury, and assessment of PCS at 3 months. Healthy community controls (*n*=78) also underwent MRI. Differences in 8 DTI and DKI metrics between patients with PCS, patients without PCS, and controls were examined with tract-based spatial statistics. All analyses were performed in the total sample, in patients without traumatic intracranial findings on clinical MRI (i.e., uncomplicated MTBI), and with estimated intelligence both included and excluded from the statistical models.

Results: Patients with PCS (*n*=35, 20%) had lower fractional anisotropy and kurtosis fractional anisotropy, and higher radial diffusivity, than patients without PCS (*n*=141). In the uncomplicated MTBI sample, significant differences in fractional anisotropy between patients with and without PCS were still present. Compared to controls, patients with PCS had widespread differences in all 8 diffusion metrics. When including estimated intelligence in the statistical models, no significant differences in diffusion metrics between patients with and without PCS were present, but patients with PCS still had significantly higher mean, radial, and axial diffusivity than controls.

Conclusion: Acutely after the injury, patients with PCS had poorer white matter microstructural integrity than patients without PCS and healthy controls. However, these differences became less pronounced when estimated preinjury intelligence was controlled for, suggesting that preinjury differences, and not only the MTBI, accounted for some of the observed differences in white

matter integrity. Thus, poor white matter integrity might be considered *both* a preinjury risk factor and an injury-related biomarker for poor outcome after MTBI.

Introduction

Mild traumatic brain injury (MTBI) is associated with good outcome for the majority of patients, but a minority report symptoms for months to years after the injury, commonly referred to as postconcussion symptoms (PCS).[1] Evidence suggests that outcome after MTBI is best understood from a biopsychosocial perspective, where both preinjury, injury-related, and postinjury factors contribute.[1] One key variable among the injury-related factors is the magnitude of brain pathology induced by the injury. However, few patients with MTBI have visible traumatic lesions on CT or clinical MRI (i.e., complicated MTBI), and the associations between lesions detected on clinical MRI and outcome is weak.[2] Therefore, methods like diffusion tensor imaging (DTI), that can reveal microstructural abnormalities in white matter, are promising in MTBI research.[3,4] In the majority of previous studies, DTI has been performed in the subacute or chronic phase after the MTBI and differences in DTI metrics between patients with and without PCS have been demonstrated in some, but not all, of these studies.[5–15] From a clinical perspective, it is essential to identify patients at risk of poor outcome early, and acute DTI could potentially serve as a biomarker for poor long-term outcome. However, there is a paucity of studies examining whether acute (i.e., within 72 hours after the injury) DTI predicts later PCS. In a small pilot study (n=25), we identified differences in acute DTI metrics between patients with MTBI and healthy controls, but no differences were evident in the acute DTI metrics between patients reporting and not reporting PCS at 3 months.[16]

In contrast to DTI, Diffusion Kurtosis Imaging (DKI) does not assume a Gaussian distribution of diffusion. Deviations from a normal distribution of diffusion are expected in complex brain tissue, and DKI has been proposed to be more sensitive than DTI in identifying microstructural abnormalities in areas with high heterogeneity.[17,18] Deviating DKI metrics have

been reported in both white and gray matter, in the acute to chronic phase, following MTBI.[16,19–25] However, few studies have examined DKI alterations across the whole white matter skeleton, and findings on the association between DKI metrics and PCS are inconclusive.[15,16,24,25]

One complicating factor when comparing findings from previous studies is that the proportion of patients with complicated MTBI vary considerably between study samples.[8,14] Moreover, differences in preinjury factors between patients with and without PCS have consistently been reported.[26–28] A preinjury variable of particular importance in DTI and DKI studies is general mental ability, or intelligence, as it has been shown to be associated with white matter microstructural integrity,[29–32] and shown to differ between patients with and without PCS.[28,33] Thus, both injury severity and preinjury characteristics vary between study samples, and together with the small sample sizes characterizing most of the DTI and DKI studies on MTBI, these differences likely contribute to the mixed findings on the associations between diffusion metrics and PCS.

Unlike previous studies, the present study includes a large representative sample of civilian patients with mixed-mechanism MTBI who underwent both DTI and DKI in the acute phase.[34,35] The present study aimed to compare diffusion metrics between patients with PCS, patients without PCS, and healthy controls; (1) in the total sample, (2) exclusively in patients with uncomplicated MTBI, and (3) with differences in estimated intelligence both controlled and not controlled for.

Materials and Methods

Participants

The patients with MTBI were part of the population-based Trondheim MTBI follow-up study (total n = 378), recruited from April 2014 to December 2015.[34] A total of 199 patients

participated in an extended follow-up study including acute MRI. Inclusion criteria were age 16 to 59 years and having sustained a TBI.[36] The TBI was defined as mild per the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury criteria: 1) Glasgow Coma Scale score (GCS) 13-15 at presentation in the emergency room; 2) loss of consciousness (LOC) < 30 minutes; and (3) post-traumatic amnesia (PTA) < 24 hours.[37] PTA was defined as the self-reported time after injury for which the patient had no memory, and LOC had to be witnessed in order to be defined as present. Exclusion criteria were (1) non-fluency in the Norwegian language; (2) pre-existing severe neurological disorder (e.g., stroke, multiple sclerosis), or a prior history of a complicated mild, moderate, or severe TBI; or (3) ongoing psychiatric (e.g., psychotic or bipolar disorder), somatic (e.g., cancer), or substance abuse problems, determined by the researcher responsible for inclusion and considered to be severe enough to likely interfere with follow-up. Recruitment took place at two emergency departments: a level 1 trauma center in Trondheim, Norway; and at the Trondheim Municipal Emergency clinic, a general practitioner-run, out-patient clinic.

A group of 78 age, sex, and education-matched community controls was recruited among hospital and university staff, students, and acquaintances of staff, students and patients. The exclusion criteria applied in the MTBI group were used for the controls, but in addition, controls receiving treatment for severe psychiatric disorders were excluded, even if they might be able to comply with follow-up. This criterion was slightly different for patients and controls because the goal was to have an MTBI cohort as representative as possible, and a control group with good brain health.

The study was approved by the regional committee for research ethics (REK 2013/754) and was conducted per the Helsinki declaration. All participants, and parents of participants younger than 18 years, gave informed consent.

Magnetic Resonance Imaging

Patients with MTBI underwent MRI on a 3T Siemens Skyra system (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil, the majority (91%) within 72 hours after injury (mean 52 hours ± 19 hours, range 5-130 hours). A radiologist and a resident in radiology read and reported the following MRI sequences: (1) three dimensional (3D) T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE); (2) two dimensional (2D) diffusion-weighted imaging (DWI) (3) 3D T2 space; (4) 3D T2-weighted fluid-attenuated inversion recovery (FLAIR); (5) 3D T2-weighted susceptibility-weighted imaging (SWI), reported in detail previously.[35] Patients with traumatic intracranial abnormalities visible on these clinical MRI sequences were defined as having complicated MTBI, and those without as having uncomplicated MTBI.

The DTI/DKI sequence was a single-shot balanced-echo EPI sequence acquired in 30 non-collinear directions with 3 b-values (b = 0, b = 1,000 and, b = 2,000 s/mm2). The following parameters were used: TR 8,800 ms, TE 95 ms, FOV 240 × 240 mm, slice thickness 2.5 mm, acquisition matrix 96 × 96. Sixty transversal slices with no gaps were acquired, giving full brain coverage. Five images without diffusion weighting were acquired to increase signal-to-noise ratio. To correct for image distortion, two additional b0 images were acquired with opposite phase encoding polarity.[38]

DTI and DKI Data Processing

Image analyses were performed with the fMRIB Software Library (FSL: http://www.fmrib.ox.ac.uk/fsl) and the Diffusion Kurtosis Estimator (DKE: https://medicine.musc.edu/departments/centers/cbi/dki/dki-data-processing). Non-brain tissue was removed with the Brain Extraction Tool (FSL). Artifacts due to eddy currents and movements were corrected with eddy (FSL). Correction of the susceptibility-induced off-resonance field artifacts was done by topup (FSL). DKI and DTI model fitting was performed using DKE and parametric maps and were calculated for 8 metrics: Fractional Anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), kurtosis fractional anisotropy (KFA), mean kurtosis (Kmean), axial kurtosis (Kax), and radial kurtosis (Krad).[39]

Voxel-wise statistical analysis of the diffusion data was performed using tract-based spatial statistics (TBSS).[40] Briefly, all subjects' FA data were aligned into a common space using the nonlinear registration tool FNIRT[41,42] (which uses a b-spline representation of the registration warp field).[43] A mean FA image was created from all the FA images and thinned to create a skeletonized mean FA representing the centers of all tracts common to all the subjects in the analysis. The mean FA skeleton was thresholded to FA < 0.2 to include major white matter tracts, but exclude peripheral tracts and grey matter. Each subject's aligned FA data were then projected onto this skeleton. The skeletonization process was also applied to MD, AD, RD, KFA, Kmean, Kax and Krad, and the statistical comparisons of these data were then restricted to voxels in the white matter skeleton. The resulting skeletonized data were consequently fed into voxel-wise cross-subject statistics in Randomise.

Outcome Assessment

PCS were assessed at 3 months after injury with the British Columbia Postconcussion Symptom Inventory (BC-PSI).[44] BC-PSI consists of 13 core symptoms, distributed over 4 symptom categories (i.e., somatic; emotional; cognitive; sleep disturbance), and three life problems, distributed over 2 additional symptom categories (i.e., reduced tolerance to alcohol; preoccupation with the symptoms and fear of permanent brain damage). The respondents rate the frequency and severity of each symptom during the last 2 weeks. These scores are then combined into a single score representing the frequency *and* severity of each symptom (range 0-4). The sum of the 13 core symptoms constitutes the total score. PCS was defined as having at least 3 core symptoms rated as moderate (score ≥ 3), or a total score 13-52 (i.e., 52 is the highest possible score).

Estimated Preinjury Intelligence

The Vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence[45,46] was used as an estimate of preinjury intelligence. The task is to explain the meaning of 42 words, 2 points are given for a correctly explained word, and 1 point for a partly correct explanation. Results on tests used to estimate preinjury intelligence must be relatively unaffected by brain injury. Therefore, the tests used commonly measure vocabulary knowledge in different varieties.[47,48] The Vocabulary subtest is considered an estimate of general mental ability[49] and test performance has been shown to be unaffected by cognitive impairment following MTBI.[50,51]

Statistical Analyses

Demographic variables were examined with t-tests, Mann-Whitney U-tests, and chi-square tests. In the TBSS analyses, differences in diffusion metrics between patients with PCS, patients without PCS, and the control group (i.e. 3 comparisons) were analyzed with the

Randomise tool in FSL, which is a non-parametric, permutation-based method using threshold-free cluster enhancement with a correction for multiple comparisons (family-wise error rate). A *p*-value of <0.05, corrected for multiple comparisons, was considered statistically significant. Age, age^2, sex, and scanner upgrade (due to scanner upgrade from version D13 to E11 during the inclusion period) were controlled for in all analyses. Because diffusion metrics show a non-linear association with age through adulthood (e.g., FA peaks around the age of 30[52]), both age and age^2 were included in all models. The lowest corrected *p*-value and the number of significant voxels in each contrast were extracted.

All analyses were performed with the patients with complicated MTBI both included (i.e., the total sample) and excluded (i.e., the uncomplicated sample). Further, analyses were also performed with estimated intelligence (i.e., results on the Vocabulary subtest) included as an additional covariate, to investigate whether differences in estimated intelligence between groups affected the results.

Results

Participant Characteristics

A total of 186 out of 199 patients with MTBI in the extended follow-up had DTI and DKI data from the acute assessment that passed quality control. Ten of these were not assessed for PCS at 3 months. Thus, the present study consists of 176 patients with MTBI (88% of the patients in the extended follow-up), and 18 (10%) of these had complicated MTBI (Table 1). There were no significant differences between the patients with MTBI and controls regarding age, sex, years of education, or estimated intelligence (Table 1).

A total of 35 patients (20%) with MTBI fulfilled the criteria for PCS at 3 months. The median total item score on BC-PSI in patients with PCS was 18 (interquartile range 15-23) and 2

(interquartile range 0-5) in patients without PCS. Longer PTA and complicated MTBI were more common in patients with PCS than in patients without PCS. Further, patients with PCS were more often women and had lower estimated intelligence (Table 1).

TBSS: Patients with PCS versus without PCS

In the total sample, patients with PCS had significantly lower FA and KFA and higher RD than patients without PCS (Table 2). The differences were mainly located in the corpus callosum, corona radiata, thalamic radiation, and internal capsule (Figure 1A). In the uncomplicated sample (PCS+ *n*=27; PCS- *n*=131), patients with PCS had lower FA than patients without PCS, in a larger number of voxels and more widespread than in the total sample, but no significant differences in KFA or RD were present (Table 2, Figure 1B).

When estimated intelligence was included as a covariate, no significant differences between patients with and without PCS remained, neither in the total sample, nor in the uncomplicated sample.

TBSS: Patients with PCS versus Controls

In the total sample, patients with PCS differed from controls on all diffusion metrics examined (i.e., patients with PCS had lower FA, KFA, Kmean, Kax, and Krad, and higher MD, AD, and RD, Table 2). The differences were widespread, including voxels in the corpus callosum, corona radiata, internal capsule, superior longitudinal fasciculus, and thalamic radiation. Especially for Kmean, group differences were also present in the cerebellum and brainstem (Figure 2A). In the uncomplicated sample, significant differences in all metrics, but AD, remained. As in the total sample, the differences were widespread (Table 2, Figure 2B).

When estimated intelligence was included as a covariate in the total sample, significant differences between patients with PCS and controls in MD, AD, and RD remained, but the

number of significant voxels was reduced (Table 2). When estimated intelligence was included as a covariate in the uncomplicated sample, only differences in RD in a limited number of voxels (212) remained significant (Table 2).

TBSS: Patients without PCS versus Controls

In the total sample, patients without PCS had lower kurtosis metrics (Kmean, Kax, and Krad) than controls. The findings were mainly located in the internal capsule, cerebellum, brainstem, and thalamus (Table 2, Figure 3A). In the uncomplicated sample, patients without PCS had lower Kmean and Krad (Table 2, Figure 3B). The comparisons between patients without PCS and controls were largely unaffected by including estimated intelligence as a covariate (Table 2).

Discussion

In this large prospective study of a representative sample of patients with MTBI who underwent MRI in the acute phase, patients with PCS differed from patients without PCS in FA, RD and KFA, and from healthy controls in all 8 diffusion metrics examined. Most of these differences were also present when patients with complicated MTBI were excluded from analyses. However, when differences in estimated preinjury intelligence were controlled for, differences in diffusion metrics between patients with and without PCS, and between patients with PCS and controls, were reduced. This suggests that the observed differences in diffusion metrics were not exclusively caused by the MTBI.

Differences in Diffusion Metrics Between Patients with PCS, without PCS, and Controls

Patients who developed PCS at 3 months had poorer white matter integrity than patients who did not develop PCS, as indicated by lower FA and KFA, and higher RD. When patients with complicated MTBI were excluded, only differences in FA remained, suggesting that this

finding was the most robust. In the present study, patients were examined with MRI within 72 hours after the injury, which is earlier than in most previous research on civilian patients with PCS. In our pilot study, we found no differences in DTI or DKI metrics assessed within 72 hours between patients who had or did not have PCS 3 months later, but the sample included only 9 patients with PCS, increasing the uncertainty in these results.[16] In research on sports-related concussion, early MRI is more common and associations between higher MD, AD and RD within the first 48 hours and acutely reported symptoms have been found,[53,54] but a lack of significant associations between acute DTI and DKI metrics and acutely reported symptoms have also been reported.[25,55] It is, however, difficult to compare results from studies on sports-related concussion with studies on civilian mixed-mechanism MTBI (i.e., the present study), because the variability in both age and injury mechanism is considerably larger in mixed-mechanism studies. Further, the sample sizes in the above-mentioned studies varied and were all smaller than the present study (range 30 to 96). Our finding of acutely lower FA in patients with PCS is in line with and extends previous findings from several civilian mixed-mechanism studies (sample size range 16 to 134) reporting associations between PCS and lower FA in the subacute (i.e. around or after 2 weeks)[5,6,8] or chronic (i.e., after 3 months).[9–11]

Differences between patients with PCS and without PCS were mainly located in corpus callosum, corona radiata, internal capsule, thalamic radiation. It varies between previous studies in which white matter tracts differences are observed, but differences in these tracts, especially in the corpus callosum, are commonly reported.[5,6,9,10,12,53,56] However, considering the variability in MTBI injury mechanisms, the brain areas most affected by an MTBI probably vary considerably between patients.[57] Thus, between-study variability in the location of abnormalities is expected,

and the total load of white matter deviations (e.g., the number of voxels affected) might be more informative for outcome than the specific location.

Patients with PCS also had poorer white matter integrity than controls. The most profound differences in DTI and DKI metrics were seen when these groups were compared, as indicated by widespread and significant differences in all 8 metrics examined. Greater differences in diffusion metrics between patients with PCS and controls, than between patients with and without PCS, have previously been reported in the subacute phase,[7,58] and the present results extend these findings to the acute phase. Importantly, differences in all metrics, but AD, remained when patients with complicated MTBI were excluded. This suggests that DTI and DKI have added value to clinical, conventional MRI sequences, in outcome prediction.

DKI appeared to be more sensitive than DTI to MTBI-induced alteration in white matter, independent of outcome, as the differences between patients without PCS and controls were evident exclusively in DKI metrics. These findings are in line with some previous studies also demonstrating that DKI is superior to DTI in detecting abnormalities in white matter in the acute to chronic phase after MTBI.[23,25] The present results, however, extend these observations by showing that although DKI metrics seem to be affected by the MTBI, deviating DTI metrics may be more closely related to PCS development.

The general finding from the DTI metrics assessed in the present study is that lower FA and higher MD in the acute stage of MTBI are associated with worse outcome. In previous studies, findings on the direction of change in acute DTI metrics after MTBI are inconsistent, but many argue that lower FA and higher MD is indicative of poorer white matter integrity, and possibly axonal injury. [3,4,56,59] Further, higher AD (diffusion rate along the main axis of diffusion) and higher RD (diffusion rate in the transverse direction) were associated with poorer

outcome in the present study. However, compared to AD, higher RD was present in a larger number of voxels, which aligns with the finding of lower FA in patients with PCS. Regarding the DKI metrics, we found lower kurtosis values in patients with and without PCS, when compared to controls, in line with several previous studies reporting lower kurtosis values in patients with MTBI compared to controls.[16,19–21,23] As with FA, KFA measure the anisotropy of diffusion,[17] and lower FA values can be expected to be accompanied by lower KFA values, as shown in the present study. Kmean, Kax, and Krad measure the kurtosis (i.e., the deviation from a Gaussian distribution) in different diffusion directions. Thus, values closer to zero indicate a diffusion of water molecules that is less restricted, approaching a Gaussian distribution,[18] which may be indicative of reduced tissue heterogeneity, and possibly, neuronal damage.[19]

Differences in Diffusion Metrics When Adjusting for Estimated Intelligence

Estimated preinjury intelligence appeared to be an important contributor to the observed differences in diffusion metrics, as none of the diffusion metrics remained significantly different between patients with and without PCS when estimated intelligence was adjusted for. Differences between patients with PCS and controls became less pronounced when estimated intelligence was controlled for, but remained significant for MD, AD and RD. One common finding in the MTBI literature is that patients with PCS, on average, differ from patients without PCS on several preinjury factors, such as having poorer preinjury mental and physical health[26], lower educational attainment[27] and intelligence.[28] However, this is rarely accounted for in DTI and DKI studies on MTBI, despite that many of these preinjury factors have been associated with DTI and DKI metrics outside the MTBI research context. For example, headache,[60] intelligence,[29,30] and depression[61] have been associated with white matter microstructural integrity. Thus, it is possible that the mixed findings in DTI and DKI studies on PCS result from

preinjury differences between these groups, which may vary between studies due to differences in participant recruitment. Nonetheless, when patients with PCS were compared to the control group in the present study, several differences in diffusion metrics were significant, also when estimated intelligence was controlled for, and the comparisons between patients without PCS and controls were unaffected by intelligence. Thus, although preinjury differences in intelligence seem to explain some of the differences between patients with PCS and patients without PCS, and between patients with PCS and healthy controls, the MTBI also appears to contribute to differences in diffusion metrics.

Strengths and Limitations

The main strength of this study is the large number of patients with MTBI assessed with both DTI and DKI in the acute phase after the injury. Most patients were assessed within 3 days, and all within 5. This range is both closer to the injury, and narrower, than most previous studies on MTBI. Further, the Trondheim MTBI follow-up study is population-based and recruitment took place not only at a level 1 emergency department, but also in an out-patient clinic. This enabled us to also include patients with milder MTBI, making the sample representative. However, this study has limitations that should be considered. First, even if the present study included a large number of patients, different findings in the total sample and the uncomplicated sample can be partly related to reduced statistical power when cases are excluded. Similarly, 22 (9%) of the participants were not assessed with the Vocabulary subtest (number of cases in each contrast shown in Table 2). Second, intelligence was estimated from the result on a single test, increasing the uncertainty in this measure. Intelligence is preferably measured with a battery of tests, such as the Wechsler Adult Intelligence Scale. However, in studies on brain injury, it is of importance that results on tests of intelligence are not affected by the injury (i.e., that they can

estimate *preinjury* functioning). Therefore, single tests known to be largely insensitive to brain pathology are usually used to estimate intelligence in brain injury studies. These tests are often language-based and measure vocabulary knowledge or word reading in different varieties, such as the Vocabulary subtests used in the present study, or the Wechsler Test of Adult Reading.[47,48]

Conclusion

In this large study, patients with PCS were different from patients without PCS and healthy controls in acute white matter microstructural integrity. However, some of these differences could be ascribed to preinjury differences between these groups. The findings suggest that poor white matter integrity might be considered *both* a preinjury risk factor and an injury-related biomarker for poor outcome after MTBI. Future DTI and DKI studies should carefully consider preinjury differences, including, but not restricted to, intelligence, when comparing good and poor outcome groups after MTBI.

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Table 1. Participant characteristics and injury-related factors.

	MTBI group	**Control group**	***P*[1]**	**PCS+**	***PCS-***	***P*[2]**
	n = 176	*n* = 78		*n* = 35	*n* = 141	
Age (years), median (IQR)	28.1 (22.0)	27.6 (20.0)	0.995[3]	31.5 (25.3)	27.0 (21.7)	0.411[3]
Sex, female, *n* (%)	68 (38.6)	30 (38.5)	0.816[4]	19 (54.3)	46 (32.6)	**0.017**[4]
Education (years), median (IQR)	13.0 (4.0)	13.0 (4.0)	0.663[3]	12.0 (4.0)	13.0 (4.0)	0.135[3]
Estimated preinjury intelligence						
T-score, mean (SD)	50.9 (9.2)	51.3 (8.1)	0.764[5]	47.5 (9.1)	51.6 (9.1)	**0.042**[5]
Raw score, mean (SD)	57.4 (8.6)	57.7 (7.6)	0.704[6]	54.6 (9.0)	58.0 (8.4)	**0.047**[6]
Cause of injury, *n*, (%)						
Fall	68 (38.6)			15 (42.9)	53 (37.6)	
Bicycle	33 (18.8)			5 (14.3)	28 (19.9)	
Sports accidents	21 (11.9)			0 (0)	21 (14.9)	
Violence	23 (13.1)			9 (25.7)	14 (9.9)	
Motor vehicle accidents	17 (9.7)			5 (14.3)	12 (8.5)	
Hit by object	12 (6.8)			0 (0)	12 (8.5)	
Other	1 (0.6)			1 (2.9)	0 (0)	
Unknown	1 (0.6)			0 (0)	1 (0.7)	
GCS score, *n* (%)						
13	4 (2.3)			0 (0)	4 (2.8)	
14	25 (14.2)			7 (20.0)	18 (12.8)	
15	136 (77.3)			25 (71.4)	111 (78.7)	
unknown	11 (6.3)			3 (8.5)	8 (5.7)	
LOC, *n* (%)						0.103
Yes	85 (48.3)			15 (42.9)	70 (49.6)	
No	30 (17.0)			3 (8.6)	27 (19.1)	
unknown/not witnessed	61 (34.7)			17 (48.6)	44 (31.2)	
PTA (%)						**0.002**
< 1 hour	123 (69.9)			17 (48.6)	106 (75.2)	
1-24 hours	53 (30.1)			18 (51.4)	35 (24.8)	
Complicated MTBI, *n* (%)						**0.006**
Yes	18 (10.2)			8 (22.9)	10 (7.1)	
No	158 (89.8)			27 (77.1)	131 (92.9)	
Level of Care, *n*, (%)						
Not admitted	124 (70.5)			20 (57.1)	104 (73.8)	
Observed < 24 hours	27 (15.3)			6 (17.1)	21 (14.9)	
Admitted neurosurgery department	16 (9.1)			7 (20.0)	9 (6.4)	
Admitted other department	9 (5.1)			2 (5.7)	7 (5.0)	

Note: 19 patients with MTBI, and 4 controls did not perform the Vocabulary subtest (used to estimate preinjury intelligence). 10 patients with PCS, and 9 patients without, had missing vocabulary scores.[1]*p*-value from MTBI/Controls comparison; [2]*p*-value from PCS+/PCS- comparison. No statistical comparisons were performed for cause of injury, GCS, and level of care because of low *n* in some cells; [3]Mann Whitney U-test; [4]Chi-square test; [5]t-test; [6]Multiple regression with age and sex as covariates. MTBI= Mild Traumatic Brain Injury; PCS+/PCS- = Patients with and without postconcussion symptoms.

Table 2. Comparisons with significant findings: number of participants, direction of change, lowest adjusted *p*-value, and the number of significant voxels.

Comparison	*n*	Direction < / >	Lowest *p*-value	Number of sig. voxels
PCS+ vs PCS-				
Total sample				
FA	35/141	PCS+<PCS-	0.035	3695
RD	35/141	PCS+>PCS-	0.044	411
KFA	35/141	PCS+<PCS-	0.026	9544
Uncomplicated sample				
FA	27/131	PCS+<PCS-	0.028	6950
PCS+ vs Controls				
Total sample				
FA	35/78	PCS+<Controls	0.002	12818
MD	35/78	PCS+>Controls	0.019	25329
AD	35/78	PCS+>Controls	0.015	2245
RD	35/78	PCS+>Controls	0.005	24590
KFA	35/78	PCS+<Controls	0.006	25387
Kmean	35/78	PCS+<Controls	0.032	7600
Kax	35/78	PCS+<Controls	0.028	5244
Krad	35/78	PCS+<Controls	0.026	9780
Uncomplicated sample				
FA	27/78	PCS+<Controls	0.003	22422
MD	27/78	PCS+>Controls	0.028	15915
RD	27/78	PCS+>Controls	0.010	26144
KFA	27/78	PCS+<Controls	0.018	20456
Kmean	27/78	PCS+<Controls	0.027	16713
Kax	27/78	PCS+<Controls	0.050	3
Krad	27/78	PCS+<Controls	0.027	19553
Adjusted for intelligence				
MD, Total sample	25/74	PCS+>Controls	0.038	6743
AD, Total sample	25/74	PCS+>Controls	0.029	1059
RD, Total sample	25/74	PCS+>Controls	0.047	292
RD, Uncomplicated	19/74	PCS+>Controls	0.049	212
PCS- vs Controls				
Total sample				
Kmean	141/78	PCS-<Controls	0.029	7092
Kax	141/78	PCS-<Controls	0.035	333
Krad	141/78	PCS-<Controls	0.036	4970
Uncomplicated sample				
Kmean	131/78	PCS-<Controls	0.040	3978
Krad	131/78	PCS-<Controls	0.030	6533
Adjusted for intelligence				
Kmean, Total sample	132/74	PCS-<Controls	0.023	11258
Kax, Total sample	132/74	PCS-<Controls	0.025	825
Krad, Total sample	132/74	PCS-<Controls	0.036	4838
Kmean, Uncomplicated	123/74	PCS-<Controls	0.026	10318
Krad, Uncomplicated	123/74	PCS-<Controls	0.030	9455

Note: The table shows the *p*-value for the voxel with the lowest *p*-value, the direction, and the number of significant voxels. E.g., for FA, when comparing patients with PCS to patients without PCS in the total sample, patients with PCS had significantly *lower* FA in 3695 voxels. The lowest adjusted *p*-value among these voxels was 0.035. AD = Axial Diffusivity; FA = Fractional Anisotropy; Kax = Axial Kurtosis; KFA = Kurtosis Fractional Anisotropy; Kmean = Kurtosis Mean; Krad = Radial Kurtosis; MD = Mean Diffusivity; MTBI = Mild Traumatic Brain Injury; PCS+/- = patients with and without postconcussion symptoms; RD = Radial Diffusivity.

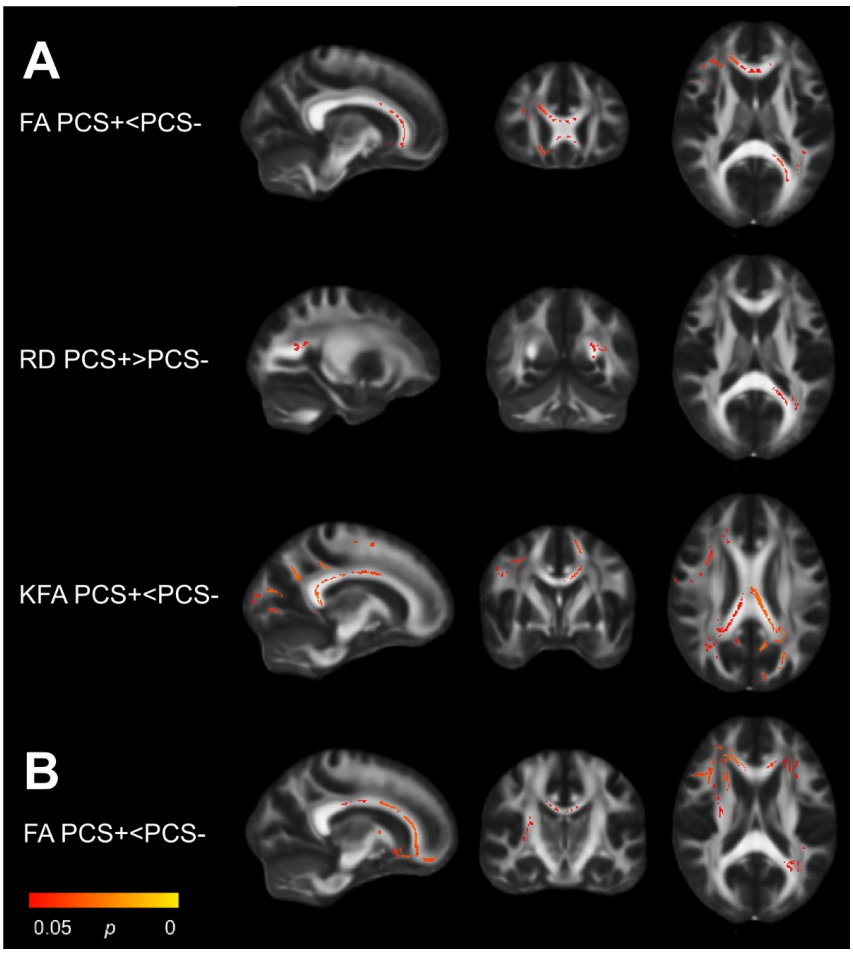

Figure 1. Significant contrasts from Tract-Based Spatial Statistics: PCS+ vs PCS-. Patients with (PCS+) vs without (PCS-) postconcussion symptoms; total sample **(A)**, uncomplicated sample **(B)**. Statistically significant voxels in red and yellow (lowest *p*-value). FA = Fractional Anisotropy; KFA = Kurtosis Fractional Anisotropy; RD = Radial Diffusivity.

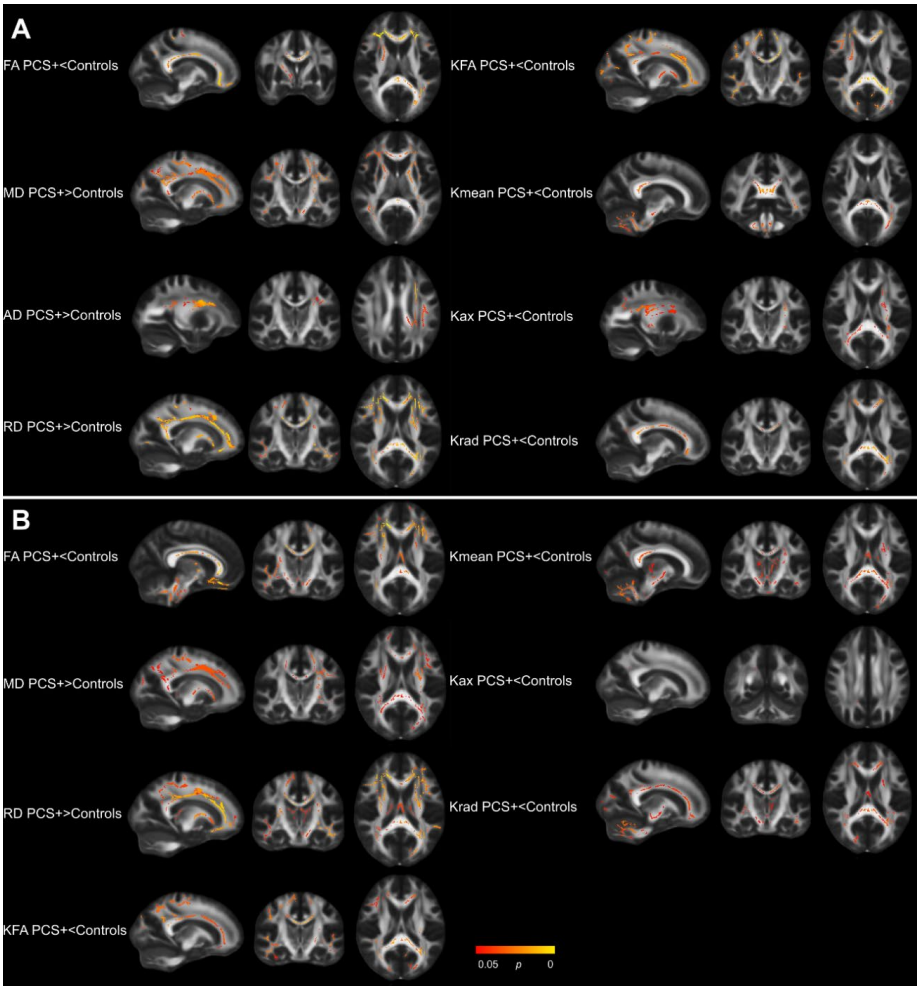

Figure 2. Significant contrasts from Tract-Based Spatial Statistics: PCS+ vs Controls. Patients with postconcussion symptoms (PCS+) versus healthy controls; total sample **(A),** uncomplicated sample **(B)**. Statistically significant voxels in red and yellow (lowest *p*-value). AD = Axial Diffusivity; FA = Fractional Anisotropy; Kax = Axial Kurtosis; KFA = Kurtosis Fractional Anisotropy; Kmean = Kurtosis Mean; Krad = Radial Kurtosis; MD = Mean Diffusivity; RD = Radial Diffusivity.

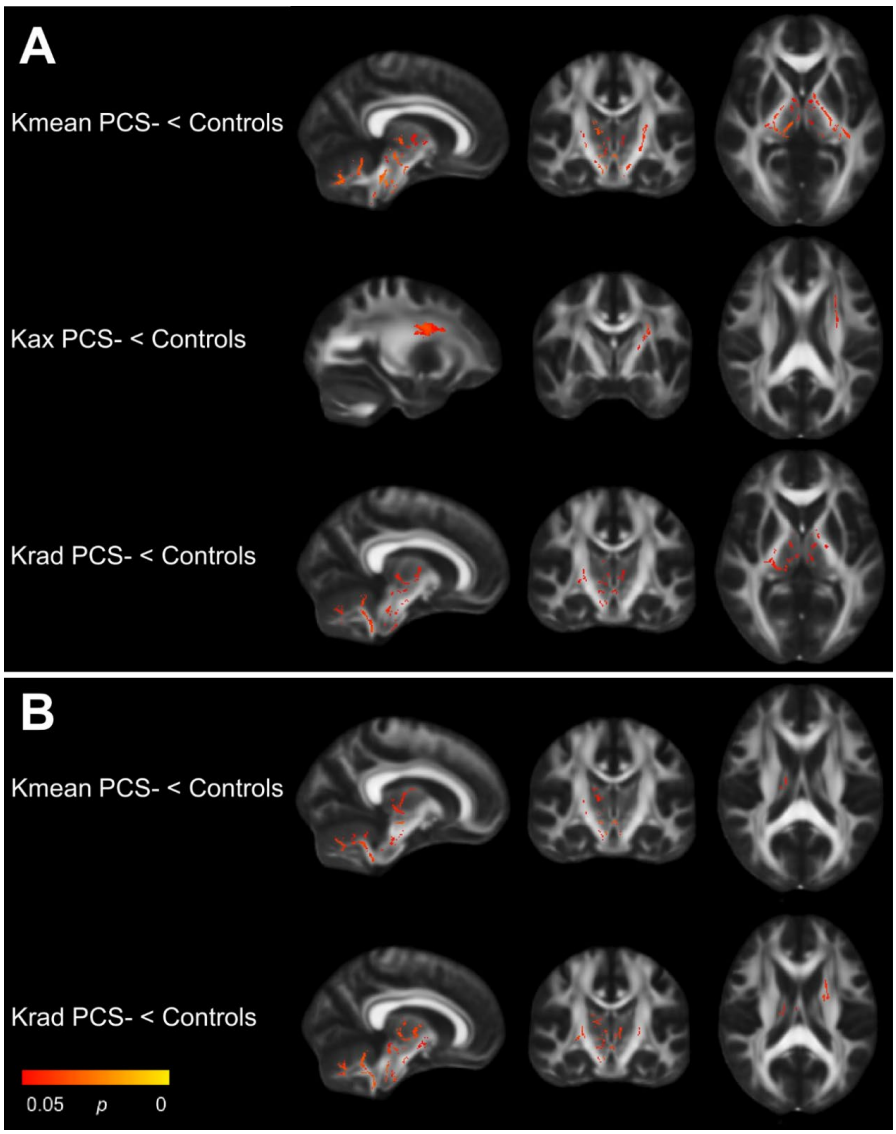

Figure 3. Significant contrasts from Tract-Based Spatial Statistics: PCS- vs Controls. Patients without postconcussion symptoms (PCS-) versus healthy controls, total sample **(A)**, uncomplicated sample **(B)**. Statistically significant voxels in red and yellow (lowest *p*-value). Kax = Axial Kurtosis; Kmean = Kurtosis Mean; Krad = Radial Kurtosis.

PAPER 4

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ORIGINAL RESEARCH

Cognitive Reserve Moderates Cognitive Outcome After Mild Traumatic Brain Injury

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Abstract

Objective: To investigate whether cognitive reserve moderates differences in cognitive functioning between patients with mild traumatic brain injury (MTBI) and controls without MTBI and to examine whether patients with postconcussion syndrome have lower cognitive functioning than patients without postconcussion syndrome at 2 weeks and 3 months after injury.

Design: Trondheim MTBI follow-up study is a longitudinal controlled cohort study with cognitive assessments 2 weeks and 3 months after injury.

Setting: Recruitment at a level 1 trauma center and at a general practitioner-run, outpatient clinic.

Participants: Patients with MTBI (n=160) according to the World Health Organization criteria, trauma controls (n=71), and community controls (n=79) (N=310).

Main Outcome Measures: A cognitive composite score was used as outcome measure. The Vocabulary subtest was used as a proxy of cognitive reserve. Postconcussion syndrome diagnosis was assessed at 3 months with the British Columbia Postconcussion Symptom Inventory.

Results: Linear mixed models demonstrated that the effect of vocabulary scores on the cognitive composite scores was larger in patients with MTBI than in community controls at 2 weeks and at 3 months after injury (P=.001). Thus, group differences in the cognitive composite score varied as a function of vocabulary scores, with the biggest differences seen among participants with lower vocabulary scores. There were no significant differences in the cognitive composite score between patients with (n=29) and without (n=131) postconcussion syndrome at 2 weeks or 3 months after injury.

Conclusion: Cognitive reserve, but not postconcussion syndrome, was associated with cognitive outcome after MTBI. This supports the cognitive reserve hypothesis in the MTBI context and suggests that persons with low cognitive reserve are more vulnerable to reduced cognitive functioning if they sustain an MTBI.
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Most patients with mild traumatic brain injury (MTBI) do not show evidence of performance-based cognitive deficits 3 months after the injury.[1] However, many patients continue to report symptoms beyond this time point, a condition described as post-concussion syndrome (PCS).[2] Studies exploring whether patients with PCS have reduced performance on cognitive testing have yielded contradictory results.[3-6] Individual differences in cognitive reserve might contribute to the heterogeneous outcome following MTBI. The cognitive reserve theory,[7] stating that the effect of brain injury on outcome is moderated by cognitive reserve, has proven useful in the context of neurodegenerative diseases[8-10] and to a certain extent in severe traumatic brain injury (TBI).[11-15] There is some support for this theory in MTBI, with studies showing associations between proxies of cognitive reserve, such as intelligence, and cognitive functioning.[16-18] However, few studies[16,19] have investigated whether the effects of MTBI and low cognitive reserve are purely additive or if there is a synergistic effect between MTBI and low cognitive reserve, resulting in lower cognitive functioning than would be expected from either factor alone. In this longitudinal study of cognition after MTBI, the aims were to investigate whether cognitive reserve moderated differences in cognition between patients with MTBI and control groups without MTBI at 2 weeks and 3 months after injury. In addition, we examined whether patients with PCS had worse cognitive functioning than patients without PCS.

Methods

Participants

The patients with MTBI in the present study were part of the Trondheim MTBI follow-up study (n=378), shown to be largely representative of patients with MTBI.[20] Patients were recruited from 2014-2015. Inclusion criteria were age 16-59 years and having sustained an MTBI per the World Health Organization criteria: (1) Glasgow Coma Scale score 13-15 at presentation in the emergency department and (2) either witnessed loss of consciousness (LOC) <30 minutes, confusion, or posttraumatic amnesia <24 hours or traumatic lesion at the computed tomography scan.[21] Exclusion criteria were nonfluency in the Norwegian language; preexisting severe somatic or neurologic (eg, stroke, multiple sclerosis) disorder; a prior history of a complicated mild, moderate, or severe TBI; and psychiatric (eg, bipolar or psychotic disorder) or substance use disorder of a severity that the researcher responsible for inclusion deemed to likely interfere with compliance with follow-up. Of the 378 patients, 199 were scheduled for comprehensive follow-up including magnetic resonance imaging (MRI) and cognitive assessments. Whether or not a patient was asked to participate in comprehensive follow-up was dependent on consent to MRI, no MRI contraindications, that MRI scanning could be performed within 72 hours (available MRI slot), and that they lived within a 1-hour drive from the study hospital. Of the 199 patients, 175 participated in cognitive assessment 2 weeks after injury. Twelve of these patients had an incomplete cognitive assessment, and 3 did not complete the measure that assesses for PCS. Therefore, 160 patients with MTBI were included in the analyses.

Samples of 71 age- and sex-matched patients with orthopedic injuries who were free from polytrauma and trauma affecting the head, neck, or the dominant upper extremity (ie, trauma controls [TCs]) and 79 age-, sex-, and education-matched community controls (CCs) not receiving treatment for severe psychiatric disorder (eg, bipolar or psychotic disorder) were recruited.

The study was approved by the regional committee for research ethics (REK 2013/754). All participants, and parents of participants younger than 18 years, gave informed consent.

List of abbreviations:

CC	**community control**
MRI	**magnetic resonance imaging**
MTBI	**mild traumatic brain injury**
PCS	**postconcussion syndrome**
TBI	**traumatic brain injury**
TC	**trauma control**
WAIS-IV	**Wechsler Adult Intelligence Scale-IV**

Procedure and clinical variables

Recruitment took place at 2 emergency departments: a level 1 trauma center in Trondheim, Norway, and the Trondheim Municipal Emergency clinic, a general practitioner-run, outpatient clinic. Intracranial traumatic findings were obtained from acute head computed tomography and MRI at 3 tesla, performed within 72 hours.[22] The TCs were recruited from the same emergency departments. CCs were recruited among hospital and university staff, students, and acquaintances of patients.

Cognitive assessment

Patients with MTBI underwent cognitive assessment 2 weeks (range, 12-24d; median, 16d) and 3 months (range, 11-16wk; median, 13wk) after injury. The TCs were evaluated 2 weeks (range, 12-24d; median, 16d) and 3 months (range, 11-18wk; median, 13wk) after injury. The CCs were assessed 3 months apart (range, 8-19wk; median, 13.5wk). Of the 160 patients with MTBI who completed the 2-week assessment, 153 (96%) completed the 3-month assessment. Of the 71 TCs who completed the 2-week assessment, 67 (94%) completed the 3-month assessment, as did 74 of the 79 CCs (94%). A licensed psychologist or students in psychology or neuroscience (supervised by a licensed psychologist) performed the assessments.

The same tests were administered at both assessments. The tests included in the cognitive composite score (details below) were all well established and commonly used in TBI research.[23,24] The Coding and Symbol Search subtests from the Wechsler Adult Intelligence Scale-IV (WAIS-IV)[25,26] assessed processing speed. Auditory Verbal Learning Test assessed learning and memory.[27] The total number of words recalled in trials 1-5 was chosen as the outcome measure because it is reliable[28,29] and less skewed than the delayed recall score. Verbal Fluency (both the letter and the semantic trial) assessed executive functioning.[27,30]

We did not administer any formal symptom validity test because the test scores were solely part of a research repository and not available to future medicolegal assessments. We did, however, perform a validity check of the results on the Coding and the Symbol Search tests, which have been suggested as embedded validity indicators.[31,32] A Processing Speed Index score (ie, combining the results from the Coding and the Symbol Search test according to the WAIS-IV manual) <80 and a discrepancy >4 between the scaled score of the Coding subtest and the Symbol Search subtest may warrant attention.[31,32] The lowest Processing Speed Index score in our sample was 76, and none of the participants with a Processing Speed Index<80 had a subtest discrepancy >4.

Table 1 Demographic and clinical characteristics of the included patients with MTBI, the TC group, the CC group, and the patients with MTBI not included in the present study

Variable	MTBI Included n=160	TC Group n=71	CC Group n=79	*P* Value MTBI/TC/CC	MTBI Not Included n=218	*P* Value Included vs Not Included
Age (y)						
Median (IQR)	27.1 (23.1)	27.0 (24.0)	28.2 (21.1)	.770*	24.4 (18.44)	.015*,¶
Mean ± SD	32.8±13.2	31.9±12.8	33.0±12.9		30.1±12.8	
Sex (% women)	33.8	38.0	39.2	.659†	35.3	.751†
Education (y)						
Median (IQR)	13.0 (4.0)	14.0 (4.0)	13.0 (4.0)	.766*	13.0 (3.0)	.025*,¶
Mean ± SD	14.0±2.6	14.3±2.5	14.0±2.4		13.4±2.3	
Vocabulary, raw score, mean ± SE	57.3±0.6	59.4±0.9	57.5±0.9	.130‡	-	
Vocabulary, T score, mean ± SD§	50.9±9.1	53.3±7.2	51.1±8.2	.153	-	
Cause of injury (%)						
Fall	38.8	29.6			33.5	.291†
Bicycle	18.1	9.9			13.3	.199†
Sports accidents	14.4	36.6			14.2	.966†
Violence	12.5	1.4			20.6	.038†,¶
Motor vehicle collisions	8.1	4.2			13.8	.088†
Hit by object	7.5	7.7			2.3	.016†,¶
Other	0.0	11.3‖			1.4	.136†
Unknown	0.6	0.0			0.1	.752†
GCS score (%)						
13/14/15/unknown	2.5/13.1/77.5/6.9				0.5/16.5/70.2/12.8	.058†
LOC (%)						
Yes/no/unknown-not witnessed	50.0/16.9/33.1				42.7/18.3/39.0	.355†
PTA (%)						
<1 h/1-24 h	71.9/28.1				71.6/28.4	.946†
Intracranial findings (on CT or MRI)						
(% yes/no)	11.9/88.1				-	
Level of care (%)						
Not admitted	71.9	84.5			66.5	.266
Observed <24 h	14.4	0.0			17.4	.425
Admitted neurosurgery department	10.0	0.0			10.6	.862
Admitted other department	3.8	15.5			5.5	.429
Type of injury, TC (%)						
Upper extremities						
Fracture		33.8				
Soft tissue (ligament, luxations)		5.6				
Wounds		0.0				
Lower extremities						
Fracture		23.9				
Soft tissue (ligament, luxations)		28.2				
Wounds		2.8				
Other injuries		5.6				

Abbreviations: CT, computed tomography; IQR, interquartile range; GCS, Glasgow Coma Scale; LOC, loss of consciousness; PTA, posttraumatic amnesia.

* Kruskal-Wallis test/Mann-Whitney *U* test.

† Pearson χ^2 test.

‡ One-way analysis of covariance with age as a covariate.

§ Raw scores converted to T score using the Wechsler Abbreviated Scale of Intelligence manual for easier interpretation. *P*-value from a 1-way analysis of variance is shown. The published normative reference values have a mean of 50 and an SD of 10.

‖ Sharp injuries, such as cuts, are included here for TC.

¶ $P<.05$.

Given that no specific cognitive domain is consistently affected following MTBI,[1] a cognitive composite score calculated according to Miller and Rohling[33] was used as a single outcome measure in this study. This composite score is commonly used and considered to be a reliable measure of cognition.[34,35] First, the scores were converted to a common metric (T scores: mean, 50±10 in the normative group) using published norms.[26,27,30,36] To compensate for varying ceiling and floor effects across norms and to avoid a disproportionate effect by unusual results on the composite score, no subject was given a T score<20 or >80 (eg, if a participant's score was converted to a T

Table 2 T scores on the 5 neuropsychological tests and the composite score for the MTBI group and the 2 control groups

	2 Weeks, Mean ± SD				3 Months, Mean ± SD			
	MTBI Group	TC Group	CC Group	*P* Value*	MTBI Group	TC Group	CC Group	*P* Value*
Variable	n=160	n=71	n=79	uncorr./corr.	n=153	n=67	n=74	uncorr./corr.
Coding	50.3±8.8	51.3±7.5	53.1±8.2	.034/.170	54.4±10.0	55.2±8.5	55.7±8.9	.316/>.99
Symbol search	52.4±8.5	51.4±7.8	54.3±8.6	.054/.270	57.1±9.3	56.3±8.8	57.3±9.8	.840/>.99
Verbal Fluency								
Letter	46.9±11.6	49.8±11.5	48.0±10.4	.238/>.99	49.8±13.0	54.1±10.9	51.1±10.6	.047/.235
Semantic	53.7±11.5	53.9±11.2	55.6±11.4	.522/>.99	54.8±12.0	54.7±10.9	56.5±10.5	.539/>.99
AVLT†	45.9±11.2	49.0±10.6	48.8±11.5	.131/.655	47.6±12.1	49.7±9.8	49.5±10.4	0.477/>.99
Composite score	49.8±7.3	51.1±6.8	52.0±6.5	NA‡	52.7±8.2	54.0±6.8	54.0±6.5	NA‡

NOTE. The published normative reference values have a mean ± SD of 50±10.
Abbreviations: AVLT, Auditory Verbal Learning Test; NA, not applicable.
* Group effect Kruskal-Wallis test. Unadjusted and Bonferroni adjusted (original *P* value multiplied with 5) are shown.
† No. of recalled words in trial 1-5.
‡ Analyzed with linear mixed model (fig 1).

score of 15, this was set to 20), which is the norm range for the WAIS-IV tests. The composite score was calculated by averaging the T scores from the 5 outcome measures.

Estimation of premorbid intelligence and cognitive reserve

The Vocabulary subtest from Wechsler Abbreviated Scale of Intelligence,[37,38] administered at the 2-week assessment, was used as an estimate of premorbid intelligence and a proxy of cognitive reserve, which is a commonly used procedure in TBI research.[39] The Vocabulary subtest is considered an estimate of general mental ability,[24] and test performance has been shown to be relatively unaffected by cognitive impairment following TBI.[40] Because vocabulary scores were not combined with other scores (as with the test scores included in the cognitive composite score), raw scores were used to account for the concerns that have been raised regarding the representativeness of the Wechsler Abbreviated Scale of Intelligence Vocabulary test norms in Norway.[41,42] To ensure that demographic variables were not affecting our results, age and sex were controlled for in analyses.

Postconcussion symptom measure

The International Classification of Diseases, 10th Edition, PCS classification for patients with MTBI was based on symptoms reported on the British Columbia Postconcussion Symptom Inventory[43] at the 3-month follow-up. The British Columbia Postconcussion Symptom Inventory consists of 13 core symptoms, distributed over 4 symptom categories (ie, somatic, emotional, cognitive, sleep disturbance), and 3 life problems, distributed over 2 additional symptom categories (ie, reduced tolerance to alcohol, preoccupation with the symptoms, and fear of permanent brain damage). PCS was defined as having at least 1 core symptom and/or life problem rated as moderate (score≥3) in 3 of the 6 different symptom categories, consistent with the International Classification of Diseases, 10th Edition, criteria of PCS.[44] The groups of patients with MTBI who did or did not fulfill this criterion, are referred to as the PCS+ group and the PCS− group, respectively.

Statistical analyses

A linear mixed model (Stata command: mixed y x || id) was used to examine whether vocabulary scores (raw scores) moderated differences in the cognitive composite scores between groups (MTBI, TC, CC) at 2 weeks and 3 months after injury. Group, time of assessment (2-wk/3-mo), vocabulary scores, age, and sex were entered as independent variables. The 3-way interaction group×time×vocabulary and the 2-way interactions group×vocabulary, time×vocabulary and time×group were examined. While a significant 2-way interaction could indicate, for example, that the effect of vocabulary scores on the cognitive composite scores was larger in 1 of the groups, a significant 3-way interaction could indicate that such an effect was unique for only 1 of the 2 assessments. The within-subject correlation was modeled by a random, subject-specific intercept. Random slopes were not included because they did not improve the model according to the likelihood ratio test. The parameters of the model were estimated by restricted maximum likelihood because it generates better variance estimates than maximum likelihood. Normality of residuals was assessed by inspection of histograms and QQ-plots and was considered satisfactory.

A similar linear mixed model was used to explore differences in the cognitive composite score between patients with and without PCS. Group (PCS+, PCS−), time, vocabulary scores, age, and sex were entered as independent variables. We did not hypothesize that vocabulary scores moderated differences in the cognitive composite score between patients with and without PCS, but the 3-way interaction group×time×vocabulary and all 2-way interaction were examined also in this model. Group differences in the cognitive composite score between patients with and without PCS were also reported with vocabulary scores excluded from the model (ie, unadjusted model).

Two-tailed *P* values <.05 were considered statistically significant. Bonferroni correction was applied in post hoc pairwise comparisons and in the evaluation of results on the individual cognitive tests. Group differences in demographic variables and individual cognitive test scores were analyzed with 1-way analysis of variance, independent *t* tests, Kruskal-Wallis tests, Mann-Whitney *U* tests, and Pearson chi-square tests. The analyses were performed in Stata, version 15.1.[a]

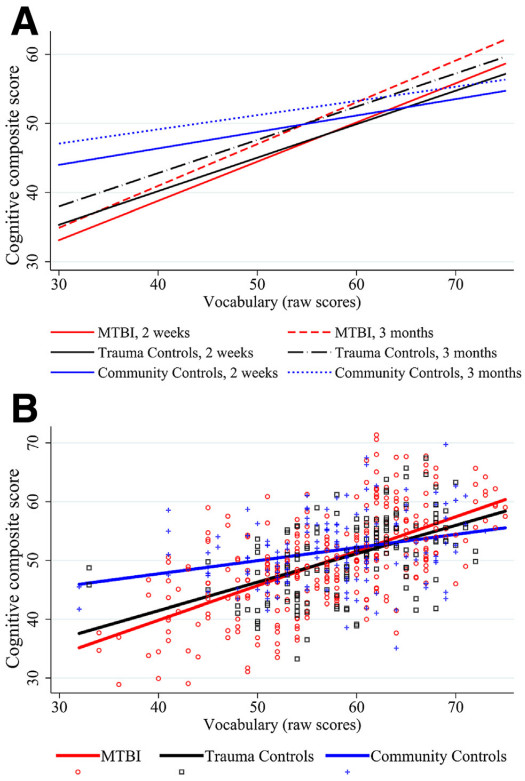

Fig 1 Effect of group, time, and vocabulary scores on the cognitive composite score, estimated with a linear mixed model. **(A)** Illustration of the nonsignificant 3-way interaction group×time×vocabulary. As evident in the figure, the effect of vocabulary scores was similar at the 2-week and the 3-month assessment. Further, although all groups had higher cognitive composite scores at the 3-month assessment, group differences in the cognitive composite score were similar across assessments. (**B**) Illustration of the significant 2-way interaction group×vocabulary (the nonsignificant 2-way interactions time×group and time×vocabulary omitted) along with a scatterplot of all observations. The effect of vocabulary scores differed significantly between the MTBI group and the CC group. Thus, group differences in the cognitive composite score varied as a function of vocabulary scores, with the largest differences seen among participants with lower vocabulary scores. In the figures, variables are set at male sex and mean age (33y).

Results

Characteristics of the MTBI group, the TC group, and the CC group

There were no significant differences between the included patients with MTBI, the TC group, and the CC group regarding age, sex, years of education, or vocabulary scores (table 1, which also shows the characteristics of the patients not included). On the individual tests that constitute the cognitive composite score, there were no significant differences between the groups when controlling for multiple comparisons (uncorrected and corrected *P* values in table 2).

Interaction between group (MTBI and control groups), time, and vocabulary scores on the cognitive composite score

The 3-way interaction term group×time×vocabulary was not significant ($P=.511$) and was omitted from the model (but is illustrated in fig 1A). Examinations of the 2-way interactions revealed that the effect of vocabulary scores on the cognitive composite score differed significantly between the 3 groups (group×vocabulary interaction: $P=.001$), and the effect of vocabulary scores was similar at the 2-week and at the 3-month assessment (time×vocabulary interaction: $P=.588$). Further, the effect of group (ie, group differences in the cognitive composite score) was also similar at the 2-week and 3-month assessment (time×group interaction: $P=.456$). The nonsignificant interaction terms were omitted for further analyses.

There was a significant main effect of time. Across the 3 groups, the cognitive composite scores were higher on the 3-month assessment (mean difference, 2.60; 95% CI, 2.20-3.00; $P<.001$). Across groups and assessments, lower age (coefficient, −0.14; $P<.001$) and female sex (mean difference, 3.73; $P<.001$) were associated with higher cognitive composite scores.

Figure 1B illustrates the group×vocabulary effect, and the estimates from this model are reported in table 3. The intraclass correlation for this model was 0.82, the estimated variance of the random intercept was 29.2, and the variance of the within-subject residuals was 6.2. Higher vocabulary scores were associated with higher cognitive composite scores in all groups across both time points. However, the effect of vocabulary scores on the cognitive composite scores was significantly larger in the MTBI group than in the CC group ($P=.001$) but not in the MTBI group compared with the TC group ($P>.99$) or in the TC group compared with the CC group ($P=.127$). Thus, group differences in the cognitive composite score between patients with MTBI and CCs varied as a function of vocabulary scores, with the largest differences seen between patients with MTBI and CCs among participants with lower vocabulary scores (see fig 1B). The magnitude of this effect can be comprehended more easily by looking at the standardized coefficients. For the MTBI group, an increase of 1 SD in vocabulary was associated with an increase of 0.64 SDs in the cognitive composite score. For the CC group, an increase of 1 SD in vocabulary was associated with an increase of only 0.24 SDs in the cognitive composite score. Because patients who have intracranial findings (ie, "complicated" MTBI) are excluded in some MTBI studies, a follow-up analysis was conducted to assess whether the stronger effect of vocabulary scores on the cognitive composite score in the MTBI group remained when the patients with complicated MTBI (n=19) were excluded. The group×vocabulary effect remained significant in this model ($P=.003$), with a significantly stronger effect of vocabulary scores on the cognitive composite score in the MTBI group compared with the CC group (estimate, 0.34; $P=.002$). Thus, this finding was not related to the inclusion of patients with complicated MTBI.

Differences in cognitive composite scores between the PCS+ group and the PCS− group

Of the patients with MTBI, 29 (18%) met the criterion for moderate PCS at 3 months post injury. Because of the nonspecific nature of concussion-like symptoms,[43] we also calculated the number of controls fulfilling the PCS criterion in the absence of a

Table 3 Estimates from the linear mixed model examining the interaction effect between group (MTBI group, control groups) and vocabulary scores on the cognitive composite score

Variable	Estimate	SE	95% CI	*P* Value*
Slopes for Vocabulary†				
MTBI group (n=160)	0.59	0.05	0.48 to 0.69	<.001§
TC group (n=71)	0.48	0.10	0.29 to 0.68	<.001§
CC group (n=79)	0.22	0.08	0.06 to 0.39	.007§
Differences between slopes				.001‡,§
MTBI vs TC	0.10	0.11	−0.16 to 0.37	>.99
MTBI vs CC	0.36	0.10	0.13 to 0.60	.001§
TC vs CC	0.26	0.13	−0.05 to 0.57	.127

* Bonferroni adjusted values (original *P* value multiplied by 3) for pairwise group comparisons in slope differences.
† Estimated increase in the cognitive composite score per unit increase in vocabulary scores, for each group.
‡ Overall interaction effect.
§ *P*<.05.

head injury. With the same criterion for PCS in the control groups as in the MTBI group, 1 CC (1%) and 5 TCs (7%) fulfilled the PCS criterion. The number of participants with PCS-like symptoms in the control groups were considered too small for separate analyses. The PCS+ group had a significantly lower mean vocabulary scores than the PCS− group (*P*=.015) (table 4). Descriptive statistics of the cognitive composite score for the PCS+ and PCS− groups are reported in table 4.

Neither the 3-way interaction term group (PCS+, PCS−)×time×vocabulary nor any of the 2-way interactions were statistically significant, and they were omitted from the model. In figure 2, the time×group interaction is shown for illustrative purposes. With all the interaction terms omitted and with age, sex and vocabulary scores controlled for, the PCS+ and PCS− groups had almost identical cognitive composite scores (mean difference, 0.16; 95% CI, −2.33 to 2.65; *P*=.901). The intraclass correlation for this model was 0.83, the estimated variance of the random intercept was 32.0, and the variance of the within-subject residuals was 6.5. When vocabulary scores were not controlled for, there was still no significant difference in the cognitive composite scores between the groups (mean difference, −2.02; 95% CI, −5.12 to 1.07; *P*=.200).

Raw scores vs normative scores for the Vocabulary test

The analyses above were completed using vocabulary raw scores. All analyses were also completed with vocabulary T scores instead of raw scores, with similar results.

Discussion

In this large, longitudinal study, differences in cognition between patients with MTBI and CCs were moderated by cognitive reserve. Moreover, patients with PCS did not have significantly

Table 4 Demographics, vocabulary scores, and descriptive means of the cognitive composite scores in the PCS+ and PCS− groups

Variable	PCS+ Group n=29	PCS− Group n=131	*P* Value
Age (y), median (IQR)	34.5 (27.0)	25.1 (20.8)	.064*
Sex (% women)	48.2	30.5	.068†
Education (y), median (IQR)	13.0 (4.0)	13.0 (4.0)	.336*
Vocabulary, raw score, mean (SE)	53.9 (1.5)	58.1 (0.7)	.015‡,**
Vocabulary, T score, mean ± SD§	47.4±9.0	51.7±9.0	.023**
Cognitive composite score, 2 wk, mean ± SD	48.6±7.5	50.1±7.3	NA‖
Cognitive composite score, 3 mo, mean ± SD	51.5±7.5¶	53.0±8.4#	NA‖

Abbreviations: IQR, interquartile range; NA, not applicable; PCS−, patients with MTBI who did not have postconcussion syndrome; PCS+, patients with MTBI who had International Classification of Diseases, 10th Edition postconcussion syndrome.
* Mann-Whitney *U* test.
† Pearson χ^2 test.
‡ One-way analysis of covariance with age as a covariate.
§ Raw scores converted to T score using the Wechsler Abbreviated Scale of Intelligence manual for easier interpretation. *P* value from a *t* test is shown. The published normative reference values have a mean ± SD of 50±10.
‖ Analyzed with linear mixed model (fig 2).
¶ 27 patients with PCS completed the 3-month assessment.
# 126 patients without PCS completed the 3-month assessment.
** *P*<.05.

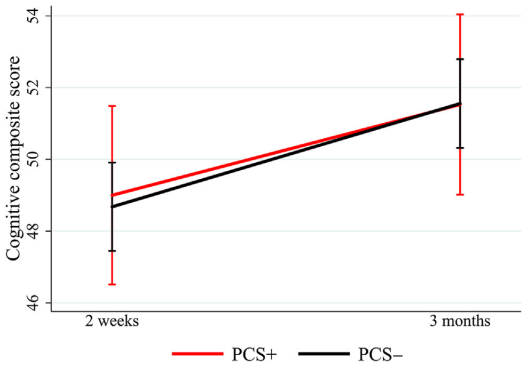

Fig 2 Differences in cognitive composite scores between the PCS+ group and the PCS− group, estimated with a linear mixed model. Estimated means of the cognitive composite score at 2 weeks and 3 months post injury for the PCS+ and PCS− group. The figure includes a nonsignificant time×group interaction. Error bars show 95% CIs. Variables are set at male sex, mean age (33y), and mean vocabulary raw score (57). Abbreviations: PCS−, patients with MTBI who did not have postconcussion syndrome; PCS+, patients with MTBI who had International Classification of Diseases, 10th Edition postconcussion syndrome.

reduced cognitive functioning at 2 weeks or at 3 months after injury compared with patients without PCS.

That estimated intelligence, a proxy of cognitive reserve, moderated the differences in cognitive functioning between the MTBI group and CCs extends the well-known association between intelligence and cognitive functioning[16-18] by illustrating that cognitive outcome after MTBI differs depending on intelligence. Our results are in line with the meta-analysis of Dougan et al on sports-related MTBI.[19] The authors concluded that differences in cognition between patients with MTBI and controls without MTBI were largest in the studies where participants had lowest education. In contrast, Steward et al did not find that the effect of estimated premorbid intelligence was larger in patients with MTBI than in controls without MTBI at 1 month after injury.[16] However, Steward et al explored 24 patients with and 28 without intracranial abnormalities separately, leading to quite low statistical power in the interaction analyses. In line with Steward et al, we did not find that cognitive reserve moderated recovery rates between the assessments (ie, the effect of cognitive reserve was similar across assessments). However, to demonstrate such an effect, patients with high cognitive reserve would need to have reduced cognitive functioning at the first assessment. Probably, this would require assessment in the very acute phase because for the majority of patients, most recovery seems to occur the first few weeks, or even days, after injury.[1] This complicates the study of cognitive reserve by recovery rates in MTBI, as also noted by Steward et al.[16]

The TC group did not differ significantly from either the MTBI group or the CC group regarding the effect of cognitive reserve on cognition. It is therefore not possible to conclude firmly whether the effect of cognitive reserve is specific for MTBI (ie, compared with trauma in general). In fact, even though the estimate (ie, the effect of cognitive reserve on cognition) was largest in the MTBI group, the estimates for the MTBI group and the TC group differed less than the estimates for the TC group and the CC group. In MTBI research, it is common to observe greater similarities between patients with MTBI and TCs than between patients with MTBI and healthy controls without MTBI. This has been reported for cognition[45] and abnormalities in white matter.[46,47] The mechanisms behind this are largely unknown and need further investigation.

There was no significant difference in cognition between the PCS+ group and the PCS− group at 2 weeks or 3 months after MTBI. The results are in line with the study of Lange et al, who did not find statistically significant differences between MTBI patients with and without PCS at 6-8 weeks after injury,[5] and with the study of Oldenburg et al, who reported small, mostly nonsignificant differences between patients with and without PCS and at 3 months after injury.[6] In contrast, Dean and Sterr reported lower cognitive performance in patients with PCS, evaluated at least 1 year after MTBI.[4] However, analyses were limited to measures of working memory and processing speed, which makes the results not directly comparable with ours. Also, the patients with PCS had lower, although not significantly, estimated intelligence, which partly could explain the lower cognitive functioning in the PCS group.

Study limitations

The strengths of the present study include the longitudinal design and the large, representative sample of mainly nonhospitalized patients with MTBI.[20] The repeated assessment of the MTBI group and the control groups enabled investigating time by group interactions, thereby separating cognitive recovery from learning effects (ie, a significantly stronger effect of time in the MTBI group compared with the control groups would be expected if cognitive recovery took place). Both CCs and TCs were recruited. These control groups are commonly used in MTBI research but rarely in the same study. A limitation of the study is that only 1 proxy of cognitive reserve was used: estimated premorbid intelligence. Cognitive reserve is often estimated also by educational and occupational attainment.[7] These parameters were less useful in the present study because many participants were young and had not completed their education. Also, for the current sample, the representativeness of the test norms used is unknown. However, because all comparisons made were between the groups in the study (and not with the normative group mean), the representativeness of the norms was less critical. Further, age and sex were included as covariates in all analyses. It is also notable that the mean cognitive composite score for the CCs at the first assessment was 52 (ie, close to the normative group mean of T 50 on the individual tests), which indicates a reasonable representativeness of the norms used. The PCS+ group was quite small (n=29), which makes the finding of no differences in cognition between the PCS+ and PCS− group somewhat uncertain. Finally, as with most MTBI studies, a number of factors not controlled for could have affected the results, among them the effects of somatic syndrome disorder, attention seeking, and diagnosis threat.[48] We have, however, no reason to believe that these effects were particularly pronounced in our study.

Conclusions

Lower cognitive reserve, but not PCS diagnosis, was associated with worse cognitive outcome following MTBI. The findings have implications for future research and clinical work. A great amount

of MTBI research is centered on identifying the subgroup of patients with prolonged symptoms, and accounting for the combined effect of MTBI and low cognitive reserve can contribute to a better understanding of the mixed findings in the field. Importantly, lower cognitive functioning should not be attributed solely to difficulties present before the injury. Rather, the synergistic effect of low cognitive reserve and MTBI appears to make persons with low cognitive reserve more vulnerable to reduced cognitive functioning if they sustain an MTBI. Whether this is specific to brain injury, and not trauma in general, has to be further explored.

Supplier

a. Stata 15.1; StataCorp LLC.

Keywords

Brain injuries; Cognitive reserve; Longitudinal studies; Neuropsychology; Post-concussion syndrome; Rehabilitation

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