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Life after Traumatic Brain Injury – cognitive, emotional and behavioural function after moderate and severe traumatic brain injury.

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Å leve med traumatisk hodeskade – kognitiv funksjon og mental helse etter moderat og alvorlig traumatisk hodeskade

Traumatisk hodeskade (traumatic brain injury – TBI) kan oppstå etter trafikkulykker, fallulykker eller slag mot hodet, og regnes blant de fremste årsaksfaktorene til uførhet og død blant unge i industriland. Overlevende etter moderat og alvorlig TBI er en heterogen gruppe, med store variasjoner i funksjon etter skaden. Redusert kognitiv funksjon forekommer ofte. I tillegg kan emosjonelle og atferdsmessige vansker oppstå etter skaden. I noen tilfeller er funksjonsendringen kronisk, i andre tilfeller vil funksjon kunne normalisere seg. Derfor er det viktig for den skadde, de pårørende og for hjelpeapparatet at man så tidlig som mulig kan si noe om hvilke konsekvenser skaden kan medføre. Dette kan også gi en indikasjon på behovet for opptrening og tilrettelegging i tiden etter skaden. Det finnes få prospektive studier hvor kartlegging av kognitiv funksjon og mental helse er fulgt over lengre tid. I tillegg savnes prospektive langtidsstudier hvor sammenhenger mellom tidlige mulige prediktive faktorer og senere kognitiv, emosjonell og atferdsmessig funksjon er kartlagt.

Avhandlingens målsetting var å undersøke ulike følgetilstander etter moderat og alvorlig TBI – særlig kognitiv funksjon og psykisk helse. Prosjektet har fulgt pasienter med moderat og alvorlig TBI ved St. Olavs Hospital fra innleggelse og opp til 5 år etter skaden. Prosjektet har utspring i et større hovedprosjekt, «Hodeskade-prosjektet», som undersøker mange ulike aspekter ved utredning, behandling og forløpsmonitorering etter TBI. Pasienter rekruttert fra «Hodeskade-prosjektet» har blitt kartlagt med nevropsykologiske tester og spørreskjema i forhold til depresjon 3 måneder og ett år etter skade. Som en del av et større oppfølgingsprosjekt, ble pasienter rekruttert fra «Hodeskade-prosjektet» kartlagt på nytt med tester og spørreskjema vedrørende kognitiv, emosjonell og atferdsmessig funksjon 2-5 år etter skaden. På alle undersøkelses-tidspunkt ble de sammenlignet med en kontrollgruppe med samme alders, kjønn og utdannings-sammensetning som TBI-gruppa.

Prosjektet viste redusert kognitiv funksjon 3 måneder etter moderat og alvorlig TBI sammenlignet med friske kontroller. Spesielt framkom redusert tempo ved bearbeiding av informasjon, samt vansker med innlæring og hukommelse av verbal informasjon. Redusert kognitiv funksjon 3 måneder etter TBI var videre assosiert med generelle plager eller funksjonsnedsettelse ett år etter skaden. Ved å differensiere mellom moderat og alvorlig TBI, fant vi store forskjeller i forekomst av kognitiv funksjonsnedsettelse og bedring av kognitiv funksjon i tiden fram til ett år etter skaden. Ett år etter skade hadde personer med moderat TBI fremdeles reduserte kontrollfunksjoner og evne til problemløsning (eksekutive funksjoner), men presterte for øvrig på samme nivå som friske. Personer med alvorlig TBI hadde redusert tempo på motoriske oppgaver og ved bearbeiding av informasjon, samt redusert verbal hukommelse og eksekutiv funksjon. Tempo ved bearbeiding av informasjon, samt visuell hukommelse var de eneste områdene hvor *begge* gruppene viste bedring. Imidlertid fant vi at en del personer med moderat TBI presterte tilnærmet på samme nivå som friske personer på nevropsykologiske tester både 3 måneder og ett år etter TBI. Disse funnene kan indikere at kognitive funksjonsvansker er mindre omfattende etter moderat TBI enn tidligere antatt. Uavhengig av skadens alvorlighet, var eksekutive funksjoner viktig for deres funksjon blant annet i forhold til arbeid, sosiale relasjoner og rapportering av generelle plager.

Sammenlignet med friske, fant vi at personer med moderat og alvorlig TBI i større grad rapporterte eksekutive funksjonsvansker 2-5 år etter skaden – spesielt redusert oppmerksomhetskontroll, arbeidsminne og emosjonell regulering. De rapporterte også i større grad symptomer på depresjon, angst, og aggresjon 2-5 år etter skaden. Forekomst av depressive symptomer det første året etter skade, samt forekomst av diffus aksonal skade på MR-bilder var assosiert med høyere forekomst av rapportert eksekutive, emosjonelle og atferdsmessige vansker 2-5 år etter skaden. Våre funn viser at utvikling av kognitive, emosjonelle og atferdsmessige vansker er et resultat av et samspill mellom demografiske, nevropatologiske og psykologiske faktorer etter TBI, og kan best forstås i lys av en biopsykososial forståelses-modell. Studien understreker også viktigheten av tidlig MR, samt gjentatt screening av kognitive og emosjonelle vansker for å kunne oppdage personer med høy risiko for utvikling av senere plager. Dette vil også kunne ha konsekvenser for behandling og videre pasientforløp på lang sikt.

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Table of Contents

List of papers

The thesis is based on the following papers which are referred to by their Roman numbers I-III

Paper I

Skandsen T, Finnanger TG, Andersson S, Lydersen S, Brunner JF, Vik A. Cognitive Impairment 3 months after moderate to severe traumatic brain injury: a prospective follow-up study. Archives of Physical Medicine and Rehabilitation 2010; 19; 12; 1904-1913.

Paper II

Finnanger TG, Skandsen T, Andersson S, Lydersen S, Vik A, Indredavik MSI. Differentiated patterns of cognitive impairment 12 months after severe and moderate traumatic brain injury. Brain Injury 2013,27(13-14):1606-16

Paper III

Finnanger TG, Olsen A, Skandsen T, Lydersen S, Vik A, Evensen KAI, Håberg AK, Andersson S, Indredavik MS. Self-reported executive, emotional and behavioural function 2-5 years after moderate and severe traumatic brain injury – a prospective follow-up study.

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ASEBA	Achenbach System of Empirically Based Assessment
ASR	Adult Self-Report
BDI	Beck Depression Inventory
BRI	Behaviour Regulation Index
BRIEF-A	Behaviour Rating Inventory of Executive Function – Adult
CI	confidence interval
CFT	Complex Figure Test
CPT	Continuous Performance Test
CT	computed tomography
CVLT	California Verbal Learning Test
CVMT	Continuous Visual Memory Test
CWIT	Colour-Word Interference Test
DAI	diffuse axonal injury
D-KEFS	Delis-Kaplan Executive Function System
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
FLAIR	fluid-attenuated inversion recovery
GAD	generalized anxiety disorder
GCS	Glasgow Coma Scale
GEC	Global Executive Composite
GOSE	Glasgow Outcome Scale Extended
HI	Head Injury
HISS	Head Injury Severity Scale
IQ	intelligence quotient
MI	Metacognitive Index
MRI	magnetic resonance imaging
PTA	post-traumatic amnesia
PTSD	post-traumatic stress disorder
SD	standard deviation

SDMT	Symbol Digit Modality Test
TAI	traumatic axonal injury
TBI	traumatic brain injury
TMT	Trail Making Test
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbriviated Scales of Intelligence
WCST	Wisconsin Card Sorting Test

Clarifications

Within the larger Head Injury Project the candidate has contributed substantially with the selection of neuropsychological tests and questionnaires applied, has contributed to the recruitment of the patients and the control groups, contributed to both neuropsychological and outcome assessment, as well as collection, analyses and interpretation of the neuropsychological and self-report data. For paper I the candidate has in collaboration with the first author contributed in all phases of writing and revision of the article. As first author for paper II and III the candidate has been main responsible for the writing process and revised according to reviews from the co-authors.

I would further like to clarify the literature and terms used in this thesis.

The study was initiated in 2004, and outcome measures were selected in accordance with the literature available at that time. In addition, Paper I was written in 2010 and Paper II was written in 2012, and their respective findings were therefore discussed in light of then-contemporary research. In this thesis, an attempt was made to review more recent literature in order to provide more up-to-date information. Hence, recent literature is described in Section 1 and discussed in Section 5 when relevant and appropriate.

Furthermore, since the beginning of this study there has been a shift toward referring to traumatic diffuse axonal injury as TAI rather than DAI. Therefore, these abbreviations should be considered to describe the same phenomenon. However, as DAI was used in Papers I and II, this abbreviation will be used throughout the thesis. The only exception is in Paper III, which used the abbreviation TAI when it was submitted.

Summary

Traumatic brain injury (TBI) may occur after motor vehicle accidents, falls, or blows to the head. TBI may be classified as mild, moderate or severe depending on a number of factors, but primarily by level of consciousness after the trauma. Survivors after moderate and severe TBI comprise a heterogeneous group with great variability in terms of reduced function. They often experience impairments across a range of cognitive abilities, some of which may become chronic. In addition, secondary symptoms of emotional and behavioural problems may develop over time after the injury. Furthermore, all of these problems may affect the ability to resume work and engage in social activities; they may also affect the relationship to family and friends. There are few prospective studies examining cognitive, emotional, and behavioural function over a significant period of time. In addition, prospective studies on predictors of and associates to long-term cognitive, emotional, and behavioural function are still warranted.

The main objective was to describe cognitive, emotional, and behavioural problems at several time points after TBI with emphasis on the long-term perspective. In addition, we wished to explore a broad array of demographic and injury-related factors hypothesized to be associated with cognitive, emotional, and behavioural outcomes after TBI.

The study includes patients admitted to St. Olav's Hospital, Trondheim University Hospital with moderate and severe TBI, from acute care to 5 years post-injury. It is part of a larger project, "The Head Injury Project", which studies several aspects of the assessment, treatment, and clinical management of patients with TBI. The participants in the present study were recruited from the database of the "Head Injury Project". Two overlapping but not identical populations (injured 2004-2007) and one extended population (injured 2004-2008) were included. Injury severity and level of consciousness were monitored and registered for all participants, and examination with MRI was performed within 4 weeks post-injury. At 3 months (n=61) and 12 months (n=50) post-injury, participants aged 15-65 years at the time of injury were assessed with neuropsychological tests and completed a questionnaire reporting symptoms of depression. The extended population (n=67) completed questionnaires concerning cognitive, emotional, and behavioural function 2-5 years post-injury. The results were compared with those of a control group consisting of healthy people matched by age, gender, and education.

Our study demonstrated that differentiating between individuals with moderate and severe TBI revealed important differences regarding which cognitive functions were affected and the degree of cognitive impairment at 3 and 12 months post-injury; it also yielded a more nuanced description of cognitive deficits and their improvement over time. Cognitive function was affected by both moderate and severe TBI at 3 and

12 months post-injury, and was associated with global outcome 12 months post-injury. The groups differed regarding which cognitive functions improved from 3 to 12 months post-injury; only processing speed and visual memory improved for both groups. At 12 months post-injury, individuals with severe TBI exhibited reduced motor function, processing speed, verbal memory, and executive function. However, only executive function was reduced among patients with moderate TBI compared with healthy controls. Nevertheless, a larger proportion of individuals with moderate TBI had low scores (-1.5 SD below normative average) on tests that assessed executive function and processing speed at 12 months post-injury. Still, a significant proportion of individuals with moderate TBI exhibited normal performance on most neuropsychological tests at both 3 and 12 months post-injury – a finding that lends strength to previously raised concerns that cognitive problems after moderate TBI may be overestimated. Furthermore, executive function appears to be important for patients' ability to resume independent living, employment, and leisure activities regardless of injury severity.

Persons with moderate and severe TBI reported more pronounced difficulties in aspects of executive functions related to attentional control, working memory and emotional regulation, as well as emotional and behavioural problems related to symptoms of depression, anxiety, and aggression 2-5 years post injury compared to healthy controls. Reported symptoms of depression during the first year after injury and detection of traumatic diffuse axonal injury (DAI) on early MRI were important predictors of later self-reported executive, emotional, and behavioural problems. Our findings indicate interplay between demographic, neuropathological, and psychological factors during the development of self-reported executive, emotional, and behavioural problems for years after TBI. As such, outcomes after moderate and severe TBI are best understood within the frame of a biopsychosocial model. Hence, early radiological examination and repeated psychological evaluations screening for cognitive and emotional problems may provide clues to which patients may be at risk, and assist with the making of clinical decisions regarding long-term follow-up.

Chapter 1: General Introduction

1.1 Traumatic Brain Injury

At least once a week on average, Norwegian newspapers report incidents in which people have sustained damage caused by traffic accidents, falls during work-related or recreational activity, or violence. For instance,

Johnny, a boy aged 16 training to become a carpenter, is involved in a traffic accident when driving home on his motorcycle. He is unconscious and observed to have multiple fractures. An ambulance helicopter transports him quickly to the nearest Level 1 trauma centre. Or Nina, a well-educated female of 41, loses control of her bicycle on a steep downhill track during her daily exercise. She is initially unconscious, then confused upon recovery. Because of a broken arm and the confusion, she is transported to the hospital for examination. The newspaper reports that Johnny has sustained a severe head injury, and his condition remains unstable. On the other hand, Nina is reported to be in stable condition, but in need of continued observation by health care personnel.

And there the stories end in the news. But what awaits Johnny and Nina in the future?

The focus of this thesis is how the lives of individuals with traumatic brain injury (TBI) are affected by their injury. Worldwide, the incidence rates of TBI are in the range of 200–300 per 100,000, with one peak occurring during late adolescence and a second peak during elderly age.(1) Incidence rates for males are at least twice that for females. European estimates of the number of people hospitalized for or dying from TBI are approximately 235 per 100,000.(2) In Norway, the incidence of severe TBI was 5.2 per 100,000 in 2009.(3) TBI is among the leading causes of mortality and disability among young individuals in high-income countries, and the World Health Organization (WHO) has projected that by 2020, traffic accidents will be the third greatest cause of the global burden of disease and injury.(1, 2, 4)

1.1.1 Definition of TBI

In their review of moderate and severe TBI in adults, Maas et al. defined TBI as “a heterogeneous disorder with different forms of presentation. The unifying factor is

that brain damage results from external forces, as a consequence of direct impact, rapid acceleration or deceleration, a penetrating object (e.g., gunshot), or blast waves from an explosion."(4) The definition of injury to the head has not always been consistent in the research literature. Sometimes the term Head Injury (HI) has been used synonymously with the term Traumatic Brain Injury (TBI). While the term TBI clearly indicates neuronal damage in the brain, the term Head Injury also includes injuries that do not lead to brain damage (minimal HI) — as opposed to Extracranial Injury, which may include limb fractures, damage to internal organs, and so forth. As this thesis focuses on moderate to severe injuries, the terms HI and TBI may be used interchangeably. However, the term TBI will be used throughout the rest of this text.

1.1.2 Classification of TBI

Classification of the injury is important for treatment planning, communication among healthcare personnel, organization of research, and prognosis. TBI may be classified by mechanisms of injury and assessment of structural damage, as well as by clinical severity.(4)

1.1.2.1 Neuropathology

Neuropathological descriptions comprise one way of classifying TBI.(4) The nature, intensity, direction, and duration of the mechanical forces to the head determine the extent of the damage to the brain. TBI in humans is heterogeneous, reflecting various pathologies in differing proportions.(5) The injuries observed after TBI are typically referred to as *focal* and *diffuse* injuries, although both types often occur in coexistence in moderate and severe TBI.(6) Damage caused by the mechanical forces during the accident is referred to as *primary damage* (contusions, diffuse axonal injury, intracerebral haemorrhage, and extracerebral haemorrhage).(5, 6) These injuries may initiate further pathophysiological mechanisms that result in *secondary damage*, which may evolve over time and occur widespread throughout the brain.(4) The secondary mechanisms often occur simultaneously and with synergistic effects, including excessive neurotransmitter release, metabolic disruption, membrane dysfunction, inflammatory responses, gene activation, and the generation of free radicals.(4, 6, 7)

Focal injury includes contusions, haematomas, and mass lesion formations that are typically found in grey matter or in the interface between grey and white matter.(6) Focal contusional damage is mainly found in the ventral and polar frontal lobe regions.(8) Haemorrhagic lesions contribute to local neuron destruction and ischemia.(6) The initial injury is followed by impaired cerebral blood flow (CBF) regulation and metabolic changes, which may eventually lead to the necrotic and apoptotic neuronal cell death that are often observed in and around the contusion.(6, 7, 9)

Diffuse injury includes diffuse axonal injury (DAI), hypoxia, and damages due to brain swelling.(5) DAI is the result of rotational and rapid acceleration/deceleration forces,(4, 10, 11) and has been identified as widespread damage to the axons of the parasagittal white matter of the cerebral cortex, the corpus callosum, and in the interface between grey and white matter in the cerebral cortex and the brainstem.(8, 10) It was initially believed that DAI was caused by shearing of the axons.(5, 12) However, such primary axonal shearing is rare.(11) Povlishock et al.(6) have proposed that DAI is the result of focal alteration of the axolemma, which is followed by secondary changes such as the breaking of axonal microtubules that obstructs axonal transport and subsequently lead to a local swelling of the axon prior to its eventual detachment from its downstream segment, followed in turn by Wallerian degeneration.(6, 11, 13) While this process has been thought to occur during the acute and subacute period, axonal degeneration has been identified in human brain material for years following injury, suggesting TBI may precipitate a progressive, long-term neurodegenerative process.(14) Although myelinated fibres have been most prone to DAI,(11) axonal damage has also been demonstrated in unmyelinated fibres.(15, 16)

Adams et al. developed a grading system for DAI based on the extent and distribution of pathology, in which most of the damage was only identifiable microscopically.(11, 17, 18) DAI grade 1 was defined as microscopic change in white matter in the cerebral hemispheres, corpus callosum, brainstem, and cerebellum; DAI grade 2 was defined as focal lesions in the corpus callosum in addition to grade 1 damage; and DAI grade 3 was defined as focal lesion in the

brainstem in addition to grade 2 damage. Other fields where widespread white matter damage could be found have adopted the term DAI. In an effort to underscore the etiology of the axonal injury in TBI, terms such as "diffuse traumatic axonal injury (dTAI)" or "traumatic axonal injury (TAI)" have been proposed and increasingly used.(11) In this text the terms DAI and TAI refer to the same phenomenon and the term DAI will be used throughout.

1.1.2.2 Imaging and DAI

In vivo detection of DAI has proven to be challenging; however, increasing evidence suggests that novel advanced neuroimaging techniques may be useful for detecting DAI in vivo.(6, 10, 19, 20) DAI is detected as white matter hyperintensities or microhaemorrhages on in vivo magnetic resonance imaging (MRI).(18, 21) While computed tomography (CT) scans are important during the acute phase, the sensitivity of CT is limited when it comes to detecting DAI. The lesions detected on CT often represent only the "tip of the iceberg", as illustrated in Figure 1. Due to the microscopic changes in the brain, only minimal changes are noted on CT.(10, 20, 22) Different MRI sequences are superior to CT in the detection of DAI.(20, 23) Diffusion tensor imaging (DTI) has emerged as a more promising technique that assesses white matter integrity by measuring the anisotropic diffusion of water molecules.(22, 24-26) However, DTI is not yet applicable in the clinic, as normative data is not yet sufficiently developed for diagnostic use in individual patients. Clinical MRI scanning protocols recommended to detect DAI typically include T2 sequences such as conventional T2-weighted imaging (T2WI), fluid-attenuated inversion recovery (FLAIR), T2*-gradient recalled echo (T2*-GRE), and susceptibility-weighted imaging (SWI).(27, 28) T2*-GRE reportedly have higher inter-rater reliability and better sensitivity in detecting microscopic haemorrhagic lesions compared with FLAIR and T2WI,(27) while FLAIR appears to be good at detecting non-haemorrhagic lesions. Recent literature has observed that performing early MRI is important because the number and volume of the lesions reduces over time, which increases the risk of underestimating the extent of the damage.(29)

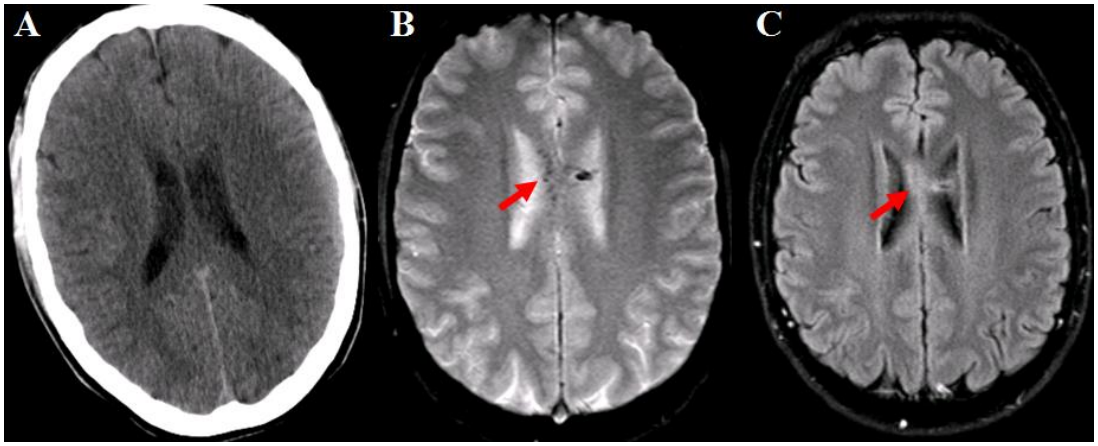

Figure 1
Illustration of the differential sensitivity of different imaging techniques. The patient was registered with GCS score 9 upon hospital admission. The admission CT (A) did not reveal any parenchymal injuries to the brain. However, the conventional 1.5 T MRI showed multiple microhaemorrhages in the corpus callosum in the T2*GRE image (B) and a confluent lesion in the corresponding area in the FLAIR image (C).

1.1.2.3 Clinical severity

TBI may also be classified by clinical injury severity.(4) In 1974, the Glasgow Coma Scale (GCS) was developed to assess alterations in consciousness or depth of coma.(30) Since then, the GCS has been widely used and has been incorporated into most scales that assess clinical injury severity.(31) Standardized assessment and observation of the patient's motor responses, verbal responses, and eye opening after various types of stimulation are recorded on a rating scale ranging from 3 to 15. Originally, GSC scores ranging from 3 to 8 indicated severe injury, 9 to 12 indicated moderate injury, and 13 to 15 indicated mild injury.(30) However, patients with a GCS score of 13 have been found to have a higher risk of subsequent complications such as intracranial haematoma, intracranial lesions on CT scans, and neurosurgical treatment compared with patients with GCS scores of 14-15. Furthermore, these characteristics more closely resemble patients with GCS scores of 9-12.(4, 32, 33) As a result, it has been proposed that patients with a GCS score of 13 should be classified with moderate TBI.(31, 33, 34)

Loss of consciousness (LoC) lasting >30 min or post-traumatic amnesia (PTA) lasting >24 h constitute additional criteria for classifying an injury as moderate rather than mild.(34, 35) However, the Scandinavian guidelines for management of head

injury categorize an injury as moderate if LoC lasts ≥5 min.(36) Table 1 illustrates clinical indices of injury severity according to the Scandinavian guidelines.

Table 1 Classification of injury severity according to the Scandinavian guidelines.

Clinical measures	Mild TBI	Moderate TBI	Severe TBI
GCS Score	13[1]-15	9-12, 13[2]	3-8
Duration of PTA	<24	1-7 days	> 7 days
Duration of LoC	< 5 min[3]	≥ 5 min to 36 h[3]	> 36 h

[1]If LoC < 5 minutes, no complications
[2] If LoC ≥ 5 minutes, or with complications
[3]Adapted from Stein & Spettell (31); Ingebrigtsen et al (36)

1.1.3 Phases of clinical recovery – disorders of consciousness

After the injury, patients with TBI go through a pattern of recovery that occurs in a similar fashion across the spectrum of severity – unconsciousness, then PTA, followed by a phase during which cognitive functions gradually improve (chronic phase).(6, 37) The durations of the respective phases vary; they can last for seconds, days, months, or even years depending on the severity of the injury. Patients enter the phase of *unconsciousness* immediately after the injury. This phase incorporates three mental states or disorders of consciousness: coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS),(38) and minimal conscious state (MCS).(39) Although patients usually enter coma for a brief or prolonged period of time, subsequent paths can differ. Some patients may emerge from coma and suddenly be able to open their eyes, start to breathe unaided, and exhibit spontaneous or stimulus-induced movements (reflex or automatic movements).(40) While this state has historically been referred to as permanent or pervasive vegetative state (VS), the term unresponsive wakefulness syndrome (UWS) has recently been proposed instead.(38) This proposed change in the lexicon is mainly because of the negative connotation and associations connected to the term vegetative state among the lay public and media.(38)

Patients may enter the minimal conscious state (MCS) directly from coma, or after UWS.(39) MCS is distinguishable from coma and UWS by limited but clearly discernible evidence of self-awareness or environmental awareness; partial preservation of consciousness; and some preserved but inconsistent motor, sensory, and communicative function.(39) However, patients in MCS may not be able to

exhibit fully functional use of objects or communicative skills. Although the prognosis has been dim, recent research has indicated that a substantial proportion of patients with prolonged disorders of consciousness recover to independent functioning 4 to 5 years post-injury.(41, 42)

When emerging into PTA, patients enter the second phase of clinical recovery.(6, 39, 43) In PTA, patients are awake and have regained some awareness of themselves; however, they still have some form of altered consciousness characterized by confusion, amnesia for ongoing events, and often suffer from behavioural agitation.(44) Patients may recover from coma or MCS directly into PTA.(39) Figure 2 illustrates the clinical course of recovery through the various phases of consciousness.

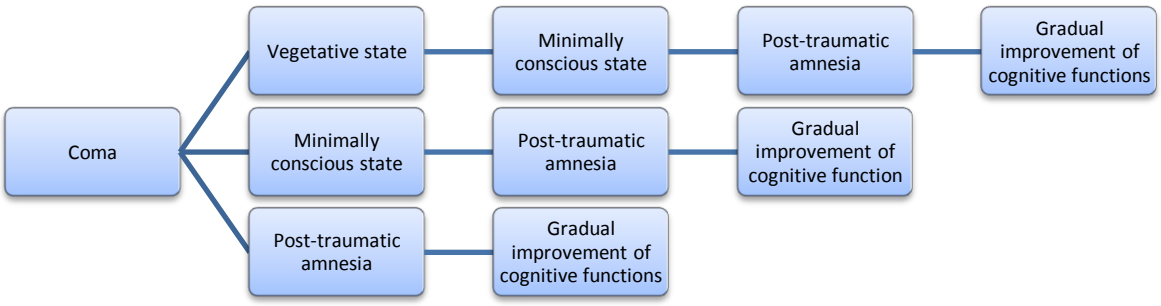

Figure 2 Visualization of the clinical phases during recovery

Most recently, research on PTA has focused on confusion and amnesia.(45) Assessing the duration of PTA has been challenging, and a host of inventories exist for assessing PTA and its duration.(45, 46) These inventories differ regarding which aspect of PTA is their main focus, and the clinical determination of resolution of PTA may depend on which inventory is used.(47) Some have considered the disappearance of confusion to be an indicator of resolution of PTA.(48) During the confusion phase, patients have problems with both temporal and spatial orientation, as well as with the processing of complex perceptual stimuli.(45, 49) Additionally,

communication may be meaningless and include perseveration for common phrases.(45, 49) Following this, many inventories today focus more on temporal and personal orientation and less on spatial orientation, which may resolve earlier in recovery.(45, 48) Another definition of the state PTA is as the period of time when the patient is unable to reliably remember day-to-day events (50) (i.e., to consolidate episodic memories).(51) Hence, some might argue that lack of orientation can be conceptualized as a disruption of access to and retrieval of autobiographical memories, problems with consolidating new memories, and difficulties updating memory.(51) The memory problems displayed during PTA constitute both anterograde and retrograde amnesia,(45) problems with new learning, and increased rate of forgetting.(45, 52)

Typically, the pattern of recovery is a gradual progression in which patients first regain orientation/memory of items related to themselves (date of birth, occupation, relations), followed by place and time.(53) New learning and free recall are typically among the last to recover.(43, 51) Other cognitive processes such as attention, working memory, and executive function are also affected during PTA.(45, 46) Recovery of attentional processes predates recovery of free recall and recovery of working memory processes.(43) Simple reaction time and speed of processing are suggested to differentiate between patients with and those without PTA particularly well.(54) It has been argued that disruption of attentional processes preclude new learning and recall.(43, 46) This discussion has led to the proposition that PTA should be relabelled as a posttraumatic confusional state (PCS).(43) Stuss et al. argue that "a confusional state can be defined as a transient organic mental syndrome with acute onset characterized by a global impairment of cognitive functions with a concurrent disturbance of consciousness, attentional abnormalities, reduced or increased psychomotor activity, and a disrupted sleep/wake cycle".(43) Although this position has been supported by many, the term PTA is so ingrained in clinical practice that its use will most likely continue in the future.(45)

In summary, there is a lack of consistent definition of PTA. However, it is generally recognized that any assessment of PTA should include assessments of both orientation and new learning.(45, 47, 49, 51, 54) In addition, it has been

recommended that future inventories also consist of measurements of deficits in judgment, insight, and attention, as well as agitation, retrograde amnesia, and anterograde amnesia.(45) One challenge when assessing duration of PTA is the need to determine whether the neuropsychological difficulties displayed by the patient are due to PTA or reflect chronic cognitive problems caused by the brain injury – the third clinical phase in which chronic cognitive impairments and recovery take place.

1.2 Cognitive function after TBI

Persons with TBI enter the third clinical phase as PTA resolves. Chronic cognitive dysfunction may emerge during this phase, and is common after moderate and severe TBI.(55, 56) TBI has been demonstrated to affect sensory-motor function,(57, 58) processing speed,(59-61) attention,(59, 61) working memory,(62) memory,(63) and executive function.(61) In addition, neurocognitive impairments after TBI have been demonstrated to have profound effects on the person's ability to resume occupational, social, and daily-living skills.(64-66) The following sections review the literature on cognitive function after TBI, beginning with basic functions including sensory/motor functions and progressing toward higher-level cognitive functions.

1.2.1 Sensorimotor function

Motor deficits after TBI are caused by a disruption in the complex system of neural networks, originating in the cortex and terminating in skeletal muscle. This network includes the association cortex, sensorimotor cortex, subcortical pathways and nuclei (including thalamus, basal ganglia, striatum, substantia nigra, and nucleus accumbens), cerebellum, and brainstem, which compute and integrate neural activity to send a signal through the spinal cord to coordinate movement. Gross motor dysfunction occurs in particular after severe TBI.(57) Most of these functions usually recover with time.(41, 42) Disruptions of fine motor skills are also common after moderate TBI.(67) However, there are very few purely fine motor behavioural tasks, and deficits caused by TBI often result from the disruption of complex motor pathways and sensorimotor integration; therefore, most of the commonly used neuropsychological tests are sensorimotor in nature. Most such tests are also timed,

which complicates the interpretation of low scores because they are affected by each individual's processing speed.(56)

1.2.2 Processing speed

Processing speed has been defined as either the amount of time it takes to process a predetermined amount of information, or the volume of information that can be processed within a prescribed amount of time.(68) Deficits in information processing speed have been amply demonstrated after TBI.(55, 60, 69-71) Reduced processing speed has been considered the result of deficits of information transfer owing to the disruption of white matter tracts.(60) The diffuse damage of white matter tracts may lead to reduced interconnectivity between networks, resulting in a generalized slowing of cognitive processing.(56, 69, 72) Two main assessment approaches have been used: reaction time (RT) paradigms,(60, 73) and timed psychomotor tasks such as the Trail Making Test A (TMT A), Symbol Digit Modality Test (SDMT), processing speed index on the Wechsler Adult Intelligence Scale – III/IV (WAIS III/WAIS IV), or Stroop reading task.(69, 74, 75) The former approach claims to assess basic, generalized slowing in information processing,(76) which underlies and accounts for the reduced processing speed observed among persons with TBI during the more complex tasks applied within the latter approach.(69) Studies controlling for basic processing speed have failed to find reduced function with respect to several aspects of attention after TBI.(69, 70, 77) However, there is a continuous debate regarding whether performance on the complex tests reflects processing speed or attention deficits.(59)

1.2.3 Attention

Individuals with TBI frequently report problems with concentration, being distractible, being forgetful, and struggling with doing more than one thing at a time. All these symptoms might be related to the broad concept of attention. Some of the first models of attention focused on limitations in early information processing (e.g., Broadbent).(78) However, although it was previously considered a single concept, most models and theories of attention today acknowledge that attention incorporates several concepts.(79-82) Some models derived from the use of neuropsychological tests in clinical work with patients with TBI have listed five attentional processes with corresponding neuropsychological tests: Focused attention (response to discrete

visual/auditory/tactile stimuli), Sustained attention (vigilance and working memory), Selective attention (ability to ignore irrelevant or distracting stimuli), Alternating attention (set shifting, mental flexibility), and Divided attention (respond to multiple, simultaneous tasks).(79, 80) Other models suggest three attentional networks: an alerting network (which maintains optimal vigilance), an orienting network (which prioritizes and follows sensory input), and an executive network/attentional network (which is instrumental in regulation and control). Some of these derive from more or less independent but interacting neural network.(78, 81) With such widespread neural networks regulating attention function, the high prevalence of DAI after TBI is hypothesized to precipitate the attentional problems that occur after TBI.

Previous studies have found that selective impairment of attention emerges as severity of the TBI increases, and that patients with TBI had impairments on several tests of attention for as long as 1 year and 3-5 years after injury.(83, 84) However, the many and somewhat overlapping conceptualizations of the attentional processes make this field confusing.(78, 85) In addition, a wide variety of tests have been used to measure the different aspects of attention, making it difficult to directly compare the findings of numerous studies even when they are examining the same aspect of attention.(59) Large and significant effect sizes among patients with severe TBI have been reported by a meta-analytic review of tests of focused and selective attention, including the Stroop Test (speed and accuracy scores of the Word Reading, Colour Naming, and Interference subtests), the Symbol Digit Modalities Test (accuracy scores for the oral and written versions) and the Digit Symbol Test (accuracy score), an Inhibition Task (speed scores from the control and interference conditions), and the Trail Making Test (speed scores for Parts A and B, and ratio A:B).(59) More moderate effect sizes were observed on tests of divided attention assessed with a reaction time (RT) measure under dual task conditions or the Paced Auditory Serial Addition Test (PASAT); the effect sizes observed with these tests were also smaller than effect sizes associated with tests of simple RT Tests of sustained attention (visual search or cancellation tests) provided large effect sizes, while tests of attentional control provided only small effect sizes.(59) As a result, it has been recommended that a broad variety of measures (including self-report inventories) be used to assess attentional function.(79)

1.2.4 Working memory

Impaired working memory for years after injury has been demonstrated among people who have sustained TBI.(67, 83, 86) Although it is commonly referred to as a single concept, the influential model by Baddeley and Hitch(87) refers to working memory as a "broad framework of interacting processes that involve the temporary storage and manipulation of information in the service of performing complex cognitive activities".(88) Their model describes working memory composed by the overall Central Executive with three subsidiary systems: the Visuo-spatial Sketchpad, the Phonological Loop, and the Episodic Buffer.(89) However, some refer to working memory as short-term memory (the activated part of long-term memory) and the processing mechanisms that help to make use of short-term memory.(90) Others reserve the term *working memory* to refer only to the attention-related aspects of short-term memory — particularly attentional control.(91) Tests of memory span could be said to assess the subsidiary systems in Baddeley's model (63); however, they also evaluate short-term memory and attentional capacity.(56) Forward memory span appears to be resistant to the effects of TBI,(56, 63, 67) while tasks that require the manipulation of stimuli (e.g., backward span, n-back tests) that relates to the executive component of working memory appear to be more sensitive to the effects of TBI.(63, 67, 83) In particular, lesions in the dorsolateral prefrontal cortex (DLPFC) have been associated with impairment of working memory function,(92) which may be important for cognitive control.(93)

1.2.5 Memory

Non-declarative (implicit) memory, such as procedural memory and priming, is usually minimally affected by moderate and severe TBI in adults.(63, 94) However; this is true only when based on reactivation of pre-existing knowledge. This is not the case when implicit memory is dependent on forming new associations.(95) Declarative or explicit memory functions such as short-term memory (memory span) also appear to be largely unaffected by TBI.(63) However, impaired declarative long-term memory has been one of the most consistent cognitive impairments after TBI.(55, 63, 83, 84) Encoding of declarative memory seems to involve structures in the DLPFC and in the medial-temporal lobe (MTL),(96, 97) with the left hemisphere particularly involved in the encoding of verbal material.(98) Consolidation of

memory involves structures in the MTL, including the hippocampus,(97) while memory storage appears to occur in the neocortex.(99) However, DAI may also play a role in memory deficits caused by reduced connectivity in the neural networks that support memory function.(100) Nevertheless, all of these structures are commonly affected to varying degrees by the neuropathological processes after moderate and severe TBI(6); broad assessment of memory impairments is required after TBI.

The processes of declarative memory can be divided into encoding, consolidation, and retrieval. Overall, TBI seems to affect encoding (e.g., learning-rate (101) and encoding strategies (102)), as well as consolidation (103) and retrieval.(104) In particular, encoding deficits affect the ability of persons with TBI to retrieve verbal material.(102) Encoding strategies have been found to affect the success of later retrieval.(105) While some studies have found evidence of steeper forgetting rate after TBI,(106) it has been argued that this is mainly due to deficits in encoding strategies.(101, 102) While some studies indicate impairment in specific memory processes,(102) others lean toward a more global memory impairment after TBI.(63) The effects of TBI on declarative verbal memory have often been assessed with the learning of word lists assumed to reflect encoding (the sum of recall across learning trials, increase in recall across learning trials), consolidation (recall difference between the last learning trial and a delayed recall trial), proactive interference, and retrieval (recognition-recall discrepancies).(56, 102) Although impairments in *visual* memory have been demonstrated,(63, 107) the methods of assessment have varied greatly and additional research is needed in this field.(63)

1.2.6 Executive function

Reduced executive function is commonly reported after moderate to severe TBI,(55) and also affects the ability to resume education, employment, and independent living.(65) The concept of executive function refers to all higher level functions related to goal-directed regulation and control of thoughts, actions, and emotions.(108) Although this overarching conceptualization of executive function is generally agreed upon, the operationalization and subcomponents included in this broader concept vary according to different models and theoretical perspectives. Some believe that the subcomponents are related yet distinct abilities that provide for

intentional, goal-directed, problem-solving action,(108, 109) and that it may not be possible to divide the central executive function beyond the overarching concept.(110) Others argue for varying degrees of subdivision.(108, 109, 111, 112) Executive function is also important for the control and regulation of other basic, domain-specific, cognitive functions such as attention, language, visuospatial skills, motor skills, and various memory functions (learning, short-term memory, and working memory) in the service of reaching an intended goal.(111)

The proposed subcomponents of executive function include but are not restricted to: holding information in mind while actively processing new information, problem solving, anticipation, goal selection, planning, monitoring, judgment, self-awareness, decision making, initiating behaviour, inhibiting competing actions or stimuli, shifting problem-solving strategies flexibly when necessary, and monitoring and evaluating one's own behaviour. Executive function also relates to emotional and behavioural control. However, typically only the executive subcomponents *updating* (constant monitoring and rapid addition/deletion of working memory contents), *shifting* (switching flexibly between tasks or mental sets), and *inhibition* (deliberate overriding of dominant responses) are assessed.(113, 114)

Executive function has been associated with several cortical and subcortical brain regions in the frontal lobes, and relies upon complex network interactions between these anatomical areas.(93, 111) Damage to the DLPFC and dorso-medial frontal cortex (DMFC) have been demonstrated to affect the processes of cognitive control and regulation: initiation and sustenance of responses, task-setting, and monitoring.(93) However, problems with emotional and behavioural regulation have been linked to damage to the ventromedial prefrontal cortex. In addition, impaired ability to integrate and coordinate more basic cognitive functions has been related to lesions in the frontal poles of the brain.(93) TBI, and especially DAI, typically causes widespread damage localized in fronto-temporal and subcortical structures.(8) Therefore, executive function may also be vulnerable to DAI.(115, 116) Taken together, assessing executive function after moderate to severe TBI requires broad assessment, often using multiple sources of information (i.e., neuropsychological tests, laboratory tests, and questionnaires).(108, 113)

1.2.7 Improvement after TBI

Cognitive recovery varies according to time since the injury; the most accelerated recovery takes place during the first 6 months post-injury, with more attenuated recovery after that.(117) Cognitive improvement over time may also differ according to the severity of the injury.(55) Although there is firm evidence that severe TBI significantly affects cognitive function more than 6 months post-injury, the evidence is less clear for patients with moderate TBI.(55) Some studies indicate that patients with moderate TBI perform significantly better than those with severe TBI on tests of memory (118-120) and executive function at 1 year post-injury.(121) Furthermore, Dikmen et al (84) observed greater improvement from 1 to 12 months post-injury among patients with longer duration of coma. However, few other studies have compared improvement trajectories for patients grouped according to injury severity. In addition, the cognitive domains have dissimilar recovery trajectories.(67, 83, 117, 122, 123) Memory, verbal abstraction, and timed tests of executive function exhibit steeper recovery between 2 and 5 months post-injury, with some indication that visual skills improve most in the months after that.(117) However, most previous prospective longitudinal studies examining these issues have used only a few tests.(86) There is need to evaluate cognitive improvement with larger battery of neuropsychological tests in future studies.

1.2.8 Neuropsychological assessment – challenges

Taken together, there are various challenges when capturing cognitive dysfunction in the course of TBI: the lack of clarity regarding definitions of the various cognitive functions, the use of a variety of neuropsychological tests across studies, variation across studies in the interpretation of what these tests measure, and the fact that no neuropsychological test commonly used in the clinic today measure “pure” cognitive functions. This makes comparisons across studies difficult. Furthermore, examining recovery of cognitive function also demands the use of tests that are less sensitive to re-test effects, which restricts the number of usable tests. In an attempt to remedy these complications, recommendations of common outcome measures of cognitive function after TBI have been developed.(75) However, cultural adaptations must still be applied because of the lack of proper translations and culturally applicable norms. Hence, comparisons to healthy control groups are needed.

In addition, the interpretation of performance on neuropsychological tests after TBI is often based on comparisons with normative data.(118, 124) While some tests that employ Anglo-American norms may be applicable in Norway,(125-127) others may not. Even if control groups are used, comparing group averages may not fully describe the large variance in neuropsychological performance that is commonly observed among patients with TBI. Therefore, detecting impaired performances may be a complementary approach to describing this patient group. However, there is no general agreement on the definition or criteria for impairment.(128) Also, healthy individuals can also exhibit "impaired" performances, to some extent.(128, 129) Further complicating the matter, patients with high intellectual ability may not be classified as impaired using only standard normative samples, despite reduced cognitive functioning compared with their cognitive capacity prior to the injury.(130-132)

Historically, clinical neuropsychological tests were used to assist in the localization and diagnosis of brain pathology.(111) The introduction of the psychometric approach through the development of intelligence testing shifted focus towards operationalization and the measurement of cognitive functions with continuously distributed variables, with comparison to normative samples.(111) This shift allowed for assessing variability in cognitive function in the individual, as well as monitoring cognitive recovery or decline over time.(111) With the development of imaging techniques, the scope of neuropsychology has broadened to make inferences about everyday behaviour — using the same tests developed to detect brain dysfunction.(133) The degree to which test performance corresponds to real world performance is referred to as *ecological validity*.(133, 134) Two approaches have been made to address the problem of ecological validity. One approach is *veridicality* — evaluating the predictive value of neuropsychological tests: how performances on traditional neuropsychological tests are empirically related to measures of real-world functioning, such as employment status, questionnaires, or clinician ratings. The second approach is *verisimilitude* — developing new assessment inventories that simulate critical everyday cognitive tasks and are better able to capture the essence of

everyday cognitive skills.(133) Both methods are recommended in the evaluation of post-TBI effects.(133)

1.2.9 Self-reported executive function

Several questionnaires and rating scales have been developed to assess behavioural changes after damage to the frontal lobes. Some of the most used scales with research that supports their validity and utility are the Behaviour Rating Inventory of Executive Functions (BRIEF), the Dysexecutive Questionnaire (DEX), the Frontal Systems Behaviour Scale (FrSBe), the Frontal Behavioural Inventory (FBI), the Neuropsychiatric Inventory (NPI), and the Iowa Rating Scales of Personality Change (IRSPC).(135) However, each of these questionnaires categorizes executive function differently, with more or less specific functions denoted. Generally, although persons with TBI report significantly higher levels of executive problems,(135-139) group averages are noted to be within the normative average.(138, 140) Nevertheless, one study found that 26.6% reported problems with planning and organizing within the clinically impaired range assessed by BRIEF-A approximately 1 year after moderate and severe TBI, while their families reported problems with task monitoring, shift/flexibility, and inhibition in the clinical range (30%, 26.6%, and 23.6%, respectively).(138) Furthermore, while the FrSBe categorizes executive function into apathy, disinhibition, and executive dysfunction, self-reported executive dysfunction in particular is associated with concurrent community integration.(136)

The inventories reviewed by Malloy et al (135) were initially developed as cost- and time-effective tools to assess executive function and to capture the real-world behavioural manifestations of executive dysfunction.(108, 141, 142) Although Wilde et al.(75) have recommended the FrSBe as a common outcome measure after TBI, the BRIEF-A is the most comprehensive regarding the number of items and executive domains assessed.(135, 143) It features sound psychometric properties,(143, 144) good reliability, and large-scale norms.(135) Its increasing popularity in rehabilitation clinics must also be taken into account. However, the few studies that have employed the BRIEF-A as an outcome measure after TBI have had relatively small sample sizes,(138, 140, 145) been retrospective in design,(140, 146)

and lacked comparisons with large demographically matched healthy control groups. Therefore, its utility must be evaluated further in this patient group.

1.2.10 Functional outcome

Cognitive dysfunction observed after TBI may also affect the ability to resume leisure activities and employment,(147) cause problems with independent living, and impair social relationships,(64, 148) all of which may be termed functional or global outcomes.(149) Although a wide array of studies has aimed to assess functional outcome after TBI, there are large differences among studies regarding the outcome measures used, patient selection, and time since injury. There are also large differences among countries with regard to social and healthcare services provided, employment rates, and social benefits, which makes it difficult to compare results across studies. In addition to the methodological weaknesses identified in many studies, it has been concluded that more studies with more rigorous methodologies are needed to provide a better framework for patients and clinicians regarding which outcomes and progressions might be expected after TBI.(150)

Describing global outcomes after moderate and severe TBI is beyond the scope of this thesis; however, we wished to investigate how global outcomes were related to cognitive, emotional, and behavioural problems. One of the most commonly used methods for assessing global outcome is the Glasgow Outcome Scale (GOS) or the Glasgow Outcome Scale Extended (GOSE).(151) Assessments of global outcome with the GOSE have observed that global outcome is associated with concurrent neuropsychological function.(149, 152) Although strong associations with executive function have been observed,(65) the evidence thus far remains inconclusive with regard to other cognitive domains.(153, 154)

1.3 Emotional and behavioural problems after TBI

Persons with TBI may also experience emotional and behavioural problems for an extended period after the initial injury.(155-159) Two main approaches have been applied when describing emotional and behavioural problems after TBI; the categorical and the dimensional approach.

1.3.1 The categorical approach – prevalence of psychiatric diagnoses

Using structured diagnostic interviews such as the Structured Clinical Interview for DSM-IV (SCID), studies have consistently demonstrated a significantly higher frequency of psychiatric diagnoses among individuals with TBI versus the general population.(157, 158, 160) In particular, people with TBI have an increased risk of developing depression,(156, 161, 162) anxiety,(158) aggression,(160, 163, 164) and substance abuse.(165) In addition, individuals with TBI may also be at increased risk of developing personality changes or personality disorders,(156, 158, 166) obsessive compulsive disorder (OCD),(158) and bipolar disorder or mania.(158)

1.3.1.1 Depression

Various studies have reported the prevalence of depression after TBI to be anywhere from 6% to 77%.(167) Some studies have found that individuals with TBI remain at higher risk of developing depression for several years post-injury.(156, 161, 162) Other studies have found an increased risk of developing depression within the first year post-injury, but with decreasing risk during the following years.(168, 169) Some have proposed that there are different trajectories for developing depression: for some patients the depressive symptoms are a continuation of pre-morbid psychiatric problems, while those that develop novel depressive symptoms often exhibit later onset of depression.(170) Others have proposed that neuropathological processes caused by the injury might initiate early-onset depression, while delayed-onset depression or the maintenance of chronic depressive symptoms is the result of psychological vulnerability, self-awareness of disability, and social disruption.(171)

1.3.1.2 Anxiety disorders

Among anxiety disorders, the prevalence of generalized anxiety disorder (GAD) has varied between 1.7% (156) and 24%.(172) Further, co-morbid GAD has been associated with slower recovery and worse outcome after TBI.(156, 158, 172) Prevalence of panic disorder has varied between 3% (173) and 9.2%.(174) In general, there are conflicting results regarding the course of development of anxiety disorders, with some findings indicating an increase of anxiety disorders during the decades after TBI,(156) and others reporting an initial increase in anxiety disorders followed by a decrease in prevalence after the first year post-injury.(168)

It has been claimed that post-traumatic stress disorder (PTSD) is incompatible with TBI, and that "patients who sustain PTSD simply cannot 'forget' the traumatic event, while patients who sustain brain injury have no recollection of the traumatic event".(175) Since then, a significant number of papers have been written about the possibility of developing PTSD after TBI. In a review of the literature in 2007, the prevalence of PTSD after TBI varied between 3% and 59%. One study has reported an increase in prevalence of PTSD from 11% at 6 months post-injury to 16% at 12 months post-injury.(176) Beyond the first year post-injury, the prevalence of PTSD appears to decrease.(168, 177)

However, the paradox of PTSD following TBI concerns whether it is possible to have a memory of the traumatic event when brain injury is so often associated with disruption of consciousness or cognitive function at the time of trauma. Nightmares, intrusive memories, and emotional reactivity related to the event are the symptoms most consistently associated with PTSD, and the most predictive for the development of PTSD. In some studies, loss of consciousness or lack of conscious memory of the trauma owing to disrupted cognitive function have appeared to protect against developing PTSD; however, others failed to replicate these findings.(158) Gil et al found that patients with TBI developed PTSD including intrusive memories despite being unable to consciously recall the trauma.(178) They proposed that the formation of explicit memories within hippocampal structures might be disrupted by stress-related glucocorticoid surges caused by the brain injury, leading to the patient's inability to consciously recall the memory.(178) Furthermore, neuronal circuits mediated by the amygdala might be instrumental in forming intrusive/emotionally charged memories, resulting in a bypass of cortical structures and leading to implicit (unconscious) memories.(178)

1.3.1.3 Challenges in assessing emotional disorders

Some of the variation in the prevalence of psychiatric disorders may be accounted for by variations in methodology: retrospective vs. prospective study design, differences in injury severity between studies, the length of the interval between the injury and the assessment of patients, and cultural differences.(158) However, some of the problem may also be the overlap between the diagnostic criteria for psychiatric

diagnoses and common cognitive and somatic sequelae after TBI. For instance, cognitive symptoms such as slowed information processing, attention problems, and reduced memory function can just as easily result from TBI as from depression. Somatic symptoms such as sleep problems, reduced initiative and energy, irritability, and mood swings may be caused by TBI, depression, or anxiety disorders.(162) Hence, when this categorical approach is used to assess emotional and behavioural problems after TBI, differential diagnostic evaluations and adapted diagnostic criteria are imperative in order to avoid overestimating the problems.(167, 179)

1.3.2 Dimensional approach – profiles of emotional and behavioural problems

Dimensional measures such as questionnaires assess a large range of symptoms associated with emotional and behavioural problems, with the possibility of providing self-reports or proxy reports from relatives or friends.(159) Extensive questionnaires offer a good framework to organize the emotional and behavioural symptoms that are frequently reported after TBI.(159) They also provide insights into elevated subclinical problems experienced after TBI, and describe the problems from the individual's perspective. This is of importance, as it is demonstrated that the patients' own perceptions of their problems may influence how well they reintegrate into the community.(180, 181)

There are two types of inventories: uni-dimensional and multidimensional. Uni-dimensional questionnaires are disease-specific inventories, such as The Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Patient Health Questionnaire–9 (PHQ-9), and Overt Aggression Scale (OAS). In comparison, multidimensional inventories assess a broad range of emotional and behavioural problems, and include inventories such as the Minnesota Multiphasic Personality Inventory (MMPI), Symptom Check List 90 (SCL-90), Personality Assessment Inventory (PAI), and the adult version of the Achenbach System of Empirically Based Assessment (ASEBA). The ASEBA is widely used among psychiatrists, but has never been used as an outcome measure after TBI in adults — despite the popularity of the children's version in the paediatric TBI population.

Assessments of emotional and behavioural problems through the use of questionnaires only overlap in part with clinical diagnoses.(159, 162) Furthermore, personality factors and cognitive style may influence how people rate themselves,(159) and there is a risk of invalid results owing to reduced self-awareness among patients with severe TBI.(180) However, several studies report good correspondence between symptoms reported by patients and their families.(138-140) Nevertheless, good health is a state of physical, mental, and social well-being,(182) and therefore it is as important to assess perceived problems as it is to provide an objective assessment of problems after TBI.

1.4 Predictors of cognitive, emotional and behavioural problems

1.4.1 Predictive factors of neuropsychological test performance

Several factors have been proposed to account for outcomes after TBI.(183-185) Lower performance on neuropsychological tests has been observed with older age at injury (67) and fewer years of education.(56, 86) Some studies have found a dose-response relationship between neuropsychological test performance and injury severity measured in LoC or time needed to follow command.(84) However, duration of PTA has been suggested as one of the best predictors of outcome after TBI.(43, 55, 185, 186) In particular, patients with PTA duration >4 weeks have poorer outcomes.(55) Good recovery is observed to be associated with PTA duration of 1-7 days, and moderate disability to be associated with PTA duration exceeding 14 days.(187) TBI usually is a mixture of focal lesions and DAI,(4, 6) both of which may affect later cognitive function. However, detection of DAI has been problematic in studies that use CT scans during the early phase, and additional studies that assess DAI using MRI are warranted.

1.4.2 Predictive factors of self-reported cognitive function

Firm evidence of an association between age at injury and length of education to self-reported executive function after moderate and severe TBI has not yet been established. Although some studies have reported a positive relationship between self-reported executive problems and GCS score,(188, 189) to our knowledge reports of an association with duration of PTA are lacking. No association has been established between self-reported executive problems and findings on early CT

scans.(188) However, focal lesions in the orbitofrontal cortex demonstrated on MRI have been observed to be associated with perceived executive dysfunction.(140) Moreover, TBI and especially DAI typically causes widespread damage localized in fronto-temporal and subcortical structures, and therefore affecting functional neural networks.(8) Especially complex and multidimensional functions such as executive functions rely upon network interactions between several cortical, subcortical, and cerebellar brain regions with frontal projections.(190-192) Therefore, perceived executive functions may be hypothesized to be vulnerable to DAI.(115, 116, 193) To our knowledge, such an association has not yet been reported.

The relationship between self-reported and performance-based executive function after TBI is far from established, which further complicates the picture.(114, 133, 134) In cases in which associations were observed, they were in the small to moderate range.(114, 134, 138, 142) In addition, self-reported cognitive complaints are affected by emotional symptoms.(140, 194, 195) Notably, the presence of depression and other mood disorders has been observed to affect both performance-based executive function and subcortical circuitry in non-TBI populations, as well.(196) Taken together, exploration of associations between demographic factors and injury characteristics, as well as early emotional and cognitive function, and long-term self-reported executive function is still warranted.

1.4.3 Predictive factors of emotional and behavioural problems after TBI

Among pre-injury factors, the development of depression and anxiety after TBI is observed to be associated with low socioeconomic resources (i.e., fewer years of education, occupational problems) (157, 158, 197) and increased age at injury,(157) while aggression and anti-social personality problems are associated with pre-injury aggression and substance abuse in addition to age at injury.(158, 159, 198) Evidence of associations between measures of injury severity and later neuropsychiatric problems have been conflicting,(158, 159, 169, 199) with some studies reporting no association at all.(197, 200) While this finding is especially true for the development of depression and anxiety disorders, there is some evidence that more severe injuries are associated with aggressive behaviour after TBI.(157) The structural and metabolic changes associated with symptoms of depression after TBI are lesions in

the dorsolateral prefrontal cortex, anterior cingulate, hippocampus, orbitofrontal cortex, left anterior hemisphere (major depression), or right hemisphere; lateral versus medial lesion location; toxic levels of glutamate; and disruption of dopaminergic and cholinergic pathways (mostly in animal models).(157, 158, 167) However, only a few studies purporting to examine factors associated with emotional and behavioural problems after TBI have included magnetic resonance imaging (MRI) findings,(201, 202) and reviews in the field are inconclusive.(158, 159) Left temporal lesions and increased lesion volume,(157) as well as disruption of neural circuits that regulate anxiety, are reportedly associated with the development of anxiety after TBI.(203) The development of aggression is associated with lesions in the frontal lobe,(157, 197) particularly the orbitofrontal and ventromedial regions.(113) In addition, a myriad of environmental and post-injury factors may influence the development of psychiatric problems, such as chronic cognitive problems due to TBI, lack of social support systems, being out of work, increased environmental demands, relationship problems (family, spouse, friends), and inflexible and maladaptive use of coping strategies.(159)

1.5 The biopsychosocial model

The biopsychosocial model, first proposed by Engel in 1977,(204) provides a useful frame for understanding the total symptom burden after moderate and severe TBI. The biopsychosocial model allows for understanding the pattern of symptoms as a product of interacting mechanisms at cellular, neuronal, neuronal network, behavioural, personal, family, and environmental levels.(205) This way of understanding a disease also underlies the International Classification of Functioning, Disability and Health (ICF) model proposed by WHO in 2001.(206) The functional consequences of health and illness are described on three levels: impairment at the level of body structure or function (i.e., anatomical and physiological) level, activity limitation at the personal level (i.e., cognitive impairment), and restriction of participation at the social level (i.e. work).(206) The model also gives self-reported (subjective) health status importance equal to that of medical data (objective) for understanding the disease. The biopsychosocial model and the ICF model each propose an interactive model that is specific for each

individual. It states that each component must be seen in relation to the others, and changes in one component affect the performance of other parts of the system.(205)

In addition to the factors discussed in section 1.4, Iverson et al (207) proposed a model for understanding symptom-reporting based on the biopsychosocial model. In their model, other factors derived from the field of social psychology and personality theories are also included. Figure 3 provides an overview of some (but not restricted to) factors that influence self-reported function.

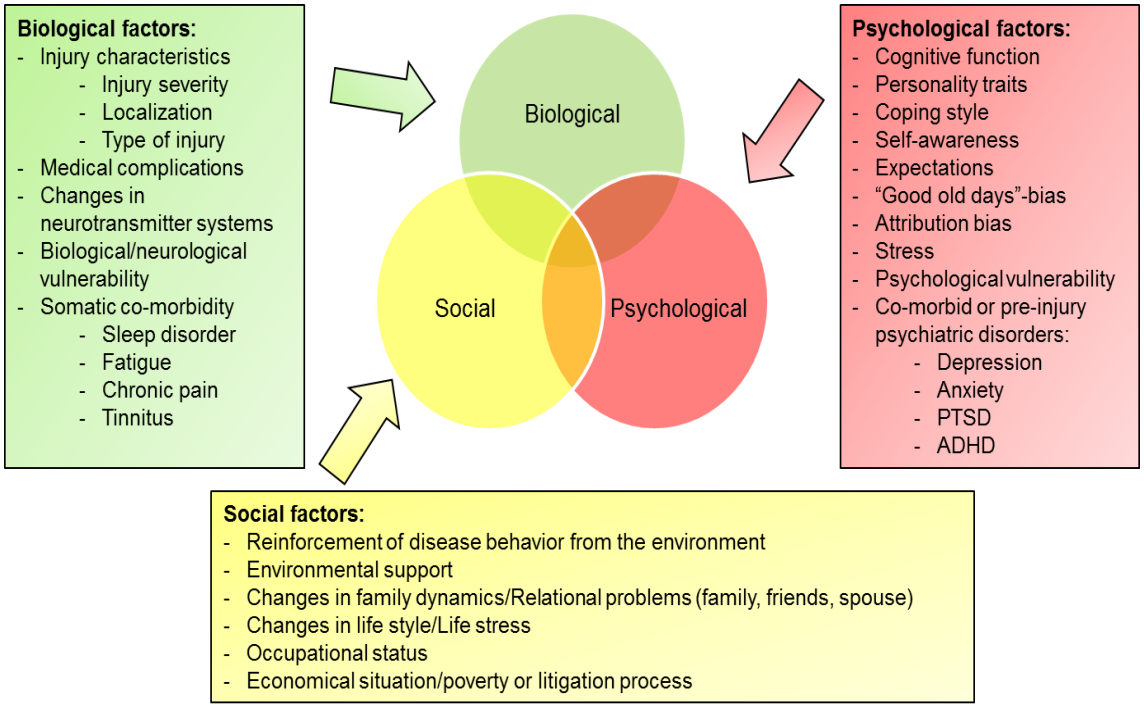

Figure 3
Overview of biological, psychological and social factors that may influence symptom reporting after traumatic brain injury based on the biopsychosocial model.

Some of the previous sections have reviewed some of these factors, and will not be discussed further here. Psychological factors, such as personality traits,(208) expectations, coping styles,(209) and misattribution of symptoms (207) also contribute to the pattern of symptom reporting.(207) Iatrogenesis is one form of attribution bias, although originally referring to adverse effects caused by the medical treatment.(207, 210) However, Iverson et al.(207) comment that when health personnel attribute persistent symptoms reported by the individual (e.g., fatigue) solely to a previous brain injury when such symptoms are more likely caused by

treatable conditions (e.g., depression or sleep disturbance), they do patients a disservice. This misattribution may reflect iatrogenesis according to Iverson et al.(207) Furthermore, patients may expect to experience certain symptoms or reduced performance after experiencing TBI, resulting in attribution of otherwise "benign" symptoms to the injury rather than environmental factors ("expectation as etiology").(211) Patients may also have generalized expectations of negative outcomes when they become injured or sick, and these expectations can cause or worsen their illness, also known as the Nocobo Effect.(212) Individuals with TBI in the mild/moderate range may have a particular tendency to overestimate the actual degree of change post-injury, and retrospectively recall fewer problems in the past – referred to as the "good old days" bias.(207, 212) In contrast, when TBI is in the severe range, there is an increased risk of under-reporting problems because of reduced self-awareness.(180) Maintenance of symptoms may also be affected by litigation, followed by increased stress, exaggeration, and malingering (e.g., over-reporting or faking symptoms). All of these factors must be taken into account to understand the effects of TBI.

1.6 What remains?

While there has been a considerable amount of research in this field, there is still a need for more prospective studies describing cognitive, emotional, and behavioural function over the course of several years after TBI. Despite the fact that moderate and severe TBI comprise a heterogeneous group,(4, 213) many studies reporting cognitive outcomes after TBI have not differentiated between moderate and severe TBI. Therefore, these studies may have overestimated impairments for moderate TBI, and underestimated them for severe TBI.(56, 214) As described previously, there is still conflicting evidence of the associations between measures of injury severity such as GCS, duration of PTA, and findings on brain images, and later cognitive, emotional, and behavioural problems. Because of the challenges of detecting DAI on traditional CT scans that are most often used in the clinic during the acute phase, DAI's impact on later cognitive, emotional, and behavioural problems may be underestimated. Hence, studies are needed that explore the associations between findings on MRI and cognitive, emotional, and behavioural problems after TBI.

Chapter 2: Aim of the thesis

The main aim of this thesis was to describe cognitive, emotional, and behavioural problems at several time points after TBI, with emphasis on the long-term perspective. In addition, a broad array of demographic and injury-related factors hypothesized to be associated with cognitive, emotional, and behavioural outcomes after TBI was explored. Following the broad understanding of health outlined by the biopsychosocial (204) and ICF (206) models, another aim was to assess perceived problems, as well as provide functional and performance-based assessments of problems after TBI.

2.1 Study 1

The aim of the study was to explore the magnitude and frequency of cognitive impairments 3 months after moderate or severe TBI in comparison with healthy controls and with normative data. Furthermore, we sought to relate the level of cognitive functioning at 3 months to measures of global functioning at both 3 months and 1 year post-injury.

2.2 Study 2

The aim of this study was to assess cognitive function 12 months after TBI in patients with moderate and severe TBI, and to describe improvement from 3 to 12 months post-injury. In particular, we wanted to differentiate between patients with moderate and severe TBI to explore whether this provides a more nuanced description of cognitive function. We also wanted to examine whether performances on neuropsychological tests at 12 months were associated with concurrent measures of global function.

2.3 Study 3

The aim of this study was to delineate the magnitude and profile of self-reported executive and emotional function 2-5 years after moderate and severe TBI. Secondly, we aimed to explore a broad array of demographic and injury related factors hypothesized to be associated with self-reported executive and emotional function 2-5 years post-injury. Adding to previous research literature, we specifically investigated the predictive value of injury severity measures such as GCS score,

duration of PTA, and MRI findings recorded in the acute phase. Finally, we extended our analyses to include an exploration of whether clinical observations during the first year post-injury, such as performance-based measures of cognitive function, symptoms of depression, and global outcome, were associated with later self-reported function.

Chapter 3: Method

3.1 Setting

3.1.1 The Head Injury project

The Head Injury Project started in 2004, and is an ongoing prospective cohort study in which patients with moderate and severe TBI as defined by the Head Injury Severity Scale (HISS) criteria (31) and the Scandinavian Guidelines for clinical management of patients with TBI (36) are registered consecutively in a database upon admission to the Neurosurgical Department, St. Olav's Hospital, Trondheim University Hospital, Norway. There are no exclusion criteria in the main database. The hospital is the only Level I trauma centre in the region of Central Norway, with approximately 696,000 inhabitants by January 2014. The project is run as collaboration between several hospital departments. In addition, the project has led to the founding of Trondheim TBI Group – a research group including researchers with backgrounds from several medical and psychological disciplines, performing research covering neurosurgery, intensive care medicine, neuroimaging, rehabilitation, and long-term outcomes.

3.2 Study populations

Participants were 15-65 years of age at the time of injury. They were recruited from the Head Injury Project Database if they met the following criteria: (1) no ongoing or pre-injury substance abuse, diagnosed neurological or psychiatric condition, or previous moderate to severe head injury as endorsed in the clinical interview during the hospital stay; (2) ability to cooperate during testing (without disorders of consciousness); and (3) fluency in the Norwegian language. The main inclusion periods were from October 2004 to September 2007 (Study 1), October 2004 to October 2007 (Study 2), and October 2004 to July 2008 (Study 3).

3.2.1 Study 1

The sample consisted of 52 participants (85% of the eligible sample) who consented to be assessed with a standardized neuropsychological test battery 3 months post-injury. For the purpose of increasing the sample, we also included 9 participants with

TBI who had been injured and registered in the main database after the first inclusion period and who were evaluated at 3 months follow-up. Selection of the participants is described in Figure 4. At 4 months post-injury, seven of the patients that were unable to cooperate were in a vegetative state, three were in MCS, and two were in PTA. All had poor global outcome at 12 months post-injury. Of the participants that rejected testing at 3 months post-injury, 11 had moderate TBI, and three had severe TBI. Eleven had good outcome at 12 months post-injury.

The control group consisted of 47 healthy participants, matched to the total sample of patients regarding age, sex, and education. They were recruited through advertisements, among family and friends of patients with head injury, and among acquaintances of researchers and staff.

3.2.2 Study 2

The sample consisted of 50 participants (71% of the eligible sample) from the main database who consented to be assessed with a standardized neuropsychological test battery at both 3 and 12 months post-injury. Therefore, participants unable to cooperate or who declined assessment in Study 1 were not included. The convenience sample in Study 1 was also not included. Within the study period, 70 patients met the inclusion criteria. Of these, 10 patients rejected testing at either 3 or 12 months post-injury and 10 patients were unable to participate in testing both times because of long geographical distances or could not be reached (17 with moderate TBI, and 3 with severe TBI). Selection of the participants is described in Figure 5. The control group described in Study 1 also participated in Study 2.

3.2.3 Study 3

The sample consisted of 67 participants (recruited from the main database) that sustained TBI >1 year ago. Seventy-four (78% of the eligible participants) consented to take part in the study, and seven were excluded from analysis owing to invalid questionnaire completion. This left 67 TBI survivors for the full analysis. Because the study in Paper III was part of a large follow-up study that used advanced MRI and EEG for diagnosis and outcome assessment in TBI patients, an added exclusion

criteria was applied: (3) Glasgow Outcome Score Extended (GOSE) score ≥5. Because of challenges in comparing paediatric and adult versions of the questionnaires, only participants who were between 15 and 65 years of age at the time of injury were included in this study; these patients were between 18 and 65 years of age at follow-up. There were no significant differences between eligible participants with TBI and participants with TBI who did not participate (n=28) regarding age at injury, sex, injury mechanisms, severity of TBI measured with HISS, or duration of PTA. MRI data were missing for one participant and eight non-participants; however, cortical contusions, presence of DAI, and location of DAI did not differ between participants and non-participants with MRI data present ($p \geq 0.1$). Participant selection and non-participants are described in Figure 6.

A subgroup of the individuals with TBI (n=49; 73% of the final sample) had participated in Study 1. These patients were included in a subgroup analysis investigating the association between subacute neuropsychological test performance and self-reported cognitive, emotional, and behavioural function at 2-5 years post-injury.

Recruitment procedures were the same as in Studies 1 and 2 with regard to the sex-, age-, and education-matched healthy control participants. Some control participants from Studies 1 and 2 also participated in Study 3 (n=27). Six of the 78 recruited controls were excluded because of previously diagnosed psychiatric or neurological conditions (n=3) or invalid completion of the forms (n=3). As a result, 72 control participants were included, some of which also participated in Studies 1 and 2.

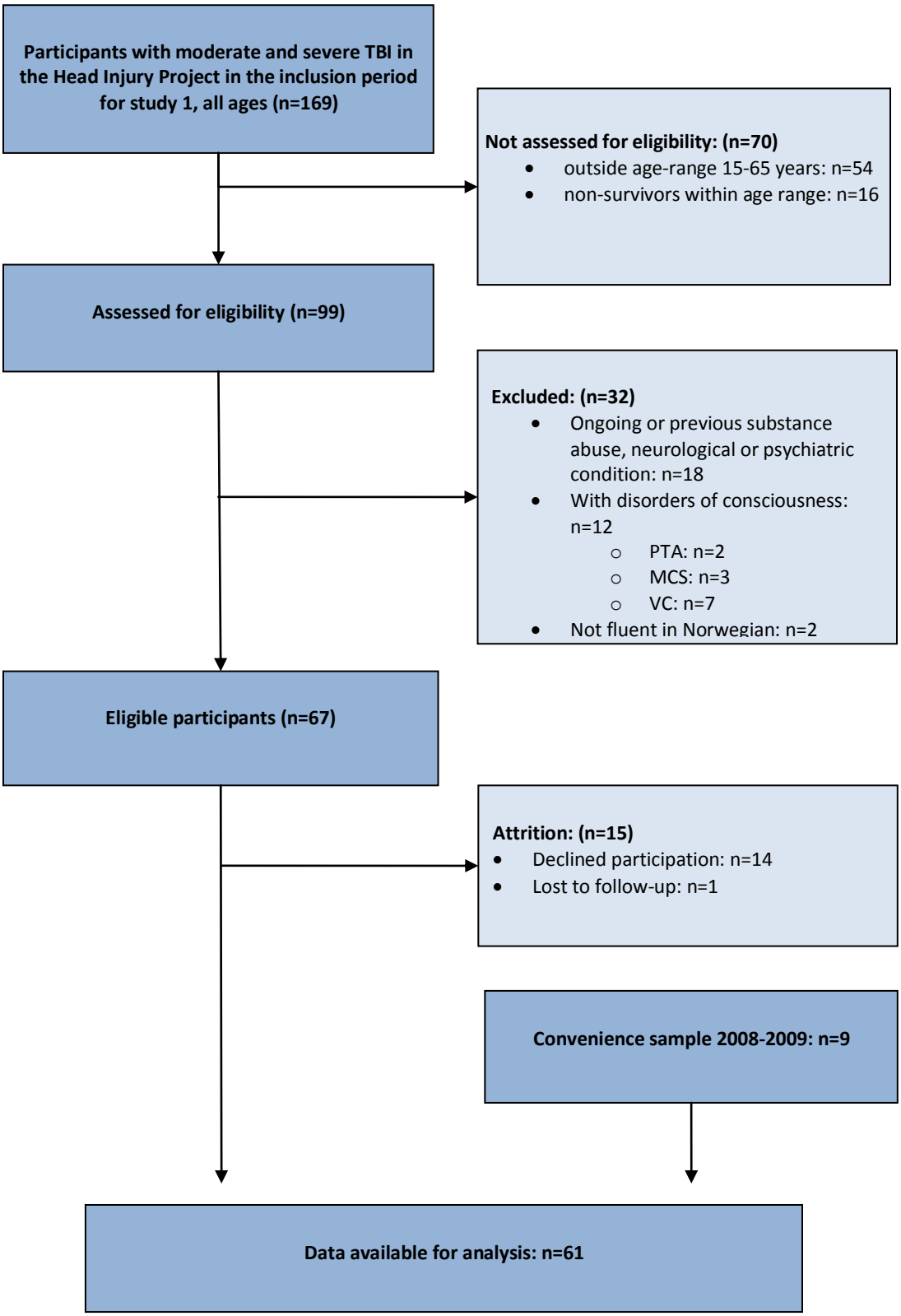

Figure 4
Flow-chart illustrating sample selection and description of non-participants in study 1.

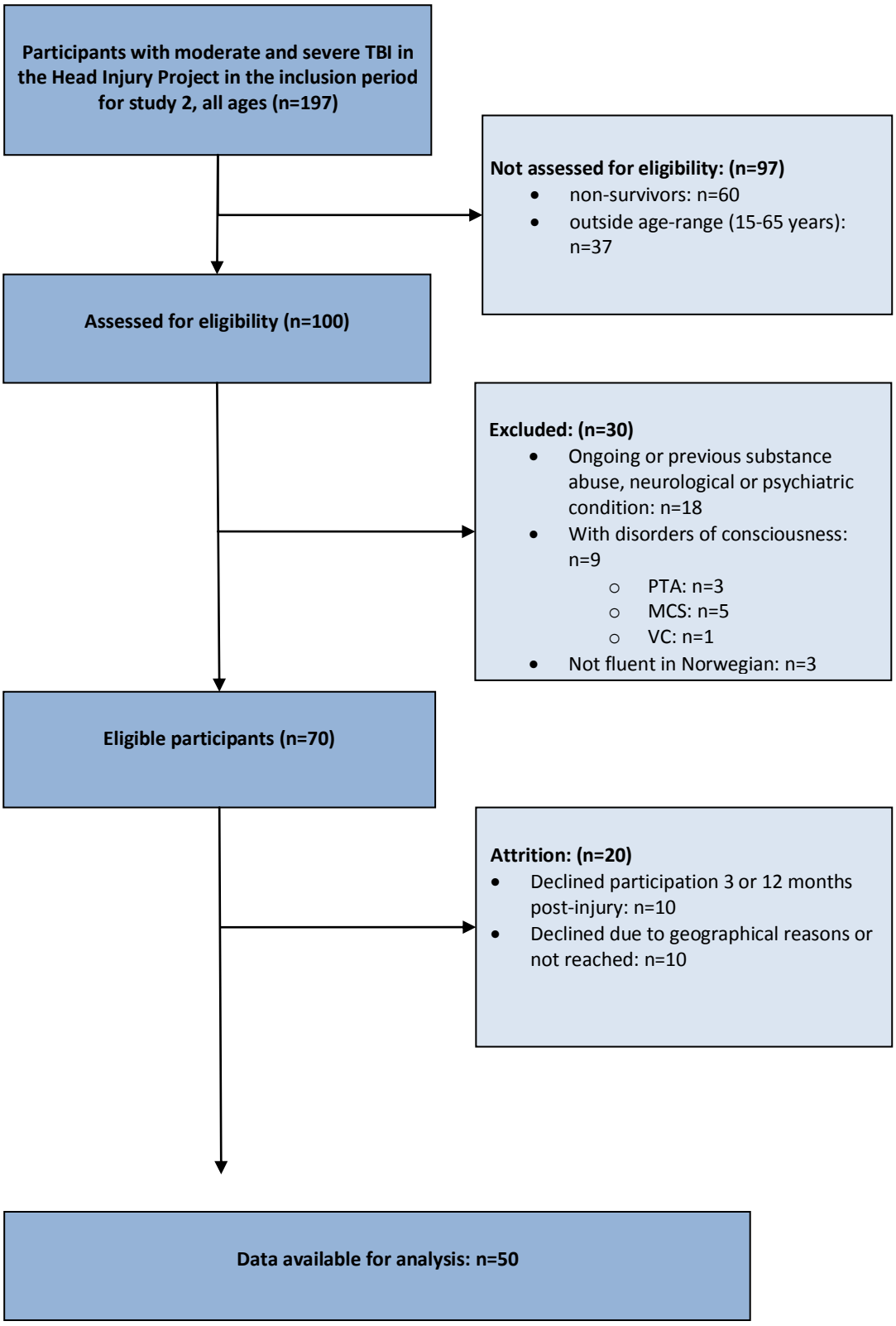

Figure 5
Flow-chart illustrating sample selection and description of non-participants in study 2.

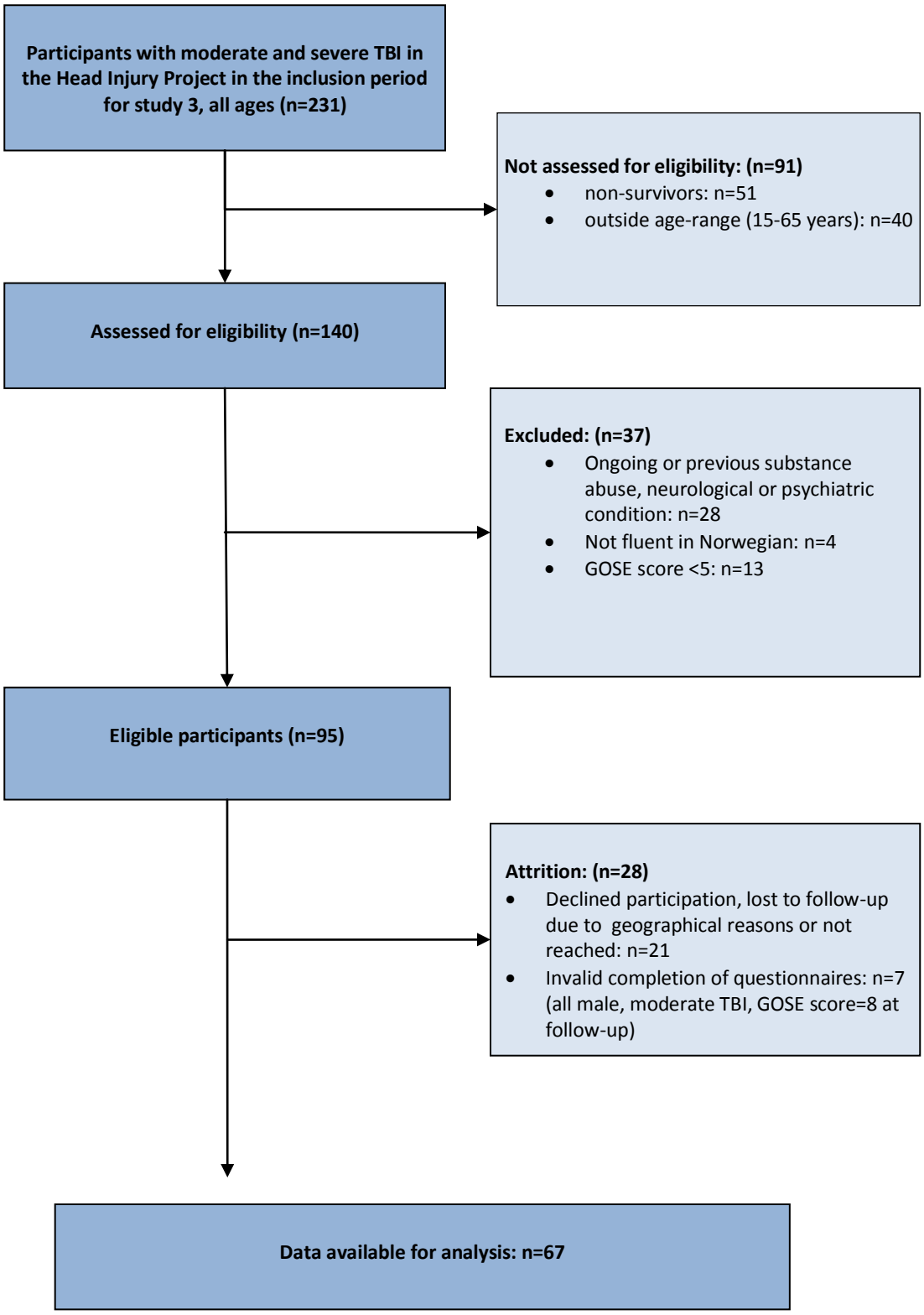

Figure 6
Flow-chart illustrating sample selection and description of non-participants in study 3.

3.3 Procedures for data collection and measures

Residents and research assistants at the study hospital identified patients to be included in the main database. Evaluation of pre-injury or ongoing substance abuse and neurological or psychiatric conditions were made by clinical interview during the initial hospital stay, or at follow-up. Demographic variables were collected by clinical interview of patients or relatives, or from their medical journal. Procedures and measures of the variables of interest in this thesis are described in sections 3.3.1 through 3.3.4.

3.3.1 Ethics

The Regional Committee for Medical Research Ethics (REK) approved the study protocol (REK Midt-nr: 135/04 for Studies 1 and 2, and 4.2009.1019 for Study 3). Patients or relatives were provided with oral and written information about the study, and those who consented to participate also provided permission to collect data from medical journals. Written informed consent was obtained from patients that were ≥16 years of age at injury and from both participants and their parents if patients were <16 years old.

3.3.2 Education

In Studies 1 and 2, years of education prior to the injury were collected in the clinical interview at the time of testing. In Study 3 we used a self-report form and an interview to estimate the number of years of education completed at 2-5 years post-injury. Information about marks from school attendance prior to the injury was provided in the clinical interview at the time of testing (3 or 12 months post-injury). A 6-interval scale was used, rated from low (0) to high (6) level of performance, and an estimated mean of marks were used to estimate pre-injury academic function in Study 2.

3.3.3 Measures of injury severity

The resident first examining the patient upon admittance collected injury-related variables by completing a form designed to record variables of interest. Experienced physicians in charge of the Head Injury Project were available if residents needed to discuss evaluation and recording of the variables.

3.3.3.1 Glasgow Coma Scale

Each patient's GCS score was recorded at or after admittance if the patient deteriorated, or before intubation in cases of pre-hospital intubation. GCS has demonstrated adequate reliability,(30, 215) and is incorporated into many clinical inventories that assess injury severity.(31, 216) In our study, GCS scores of 9-13 were classified as moderate TBI and scores ≤8 were considered severe TBI.(30, 31, 36)

3.3.3.2 The Head Injury Severity Scale (HISS)

The HISS is based on both injury severity assessed by GCS and presence or absence of complications related to the severity category.(31) Use of this scale is recommended in the Scandinavian guidelines for clinical management of TBI, and it is widely used. The HISS defines moderate injury as GCS score ≤13 or loss of consciousness (LoC) for ≥5 min. In our studies, the further subdivision into severe injury (GCS score 5-8) and critical injury (GCS score 3-4) was collapsed into a single category, which was referred to as severe injury.

3.3.3.3 Duration of Post-Traumatic Amnesia

In our study, the duration of PTA was evaluated and categorized by co-author Toril Skandsen (PhD, MD) according to clinical evaluation of the participants observed or described behaviour the acute stage. Categories were: 1) oriented state, or 2) post-traumatic confusion (PTA) – which also included minimally conscious state (MCS) or vegetative state (VS). In our studies, the patients categorized as in PTA were not oriented (temporal and spatial orientation) and were unable to recall day-to-day events (reduced episodic memory). Duration of PTA was categorized as ≤1 week or >1 week.

3.3.3.4 MRI

Two experienced neuroradiologists scored the imaging findings based on visual inspection, in accordance with predefined variables. A third radiologist, blinded to clinical information and previous classification, scored 31 randomly selected cases to evaluate reliability. MRI findings were categorized as cortical contusions, diffuse axonal injury (pure DAI), and combined contusions and DAI in Studies 1 and 2. MRI findings were categorized as the absence or presence of DAI in Study 3.

The scan protocol consisted of five different imaging methods as reported by Skandsen et al. in 2010 (217):

- Sagittal turbo spin echo T2-weighted imaging: 20 slices, TR 4300 ms, TE 110 ms, echo train length 14, number of excitations 4, FOV 23 cm, bandwidth 130 Hz, acquisition time 148 s, matrix 291 × 512, pixel size 0.6 × 0.7 mm.
- Sagittal, transverse, and coronal T2-weighted FLAIR imaging: 24 slices; TR 9000 ms; TE 109 ms; TI 2500 ms; number of excitations 4; FOV 23 cm; bandwidth 130 Hz; acquisition time 2:44, 2:26, and 2:26; matrix 291 × 512; pixel size 0.6 × 0.7 mm. Fat saturation was used.
- Transverse T2*-weighted gradient echo imaging: 24 slices, TR 830 ms, TE 25.8 ms, number of excitations 4, FOV 21 cm, bandwidth 80 Hz, acquisition time 2:52, flip angle 20°, matrix 291 × 512, pixel size 1.0 × 0.8 mm.
- Transverse spin echo T1-weighted imaging: 24 slices, TR 430 ms, TE 7.8 ms, number of excitations 4, FOV 23 cm, bandwidth 130 Hz, acquisition time 3:44, matrix 291 × 512, pixel size 0.9 × 0.9 mm.
- Diffusion-weighted imaging: single-shot, spin echo planar imaging sequences with 19 slices of 5-mm section thickness (TR 3300 ms, TE 110 ms, number of excitations 4, FOV 23 cm, bandwidth 1240 Hz, acquisition time 1:44), obtaining baseline images (b = 0 s/mm^2) and varying diffusion gradient strength along each of three orthogonal directions (b = 500 and 1000 s/mm^2). Diffusion trace maps were computed from the isotropic diffusion image and were used to estimate the apparent diffusion coefficient.

DAI was defined as the presence of lesions in lobar white matter, corpus callosum, or brainstem. These were identified either as hyperintensities in the FLAIR sequence or DWI or as microhaemorrhages in the T2* sequence.

3.3.4 Outcome assessment

All outcome assessments were performed at 3 and 12 months post-injury, and at 2 to 5 years post-injury. Clinical neuropsychologists (including the author), two trained psychology students, and one experienced test technician at St. Olav's University Hospital performed neuropsychological testing and clinical interviews at 3 and 12

months after injury. To compensate for errors associated with several examiners, all were supplied with oral and written instructions regarding the protocol and procedures. The students received training and were able to discuss issues with the psychologists. In addition, the author of this thesis reviewed all test protocols with results. In some cases, one or more tests were not administered for various reasons or the patients were unable to complete the test because of limb damage (injury or paralysis affecting function) caused by the accident. As a result, the number of patients evaluated with each test sometimes deviated from the total sample size.

At follow-up 2-5 years post-injury, research assistants (trained psychology students) administered questionnaires. Table 2 provides an overview of the different neuropsychological tests and questionnaires used, with reliability and validity provided in Appendix, Table 1.

3.3.4.1 Estimate of intelligence

To estimate general intellectual capacity (intelligence quotient - IQ) at 3 months post-injury, the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (218) were administered. A split-half procedure was used to avoid retest effects when patients were reassessed at 12 months post-injury. The control participants were tested with all items; however, their IQ scores in this study were calculated as for the patients, using every second item to estimate a raw score.

3.3.4.2 Neuropsychological assessment

A comprehensive neuropsychological test battery designed to cover cognitive domains typically affected by TBI was used to assess cognitive function at 3 months (T1), 12 months (T2) and 2-5 years (T3) post-injury. These tests have demonstrated adequate validity and reliability,(56) and many have been recommended by Wilde et al (75) as common outcome measures after TBI.

Table 2 describes the neuropsychological tests grouped into the a priori defined domains of cognitive function.

Table 2: Neuropsychological tests assessing cognitive function.

Cognitive domain	Neuropsychological test	Subtests used	Time of assessment
Motor function	Grooved pegboard (219)	Dominant hand (sec) Non-dominant hand (sec)	T1, T2, T3
Information processing speed	Symbol Digit Modality Test (SDMT) (220)	Oral version Written version	T1, T2
	Delis-Kaplan Executive Function System (D-KEFS) (221)	Trail Making Test: Condition 2 (letter sequencing) Condition 3 (number sequencing)	T1, T2, T3
		Color-Word Interference Test: Condition 1 (color naming) Condition 2 (word reading)	T1, T2
Attention	Conner's Continuous Performance Test II (CPT-II) (222)	All measures	T1, T2
Working memory	Wechsler Adult Intelligence Scales – III (WAIS-III) (223)	Digit Span Forwards Digit Span Backwards Number-Letter Sequencing	T1, T2
Verbal memory	California Verbal Learning Test – 2 (CVLT-2) (224)	Total words Trial 1-5 Learning Slope Immediate Recall Delayed Recall	T1 (standard version) T2 (alternate version)
Visual memory	Continuous Visual Learning Test (CVMT) (225)	Hits False response Total learning Delayed recognition	T1, T2
	Taylor Complex Figure Test (226)	Immediate recall Delayed recall	T1
	Rey Complex Figure Test (RCFT) (227)	Immediate recall Delayed recall	T2
Executive function	Delis-Kaplan Executive Function System (D-KEFS) (221)	Trail Making Test: condition 4 (letter-number sequencing)	T1, T2, T3
		Color-Word Interference Test Condition 3 (inhibition) Condition 4 (inhibition switch)	T1, T2
		Verbal Fluency (Phonemic fluency)	T1 (standard version) T2 (alternate version)
		Tower (total score)	T1, T2
	Wisconsin Card Sorting Test (WCST) (228) Category test (229, 230)	Total correct Total errors	T1 T2

To minimize practice effects, parallel versions of the neuropsychological tests were administered at 12 months when available. Visual memory was assessed using the Taylor Complex Figure at 3 months post-injury and the Rey Complex Figure (227) at 12 months post-injury. However, because research has demonstrated less overlap between these tests,(231, 232) they were excluded from analyses comparing visual memory at 3 and 12 months post-injury. Raw scores were converted to T-scores using normative data provided by the manufacturers of the tests, except for the Symbol Digit Modality Test, in which a normative sample quoted by Lezak was used.(56) Standardized scores on the individual neuropsychological tests were grouped into composite scores for each cognitive domain.

3.3.4.3 Glasgow Outcome Scale Extended

Global outcome was assessed at 12 months post-injury using the Glasgow Outcome Scale Extended (GOSE) structured interview, either by telephone or in-person interview.(151) Relatives or caregivers also provided complementary information about outcome to reduce the potential errors associated with telephone interviews. The GOSE is an extended version of the Glasgow Outcome Scale (GOS), which has been used widely since 1975. The GOSE was developed to address some of the shortcomings of the GOS, such as ceiling effects; low sensitivity to subtle deficits in cognition, mood, and behaviour; and disproportionate weighting of the physical deficits.(151, 233) The GOSE measures outcome on an 8-point scale that ranges from poor outcome/death to good outcome. Poor outcomes include disorders of consciousness or being dependent on caregivers on regular basis in everyday living. Moderate disability indicates difficulties resuming work or social relationships, while good recovery ranges from lack of problems to the presence of subtle chronic symptoms caused by TBI (e.g., fatigue, pain, subjective cognitive complaints). Use of the structured interview to assess outcomes has resulted in improved inter-rater reliability,(151, 234, 235) and has shown good discriminative ability and low ceiling effects.(236) The GOS and GOSE have been frequently cited in the neurotrauma literature, and the GOSE remains the most widely used and accepted instrument for global outcome after TBI.(233)

3.3.4.4 Self-reported function

Subjectively perceived cognitive, emotional, and behavioural problems were assessed using questionnaires at 3 months, 12 months, and 2-5 years after injury. Owing to various causes (e.g., time limits in the patient's schedule, patients' reservations, fatigue, pain, nausea, reading disabilities), a few participants were unable to complete all tests or questionnaires. At 3 and 12 months post-injury, clinical neuropsychologists, trained psychologists, or test technicians administered the questionnaires. At 2-5 years post-injury, clinical neuropsychologists and research assistants administered the questionnaires. They were also available if participants needed to ask questions about their interpretation of the items in the questionnaires. In addition, the assessment at 2-5 years post-injury was completed as part of a large follow-up study (total time approximately 6 h, including advanced MRI, motor assessment, and neurophysiological assessment), which led to a need for less time-consuming methods of assessment and careful prioritizing regarding the methods of assessment that were applied at this time point.

Beck Depression Inventory – II (BDI-II)

A subsample of the participants from Study 1 who also participated in Study 3 had completed a questionnaire assessing perceived symptoms of depression with the BDI-II (237) at 3 (N=49) and 12 months (N=45) post-injury. The BDI-II is a widely used measure of depression symptom severity, consisting of 21 items that assess emotional, cognitive, and somatic symptoms of depression. Each item is scored from 0 to 3, with lower scores representing lesser symptoms of depression. Although the manual classifies BDI-II scores >13 as "clinically symptomatic" depression,(237) the recommended clinical cut-off points are >18 for individuals with mild TBI, and >34 for individuals with moderate to severe TBI.(238) Internal consistency is reportedly α= 0.86 to 0.88 in a psychiatric population,(239) and α = 0.92 in a TBI population.(240) The factor structure of the BDI-II in the TBI population indicates a three factor structure: affective symptoms, negative attitudes towards oneself, and somatic disturbance.(240) Furthermore, higher endorsement of cognitive-affective symptoms has been reported among individuals with TBI.(238, 240)

Behaviour Rating Inventory of Executive Function – Adult version (BRIEF-A)

Self-reported executive function was assessed using the BRIEF-A questionnaire,(141) which consists of 75 items that measure behavioural, emotional, and cognitive aspects of executive function. Each item is rated on a 3-point frequency scale (0 = never; 1 = sometimes; 2 = often). Five items are designed to detect invalid response styles (inconsistencies or negativity). Seventy items generate three composite index scores and nine subscale scores. The subscales Inhibit, Shift, Emotional Control, and Self-Monitor generate the Behaviour Regulation Index (BRI), while the subscales Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials constitute the Metacognitive Index (MI). In addition, a Global Executive Composite (GEC) is calculated from all 70 items. Its borderline/clinical range is classified as T-scores ≥65.(141) Internal consistency is reportedly α= 0.94 for BRI and 0.96 for MI in a TBI population.(143) Sound psychometric properties have been observed for the BRIEF-A in different populations,(143, 144) and the factor structure of the BRIEF-A in a TBI population supports that each index measures a separate latent trait.(143)

Achenbach System of Empirically Based Assessment (ASEBA); Adult Self-Report Form (ASR).

Emotional and behavioural problems were assessed using the ASEBA:ASR.(241) The ASR consists of one section that measures adaptive functioning (38 items) and one section that measures emotional and behavioural problems (126 items) on a 3-point scale (0 = statement not true; 1 = statement sometimes true; 2 = statement very true). Eight syndrome scales are generated: anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behaviour, rule-breaking behaviour, and intrusive behaviour. The form yields three composite scores: total problems, internalizing problems (sum of the scales anxious/depressed, withdrawn, and somatic complaints), and externalizing problems (sum of the scales aggressive, rule-breaking, and intrusive behaviour). The form also yields six DSM-IV-oriented scales: depressive, anxiety, somatic, avoidant personality, attention deficit hyperactivity disorder (ADHD), and antisocial personality problems. Items

considered critical to diagnostic categories in the DSM-IV constitute the critical items scale.

The ASEBA reference manual (241) recommends using raw scores when presenting descriptive data, and borderline range as the threshold in research (clinical cut-off). The clinical range is classified as T-scores ≥70 and the borderline range is classified as T-scores ≥65 for the syndrome scales; the respective ranges are classified as T-scores ≥63 and ≥60 for the composite scales.(241) The subscales inattention and hyperactivity/impulsive are set at ≥97th percentile and ≥93rd percentile, respectively. Internal consistency (α) reportedly ranges from 0.60 to 0.78 for the adaptive scales, from 0.51 to 0.91 for the symptom scales, and from 0.68 to 0.88 for the DSM-IV–oriented scales.(241) Higher scores were reported on problem items and lower scores on adaptive items for referred vs. non-referred adults.(241)

3.4 Statistical analyses

3.4.1 Data analysis

Dependent variables were checked for normality using the Shapiro-Wilks test and inspection of Q-Q plots. Demographic characteristics and injury severity characteristics are reported as mean (±standard deviation, SD) for normally distributed data, and otherwise as median with interquartile range (IQR; 25th to 75th percentile). However, in Study 3 we reported range for age at injury and age at follow-up to better clarify patient characteristics. When confronted with missing data, we used available case analysis, utilizing all cases for which the variables were present.(242) Non-parametric tests (e.g., Kruskal-Wallis test, Mann-Whitney U test, and the chi-squared test) were used for between-group comparisons when data were not normally distributed.

In Study 1, we presented raw scores for each test as mean and SD for normally distributed data and otherwise as median with IQR. Comparisons between individuals with TBI and control participants were performed using Student's *t*-test and the Mann-Whitney U test, respectively. In Study 2, we reported standardized scores (T-scores) for each test and cognitive domain, and analyses of variance

(ANOVAs) were used for between-group comparisons (controls, moderate TBI, and severe TBI) on the different cognitive domains. Scheffe's post-hoc tests were used to differentiate between the three groups and to correct for multiple comparisons when using composite scores determined a priori.(243) Paired samples *t*-tests were used to analyse differences in performance at 3 and 12 months after injury. In Study 3, independent samples *t*-tests based on 2000 bootstrap samples were used for between-group comparisons (controls vs. patients with TBI). Proportions were compared using the chi-squared test, the exact unconditional z-pooled test,(244) and the Newcombe confidence interval.(245, 246) In Study 1, proportions were compared using the exact unconditional z-pooled test as recommended for small counts when the expected value was <5 for any cell.(244)

In Study 2, ordinal logistic regression with GOSE score as the dependent variable was used to analyse associations between functional outcome and concurrent neuropsychological function. Covariates were included separately and then adjusted for injury characteristics (e.g., age at injury and duration of PTA). Simple linear regression analyses were used to examine whether demographic, pre-injury characteristics or injury-related measures influenced the magnitude of improvement in cognitive function between 3 and 12 months post-injury.

In Study 3, linear regression analyses were performed with composite scores from the BRIEF-A and ASR as dependent variables; pre-injury variables, injury-related variables, neuropsychological test scores at 3 months and 2-5 years post-injury, GOSE scores, and the BDI were employed as covariates. These covariates were included separately and then adjusted for age at injury and length of education at follow-up. An additional linear regression analysis was performed with main indices and composite scores from the BRIEF-A and ASR as dependent variables, and the presence of DAI was employed as a covariate with adjustment for the BDI. Pearson's correlation coefficient was used to analyse associations between the main indices on BRIEF-A and the symptom scales on the ASR.

Effect sizes were calculated as Cohen's d based on pooled variance (d_{pooled}). (247) In Study 1, effect sizes were also calculated as Glass' *d*, in which the denominator is the SD of the control group ($ES_{control}$).(247) The standardized effect size was estimated by dividing the difference between the median scores by the IQR of controls × 0.75 ($ES_{control}$) for the tests in which data were non-normally distributed.(247) Cohen defined a *d* of 0.8 as large, 0.5 as medium, and 0.2 as small effect sizes.(248) Where relevant, 95% confidence intervals (95% CI) are reported.

Reported *p*-values are two-sided, and generally two-sided p-values <0.05 were considered statistically significant. However, *p*-values between 0.01 and 0.05 should be interpreted with caution owing to multiple hypotheses. In Study 1, when analysing the total battery of the neuropsychological tests a *p*-value of ≤0.01 was regarded as significant to adjust for multiple tests. In Study 2, only p-values ≤0.01 were considered significant when we compared the number of scores above or below average to adjust for multiple comparisons.

In Study 1, statistical analyses were performed using the statistical software SPSS for Windows, version 16.0 (Copyright SPSS.Inc, 1995-2009) with the exception of exact unconditional tests, which were performed using http://www.stat.ncsu.edu/exact/. In Studies 2 and 3, statistical analyses were performed using SPSS 18.0.

3.4.2 Effect size

There has been a trend toward requiring researchers to report effect sizes in addition to p-values.(249) There is not yet one common definition of effect size; however, some definitions relate effect size to the null hypothesis significance testing (H_0).(250) Effect sizes provide information about the strength of the association or how much the grouping variable affects the outcome – in this case: sustaining a TBI.(243, 247) This is in contrast to the estimate of statistical significance (p-value), which only provides information about how certain we can be that the differences between groups or associations observed in our material are not due to chance.(247) In his book, Grissom defines statistical significance as the quantification of the *strength* of evidence that the H_0 (no association/difference exist between groups in

the population at large) is wrong, while effect size measures the *degree* to which the H_0 is wrong.(247)

Estimates such as correlation coefficients (*r*) or confidence intervals (CI) are some forms of effect sizes. However, when exploring the impact of TBI on cognitive function, a common approach is to look at group differences with respect to neuropsychological test performances. CIs may provide some estimate of effect size when direct and similar measures are employed. However, when abstract, indirect, or dissimilar methods are employed to assess cognitive function, there is a need to place these measures on the same scale and thereby enable their comparison or combination.(247) One common approach within neuropsychology is the standardized difference between means,(247) which is often computed as Cohen's d (248) and estimates effect size as the standardized difference between two means divided by a standard-deviation (*s*) by the data:

$$d = \frac{\bar{x}_1 - \bar{x}_2}{s}.$$

Cohen based his calculations on assumed normal distribution and equal variance in the groups. Different approaches have been proposed for use when groups are unequal; one common approach has been to compute an estimate of the pooled variance (s_{pooled}) as a replacement of the *s* in the original equation. An alternative is to use the SD in one of the groups (usually the SD of the control group), which is referred to as Glass Δ or *d*:

$$\Delta = \frac{\bar{x}_1 - \bar{x}_2}{s_2}$$

Both of these approaches have been criticized for overestimating their parameters, particularly in small samples with large effect sizes.(247) However, this bias is considered negligible in sample sizes n>20.(251)

Furthermore, the effect size is directly related to power and sample size. This is of particular concern when the standardized differences are small, which is often the case within neuropsychological research,(252) as samples need to be very large in

order to have sufficient power to detect a true effect.(247) This situation increases the risk of failing to reject H_0 when a difference or association truly exists (H_1).

Chapter 4: Summary of results

4.1 Study 1 – main results

Persons with TBI performed worse on neuropsychological tests 3 months after TBI than healthy controls, most consistently in terms of information processing speed and verbal memory. Within the remaining domains, significant differences in mean performance were shown for many, but not all, measures. No significant differences were observed with respect to working memory. In addition, individuals with TBI had lower IQ scores compared to healthy controls. However, female patients with TBI performed in a range similar to healthy controls. Among controls, there was no difference between genders.

Exploring the proportion of individuals that performed ≤ 1.5 SD below the normative mean (classified as impaired scores), up to 43% of the individuals with TBI had clinically impaired scores on any one measure across all tests. Across all tests, the tests of information processing speed, motor function, and delayed recall on the California Verbal Learning Test (CVLT) had the highest proportions of impaired scores; at the same time, they yielded very few impaired scores in the control group. On several executive tests, as well as on the working memory test and some measures of visual memory, attention, and vigilance, no significant difference in frequency of impairment was observed between groups.

Selecting nine tests associated with large effect sizes or good ability to discriminate between patients and controls in the preceding analyses; 98% of the healthy controls had no more than one impaired score on these tests. Classifying impairment as ≥2 scores -1.5 SD below the normative mean, 43% of persons with moderate TBI and 65% of persons with severe TBI demonstrated cognitive impairment. At 3 months post-injury, concurrent disability (defined as GOSE score ≤6) was present in 61% of individuals with ≤1 impaired test score and 88% of individuals with ≥2 impaired test scores. At 1 year post-injury, disability was present in 57% of those with ≥2 impaired test scores at 3 months post-injury and in 21% of those with ≤1 impaired score.

4.2 Study 2 – main results

Patients with moderate TBI had significantly shorter PTA duration than patients with severe TBI. However, the patient groups did not differ with respect to distribution of sex, age at injury, age at testing, number of days between injury and testing, years of education, intellectual capacity, or pre-injury academic grades. Both patients with moderate and severe TBI exhibited significantly lower estimated IQ than healthy controls.

One year after injury, individuals with moderate TBI exhibited reduced executive function compared with controls, while individuals with severe TBI exhibited reduced motor function, processing speed, verbal memory, and executive function. Figure 7 presents neuropsychological performance in terms of effect sizes (Cohen's *d*). A detailed overview of group differences on the individual tests and cognitive domains is provided in Appendix, Table 2.

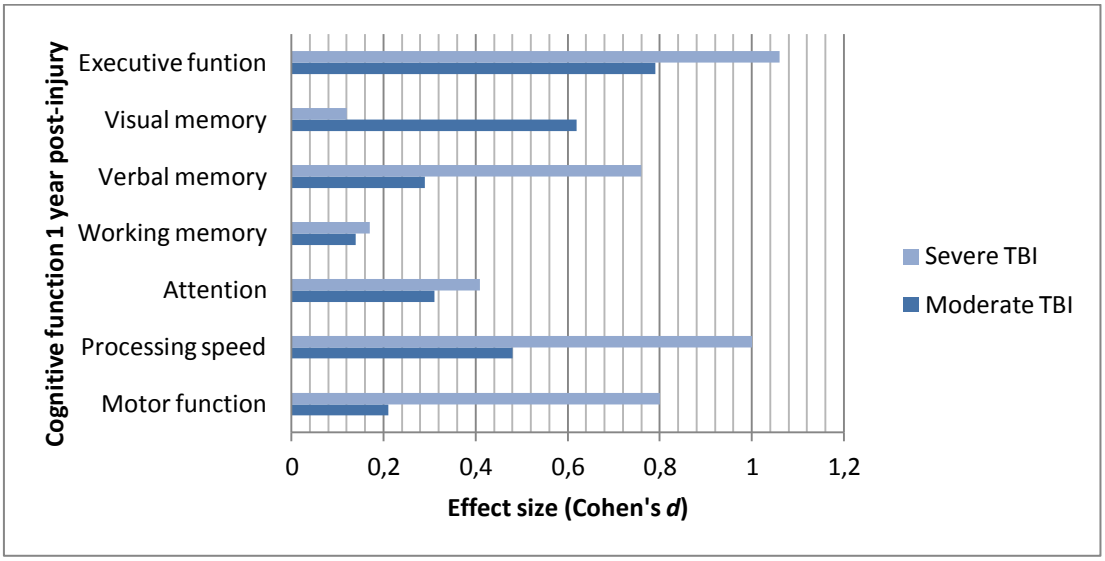

Figure 7
Neuropsychological performance 1 year post-injury presented as effect sizes.

Across all test scores, we observed that persons with severe TBI had a significantly greater proportion of low test scores (≤1.5 SD below the normative mean) compared to controls. The persons with moderate TBI had a larger number of low test scores

within the cognitive domains of processing speed and executive function, but not within the other domains. The three groups did not differ with regard to the number of high performances.

Both patient groups improved their visual memory and processing speed between 3 and 12 months post-injury. However, motor function only improved among individuals with moderate TBI, while executive function only improved among individuals with severe TBI. Figure 8 presents the improvement in the various cognitive functions for moderate and severe TBI.

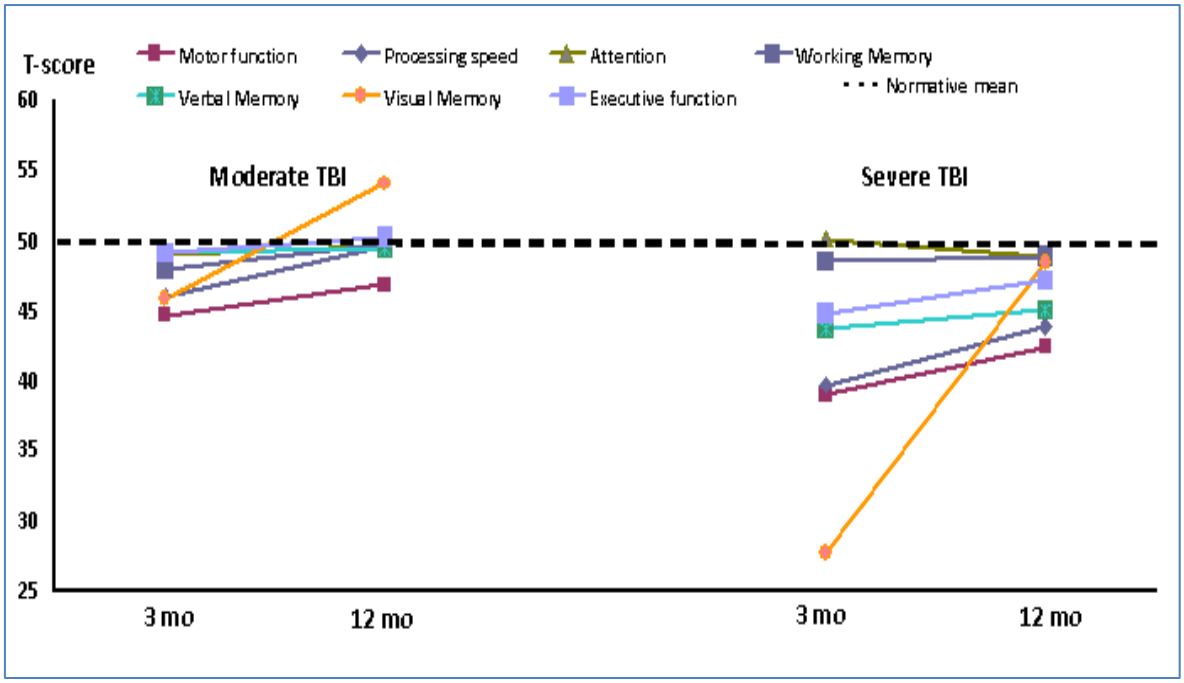

Figure 8
Improvement in the cognitive domains from 3 to 12 months post-injury for patients with moderate and severe TBI.

At 12 months post-injury, disability (GOSE scores ≤6) was present in 33% of persons with moderate TBI, and in 45% of persons with severe TBI. Younger age at injury and duration of PTA ≤1 week were associated with better global outcome. Better concurrent processing speed, attention, verbal memory, visual memory, and executive function were all associated with better global outcome in univariable analysis. However, only executive function and attention were associated with global outcome when we adjusted for age at injury and duration of PTA.

4.3 Study 3 – main results

At 2 to 5 years post-injury, a greater proportion (12%) of individuals with TBI neither worked nor attended school compared with controls. Otherwise, the individuals with TBI and healthy controls did not differ regarding distribution of sex, age at testing, or years of education. The subgroup of individuals with TBI assessed at 3 months post-injury exhibited significantly lower estimated IQ, as well as reduced processing speed, memory, and executive function compared with controls.

Overall, individuals with TBI reported more executive problems 2 to 5 years post-injury than healthy individuals. Also, a greater proportion of persons with TBI reported symptoms in the clinical range in the three composite indices of BRIEF-A. Figure 9 describes the typical BRIEF-A profile for individuals with TBI compared with healthy controls. However, the group differences observed on the individual subscales did not always indicate symptoms above the clinical cut-off.

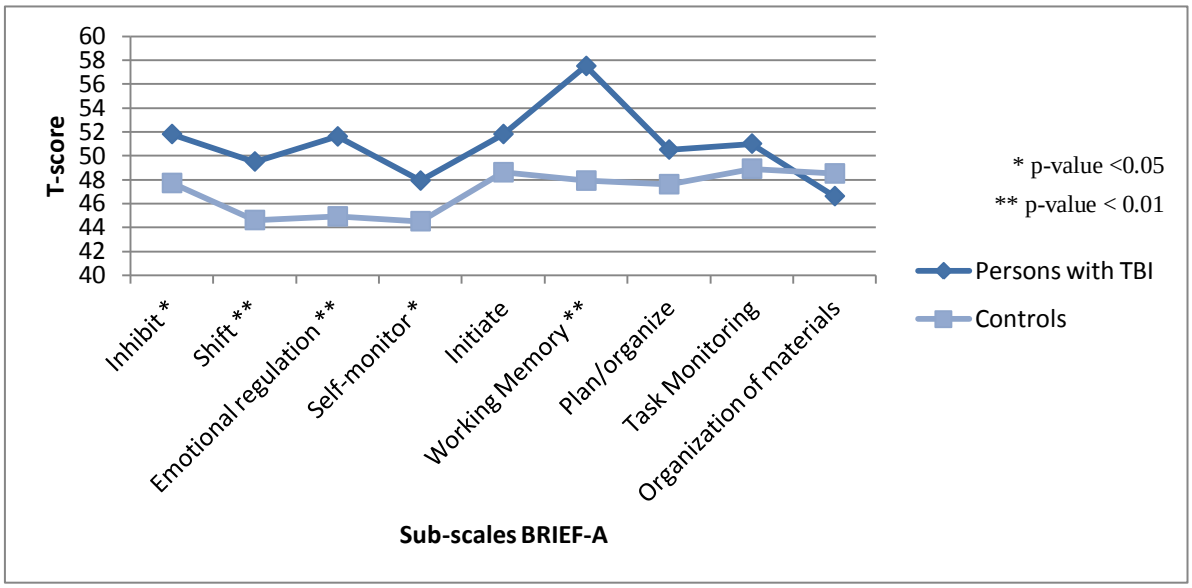

Figure 9
Profile of self-reported executive problems on BRIEF-A 2-5 years post-injury in individuals with moderate and severe TBI compared to healthy controls (T-scores).

Respondents with TBI reported significantly fewer personal strengths than healthy controls, but did not differ from controls with regard to problems in their family relationships or friendships. Individuals with TBI also reported significantly more emotional and behavioural problems than controls. Figure 10 describes the typical

profile regarding the ASR symptom scales for individuals with TBI and healthy controls.

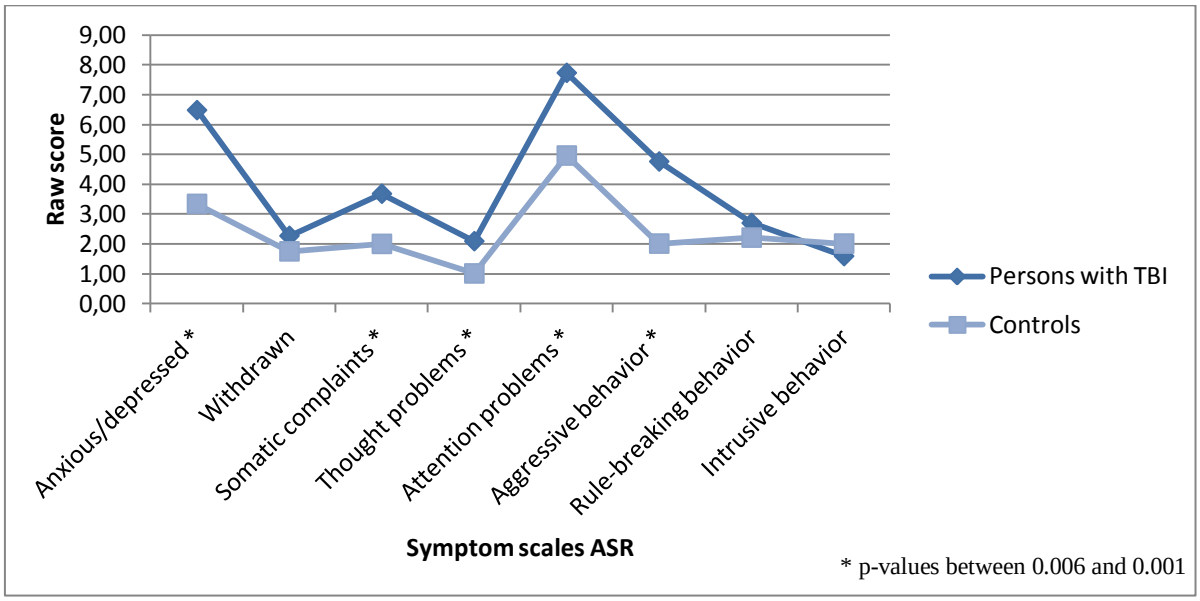

Figure 10
Profile of self-reported emotional and behavioural problems on ASR 2-5 years post-injury in individuals with moderate and severe TBI compared to healthy controls (raw scores).

A greater proportion of respondents with TBI also reported symptoms in the clinical range on the composite scales. Regarding the DSM-IV–oriented scales, respondents with TBI reported higher scores for depression, anxiety, somatic problems, and attention problems.

Younger age at injury predicted endorsement of greater problems with aggressive and rule-breaking behaviour, while fewer years of education predicted greater problems with self-reported executive function. Presence of traumatic diffuse axonal injury (DAI) in early MRI predicted later internalizing problems; this result persisted after adjustment for age, education, and early depressive symptoms. Symptoms of depression at 1 year post-injury predicted later self-reported executive, emotional, and behavioural problems. No associations were observed between performance-based measures of cognitive function and self-reported executive, emotional, or behavioural function.

Chapter 5: Discussion

In the following sections, first methodological considerations are addressed to provide the necessary groundwork for further discussion of the validity of our findings. Next, our findings are discussed in relation to the research literature, including clinical implications and indications for future research. Based on these discussions, and exemplified by the fictional cases presented in the introduction (Johnny and Nina), a summary of key consequences of moderate and severe TBI will follow.

5.1 Methodological considerations – strengths and limitations

The strengths of this study are its prospective, longitudinal design and its assessment of cognitive function using a broad neuropsychological test battery administered on more than one occasion. In addition, comprehensive questionnaires assessing perceived cognitive, emotional, and behavioural problems were administered as long as 2-5 years after the initial injury. The inclusion of a large healthy control group also lends strength to our study. Furthermore, it incorporates all important injury severity variables and MRI findings from the early phase, thereby enabling us to study the impact of injury severity on later function. The study's limitations are discussed in Section 5.1.1 through 5.1.3

5.1.1 Internal validity of the study

Internal validity refers to the degree to which valid conclusions about the population in question could be drawn from the study. In Section 5.1.1.1 through 5.1.1.5 and Section 5.1.3, the representativeness of our study population is discussed, as well as the roles of bias, chance, and confounding. The validity and reliability of the measurements of injury severity and cognitive, emotional, and behavioural function are discussed in Section 5.1.2.

5.1.1.1 Participants

The participants with moderate and severe TBI reflected the heterogeneity that is typically seen among individuals with TBI,(4) which poses challenges in terms of statistical power. To reduce heterogeneity in our sample and to increase its statistical power, we chose a strict enrolment strategy, as described in Section 3.2. Some authors consider the use of broader inclusion criteria upon enrolment and application

of covariate adjustment in the analyses to be a better strategy.(253) However, these recommendations are based on large-scale multi-centre studies, and do not apply to the limited sample in our study, which did not allow for many covariate adjustments.

We also chose to include participants with GCS scores of 13, a score defined as mild TBI in many previous studies. However, all but one of the participants with a GCS score of 13 experienced PTA for >24 h, which should be classified as moderate TBI (as opposed to mild) according to recommendations.(34, 35) Also, more than one-half of the patients had visible DAI lesions, and three-quarters had cortical contusions in the early MRI. Moreover, there is an increasing trend toward classifying a GCS score of 13 as moderate.(4)

Our samples were recruited from the Head Injury Project Database, described in Section 3.1.1. Recommendations for individuals with severe TBI in Norway are that they shall be treated at a level 1 trauma centre or a University Hospital with a neurosurgical department. This made it possible to recruit approximately the entire cohort suffering from severe TBI. However, recruitment of people with moderate TBI was not population-based to the same degree as participants with moderate injuries in the upper range (GCS scores 12-13) or individuals without clinical complications may have been treated at local hospitals. Nevertheless, our prospective study design and recruitment strategy may have increased the number of participants that were not likely to seek healthcare after discharge from the hospital.

The recruitment strategy for the healthy controls was approximately the same for all studies, and the controls were well matched with regard to age, gender, and education. Because of the larger sample of participants with TBI in Study 3, more healthy controls were needed. However, in analyses the number of healthy controls exceeded the number of persons with TBI owing to invalid completion of questionnaires by a few of the participants with TBI.

5.1.1.3 Chance – can the observations in our study be attributed to random variation?

Sample size is a major determinant of how much chance affects the findings.(254) Although our moderate sample size was largely comparable to other studies within

this field,(117, 118) the relatively small sample size in the subgroup analyses is a major limitation. Small groups may provide too little statistical power to detect small but real differences that are commonly found in outcome measures after TBI,(252, 253) and they increase the chance of committing type 2 errors. To counter this risk of committing type 1 errors due to our large battery of neuropsychological tests,(255) we adjusted for multiple measurements using the Scheffé Post Hoc test.(243) The use of stricter adjustment, such as the Bonferroni test, would reduce the risk of type 1 errors; however, because of the limited sample size, it would increase the risk of type 2 errors at the same time.(256)

5.1.1.4 Bias – can the observations in our study be attributed to systematic errors?

Not all eligible persons registered in the database consented to participate in our studies. However, 85% were recruited to Study 1, 71% to Study 2, and 78% to Study 3, which may be considered acceptable. There were no differences in the distribution of age, gender, education, or injury severity between participants and non-participants in any of the studies. To increase the sample size in Study 3, the inclusion period for recruitment was extended compared with Studies 1 and 2. Hence, our sample is larger than those of other comparable studies applying the same outcome measures. However, only 73% of the participants in Study 3 had been assessed with neuropsychological tests and the BDI at 3 and 12 months post-injury. These participants did not differ from the remainder of the sample in terms of demographic or injury characteristics, except that a larger proportion had PTA durations of >1 week (Pearson's Chi-square, p=0.042). However, neither PTA duration nor neuropsychological performance 3 months post-injury was associated with self-reported cognitive, emotional, or behavioural problems 2-5 years post-injury, suggesting that selection bias might not be of significant concern.

The healthy controls in our study were intended as a reference group to study the effect of TBI on cognition. However, the male participants in our control group performed significantly better on measures of IQ despite equal length of education. Personality traits and psychosocial background may have influenced their choice of academic pursuit, and in this respect they may still be representative of our participants with TBI. Nevertheless, the above average IQ in our control group may

introduce a systemic bias with regard to the male participants with TBI. Furthermore, people with orthopaedic or other non-head traumatic injuries have been suggested as a more appropriate reference group when assessing the effect of TBI on performance-based neuropsychological tests. It has been hypothesized that this would adjust for other trauma-related and potentially harmful effects that might exaggerate the effect of TBI. However, such a claim has not been supported.(214)

It has been claimed that individuals sustaining TBI may not be representative of the population at large.(55) Higher prevalence of pre-injury attention-deficit hyperactivity disorder (ADHD) or behavioural problems have been observed in the paediatric TBI population.(257, 258) Adolescents and young adults with ADHD have been observed to engage in risk-taking behaviour more frequently.(259) However, most studies that report life-time prevalence of such problems have reported on ADHD symptoms that developed *after* the initial TBI (260) – which are defined as secondary ADHD. Information about cognitive and behavioural symptoms has also been collected retrospectively some time after the initial injury.(257, 261) By excluding participants with ongoing or prior psychiatric diagnoses including ADHD, we may have controlled for some of these considerations. However, we cannot exclude the possibility that the participants with TBI and our control group differ with respect to the prevalence of undiagnosed neuropsychiatric disorders, subclinical attentional or behavioural symptoms, or risk-seeking personality traits.

Bias may also be of concern with respect to multiple assessors. To compensate for errors associated with several examiners with regard to the neuropsychological tests, all examiners were supplied with oral and written instructions regarding the protocol and procedures. Bias may also occur because of poor effort or malingering (exaggerating symptoms or problems). However, no free standing measure of effort or malingering was included in the test protocol, and the possibility of malingering could not be entirely excluded. All neuropsychological testing was conducted in a clinical setting and no patients were in a litigation process or seeking economic compensation at the time of assessment, which may have reduced the risk of malingering. This also held true for the time point at which the participants

completed the questionnaires. Response bias may also occur when function is assessed by questionnaires. The validity scales on the BRIEF-A revealed no response bias. Finally, observational bias may occur when assessment is performed without blinding to clinical information. Although this may pertain to MRI evaluation, re-evaluation of MRIs from a random selection of participants by a third neuroradiologist blinded to clinical information did not support a suspicion of observational bias.

5.1.1.5 Confounding – might the observations in our study result from the effect of a third factor?

In observational studies, confounding factors may be controlled for by, for example, stratification, subgroup analysis, or multivariable statistical methods.(254) This requires large samples of individuals with TBI. However, large-scale studies often do not contain resource-demanding data collections including MRI in combination with neuropsychological test scores, as our study did.(253) Although our moderate sample size was sufficient to differentiate between moderate and severe TBI, it did not allow for other subgroup analyses such as examining gender differences, the effect of DAI without contusions, and the effect of DAI grade.

Gender

Due to the relative paucity of female participants with TBI compared with male participants, sex-specific analyses were difficult to undertake. Lower estimated IQ was observed among male participants with TBI compared with females in our study. However, because of the low number of female participants with TBI, these results should be interpreted with caution. Animal models of TBI have demonstrated better outcomes after experimental TBI among females,(262) suggesting that progesterone might be a promising neuroprotector after TBI.(263) However, human studies have been inconclusive with regard to gender differences.(264) Gender differences may arise from differences in injury mechanisms,(265) premorbid brain morphology, coping styles, personality traits, or hormonal differences at the time of injury.(264) While worse outcomes have been demonstrated in some studies among women that sustain TBI when older than 65 years of age,(266) no gender differences after TBI have been observed among younger age groups.(264)

Age

The human brain is continuously changing as a result of developmental processes or normal aging. Using standardized scores may control for some effects of age. The neuropsychological tests and questionnaires applied in our study provide age-corrected norms, thereby minimizing the effect of age. Furthermore, age was controlled for in several analyses of predictive factors and correlates of outcome, which extended the findings of some previous studies.(65, 152)

5.1.2 Reliability and validity of the tests

The instruments selected in our study are considered to have acceptable reliability and validity, and assess functions that are affected by TBI. The tests are frequently used in the clinic after moderate and severe TBI.

5.1.2.1 Measures of injury severity

GCS scoring is the most common measure of level of consciousness in TBI patients.(30) However, the GCS score may be influenced by factors such as pre-hospital intubation, consumption of alcohol or other substances, or subsequent complications after the TBI such as hypoxia, hypothermia etc.(267) In our study, we corrected the initial GCS score if it clearly was affected by such factors. Because there are no standardized procedures for such correction, the final GCS scores in these cases were based on the clinical judgment of one of the experts in the project. This approach may decrease the reliability of the GCS scoring to some extent.

Ideally, resolution of PTA should have been determined using a standardized rating scale. Evaluation of PTA is challenging because of the divergent definitions of PTA, as well as practical obstacles in the clinical management of individuals with TBI. Because PTA has proven to be an important indicator of outcome after TBI,(43, 185) we chose to estimate duration of PTA from clinical information, such as patient journals and our own clinical observations. Although this method of assessment was clinically feasible, it may have led to the loss of more nuanced data. Obtaining exact estimates of PTA duration measured in days was difficult; therefore, we chose to use a fixed time point. Resolution of PTA within 1 week has previously been observed to be related to good outcome, while longer duration was related to worse outcome.(187) Furthermore, prolonged artificial sedation because of i.e. chest trauma

or orthopaedic injury may obscure registration of the resolution of PTA. In such cases, patients might exit PTA at an earlier period, but would not be registered as such. In addition, withdrawal symptoms after sedation may further complicate the assessment. Consequently, assessment of PTA may inevitably involve an element of clinical judgment. As in the case of the GCS score, this is not always accounted for in studies on TBI.

The identification of DAI on early MRI showed good inter-rater agreement.(217) MRI examination ideally should be performed at exact time points post-injury; however, this was not possible because the MRI was performed within the ordinary clinical course according to the demands of the intensive care unit and the MRI lab. Additionally, the stability and severity of the patients' medical condition affected the ability to perform MRI at a fixed time point. MRI examinations performed within the first weeks after the injury have demonstrated better detection of DAI than MRI examinations performed at later time points.(29)

5.1.2.2 Outcome measures

Because of the broad age range in our study population, it was important to use instruments that allowed for comparisons across the age groups. The main concern was that most of the instruments applied are based on Anglo-American norms; consequently, the Norwegian control group was of great importance for interpreting our results.

Neuropsychological tests

The reliability and validity of the individual tests are described in Appendix, Table 1, and concerns regarding the administration of the neuropsychological tests are discussed in Section 5.1.1. Categorization of neuropsychological tests into domains has been debated, and based on recommendations in the literature we chose to a priori categorization of the different sub-scores from the individual tests into cognitive domains.(56, 268-270) This categorization was based on both clinical considerations and common neuropsychological practice,(270) as well as reviews of the validity of the individual neuropsychological tests in previous research (75) and information from handbooks of neuropsychological assessment.(56, 269, 270) A further general discussion about the validity of these tests as estimates of their

designated cognitive domain is beyond the scope of this thesis. However, some of the neuropsychological tests chosen as a cognitive estimate had methodological concerns attached to them, and will be discussed in the following.

Averaging standardized scores to compute an estimate of each participant's level of function within one cognitive domain might reduce the effect of obtaining low scores that may appear by coincidence, something that has also been demonstrated previously among healthy individuals.(271) Comparing performances of the participants with TBI to those of a matched control group improved the interpretation of reduced cognitive function, as most of the tests are not co-normed. However, averaging across individual tests within one cognitive domain may have obscured true cognitive impairment if it presented in only one specific aspect of cognitive function, could be assessed with only one of the neuropsychological tests applied, or were present in only few individuals.(272)

We also aimed to explore the frequency of cognitive *impairment* on the neuropsychological tests. The ability to correctly identify impairment depends on the tests' sensitivity and specificity. While s*ensitivity* refers to the tests' probability of correctly identifying abnormal function in an impaired individual, *specificity* refers to the probability of correctly identifying normal function in an individual with intact function.(56) However, the application of more sensitive tests and the increase of the number of tests administered each increase the risk of finding impaired scores among healthy individuals, as well.(255) Furthermore, the accuracy of detecting actual impairment across groups decreases when the individuals being assessed have psychiatric, diffuse neurological, or milder neurological disorders,(273) and when the applied tests are not co-normed.(274) Accuracy also changes according to which threshold is applied when determining impairment.(271) As there is no universally agreed upon definition of impairment, we chose to categorize impairment as performances -1.5 SD below the normative mean, which is common in neuropsychological research.(128) However, this strict criterion increases the possibility that cognitive impairment was not detected among some individuals with moderate TBI. This may contribute to our findings that some of the individuals with

TBI that were categorized with disability 12 months post-injury nevertheless were classified with normal neuropsychological test performance.

Pre-injury IQ and education also affect the participants' level of performance. Without adjustment for these, individuals with low IQ may be at risk of being incorrectly identified as cognitively impaired, and cognitive impairment may not be identified among participants with high IQ.(128, 131, 275) In accordance with common practice in previous research, the full scale IQ (FSIQ) score on WASI was intended as an estimate of pre-injury IQ.(56) The split-half procedure chosen proved to be suboptimal. Large differences were observed in the calculated estimate of IQ between 3 and 12 months post-injury, both among some of the participants with TBI and among healthy controls. We chose to use the FSIQ at 3 months post-injury as an estimate because it was unaffected by practice effects; however, that choice did carry a risk that the scores would be affected by TBI, and particularly by severe TBI. While estimation of pre-injury IQ at some point post-injury has been demonstrated as acceptable for individuals with moderate TBI, severe TBI has been demonstrated to affect post-injury performance on the WAIS-III.(276) The WASI was developed as a reliable short-form measure of IQ,(218) and linked to performance on the WAIS-III.(277) While the Matrix Reasoning (278) and Vocabulary (279) subtests have demonstrated resilience against TBI, the timed Block Design subtest may be more vulnerable to the effects of TBI. Furthermore, the correspondence between the FSIQ estimate derived from the WASI and the WAIS-III has been demonstrated to be lower than expected.(277) Due to these concerns, FSIQ was only used as an estimate of concurrent IQ at 3 months post-injury. It is acknowledged that other estimates of pre-injury IQ could have been used, and may have been preferable. Therefore, participants' years of education and pre-injury grades were used as estimates of pre-injury intellectual functioning.

When monitoring the course of cognitive recovery after TBI, low test-retest reliability coefficients, practice effects, and the use of alternate versions of the tests may be of concern. One limitation of our study in this regard was that the control group was assessed only once, while the participants with TBI were assessed twice. This discrepancy limits our ability to assess and adjust for test-retest effects, and

evaluations of these concerns must be based on the test manuals and previous research. Furthermore, it is acknowledged that more advanced methods than simple discrepancy scores might have been used to evaluate reliable change from 3 to 12 months after TBI. However, even the more advanced methods do not account for the large individual differences, observed at any assessment time, which typically characterize individuals with TBI. Comparisons to previous research would be necessary, nevertheless.(280)

Some concern regarding low test-retest reliability has been noted, particularly for the tests from the Delis-Kaplan Executive Function System (D-KEFS). The great advantage of the D-KEFS battery is that the individual tests are co-normed and have acceptable reliability on the primary measures.(281) However, low reliability has been noted on the contrast measures and the additional measures, including the Verbal Fluency Test–Category Switching condition ($r = 0.54$) and the Tower Test–Total Achievement Score ($r = 0.61$).(56, 281) The larger concerns regarding the practice effects and test-retest reliability of D-KEFS (282) were not published until after the test protocol had already been implemented.

Larger practice effects occur on tests that are novel to the participant, are based on fluid abilities, the answers can be acquired in the setting, and the responses have not been encountered previously.(56, 280) Although longer test intervals reduce the risk of practice effects, they do not extinguish such effects altogether. Practice effects have been observed in some tests with test intervals longer than 6 months.(280) In our study, practice effects may pertain to the vast improvement on CVMT among participants with TBI, specifically regarding the reduction in the number of false alarms from 3 to 12 months post-injury. This reduction may reflect improvement in attention to visual detail and recovery of visual memory function,(56) but it may also be caused by the participants becoming more restrictive with their responses at the re-testing. It may also illustrate the effect of regression towards the mean, as the participants with severe TBI performed very poorly at 3 months post-injury. However, large differences between two assessment points on CVMT have been

observed to reflect significant change that is not merely due to chance.(283, 284) This observation strengthens our findings.

Applying alternate versions of a test may be less reliable than re-testing with the same test.(280) While lower test-retest reliability was observed when administering standard and alternate versions of the CVLT-2 compared with retesting with only the standard version,(224) practice effects are less prominent.(285) However, unintended dissimilarities in parallel versions of the Norwegian translation of the CVLT-II might also affect reliability between the standard and alternate version of CVLT-II; however, such information about the Norwegian translation is lacking.(286) This observation may also contribute to our finding that participants with moderate TBI performed worse at the second time point. These concerns also pertain to the alternate version of Verbal Fluency–Letter Fluency from D-KEFS.

Self-reported cognitive, emotional and behavioural problems

Several factors may affect an individual's responses on a questionnaire. For example, reduced self-awareness may affect responses among participants with severe TBI. Cross-informants could aid in evaluating the validity of the participant's responses. However, because we used only self-report questionnaires, we lost any additional information that might have been provided by family members. Although some studies report that cross-informant rating associations are adequate for BRIEF-A,(138, 140) only moderate associations are demonstrated for the ASR.(241) Furthermore, as our main aim was to study how individuals with TBI experience their daily life after TBI, this guided the development of the study design.

The BRIEF-A assesses goal-directed regulation of thoughts, actions, and emotions, and is one of the most comprehensive measures regarding the number of items and executive domains assessed.(135) Sound psychometric properties and good reliability have been observed in Anglo-American populations,(143, 144) including large-scale norms.(135) The inclusion of validity scales is another advantage of this inventory. While the BRIEF-A has been applied to mixed neurological and psychiatric populations in Norway,(140, 287) to our knowledge no normative study has yet been performed in a representative adult Norwegian population. Furthermore,

the lack of a broad concurrent neuropsychological test battery makes our study less optimal for exploring the validity of the BRIEF-A as a proxy for cognitive functioning assessed by neuropsychological tests. However, this is beyond the scope of this thesis. In addition, performance-based measures were available for only a subgroup, which were included ad hoc in order to further explore the predictive value of early performance-based measures of cognitive function and later self-reported measures.

The ASR has demonstrated good reliability and validity in Anglo-American populations,(241) and provide estimates across a large range of perceived emotional and behavioural problems. Although the ASR has been applied to a mixed neurological sample of young Norwegian adults,(288, 289) normative studies in the full age range for representative Norwegian adults are lacking. The ASR reflects symptoms and not psychiatric disorders as such, and was also not accompanied by diagnostic interviews in our study.

The Norwegian version of the BDI has demonstrated good psychometric properties in the adult population; however, less is known about the psychometric properties among adolescents.(290) Also, less is known about its ability to distinguish between individuals in need of psychiatric treatment and those who are not. However, the intention was only to screen for depressive symptoms. This screening was performed on a subgroup of our participants, and was included ad hoc to explore the predictive value of the BDI for later perceived cognitive, emotional, and behavioural problems.

The reliability and validity of the GOSE was discussed in Section 3.3.4. However, lower inter-rater reliability may be of concern when the GOSE is assessed by telephone rather than face-to-face,(291) which is the case for some portion of the participants in our study. Furthermore, the interviewers were not blinded to clinical information under the assessment, which may weaken the conclusions drawn. However, it may nevertheless be argued that clinical experience and clinical information reduced the risk of assigning falsely high scores on the GOSE (good function) to individuals with reduced self-awareness.

5.1.3 External validity

External validity refers to the extent to which the results of a study can be generalized to other populations or settings. The gender distribution in our study demonstrated a majority of male participants with TBI, which has also been reported in other studies.(2, 265, 292) Our participants' length of education resembled other Norwegian (152) and international (293) studies. The main external cause of injury was traffic accidents, which is in accordance with European estimates.(2) However, our sample had a greater proportion of individuals classified with moderate TBI compared with some studies.(152, 293, 294) Also, because we included individuals with a GCS score of 13, it may be argued that our sample is skewed toward the milder end in terms of injury severity compared with other studies that recruited from rehabilitation settings.(118) However, as discussed in Section 5.1.1.1, these individuals would still be classified with moderate TBI based on duration of PTA and their documented injury on MRI. Furthermore, we acknowledge that by not including individuals with previous psychiatric and neurological diseases, conclusions may not apply to the entire TBI population.

Still, based on previous discussion and the following sections, the external validity of our study may be considered acceptable.

5.2 Reflections on our main findings

5.2.1 Differentiation between moderate and severe TBI

In general, differentiating between individuals with moderate and severe TBI revealed important differences in which cognitive functions were affected by the injury, as well as differences in the degree of cognitive impairment at both 3 and 12 months after the injury, and yielded a more accurate description of cognitive deficits and their improvement over time. In our study, individuals with severe TBI exhibited reduced function in several cognitive domains at 3 and 12 months post-injury. This was evident when compared with norms and with the control group, and corroborates previous studies.(55)

While most cognitive domains were affected by moderate TBI at 3 months post-injury, only executive function appeared to be affected by moderate TBI at 12

months post-injury. Reduced verbal fluency and flexibility in problem solving (executive function) has been observed to some extent after moderate TBI.(84, 149) However, most previous studies reporting cognitive outcomes after TBI have not differentiated between moderate and severe TBI.(213) Although group averages demonstrated no significant difference between moderate TBI and controls with respect to the cognitive domain processing speed, by looking at individual tests we observed some indication of reduced processing speed. This also confirms reduced speed of information processing as a contributor to cognitive deficits in TBI (59, 69) in this patient group. Although our study did not confirm better memory function among individuals with moderate TBI compared with those with severe TBI at 1 year post-injury,(118-120) this may be associated with methodological issues discussed previously.

Furthermore, we found that the groups differed with regard to which cognitive functions improved from 3 to 12 months post-injury. Only processing speed and visual memory improved for both groups. The groups also differed regarding their rates of improvement over time. To our knowledge, only four other comparable prospective studies have examined improvement trajectories grouped according to injury severity and time post-injury.(84, 152, 295, 296) However, evaluations of injury severity have varied across the studies. For example, greater improvement from 1 to 12 months post-injury was observed among patients with longer duration of coma,(84) although another study observed no differences in rate of improvement on any neuropsychological tests between participants with severe, moderate, or mild TBI grouped according to GCS score.(152) While differential recovery rates across cognitive domains have been demontrated,(117) to our knowledge no other prospective study has explored improvement across several cognitive domains according to injury severity, as we have done in our study.

Visual memory was the cognitive domain with the most prominent improvement from 3 to 12 months post-injury. This finding indicates that visual memory may have a different time frame during which intervention is most effective compared with other cognitive functions, which has been indicated in two previous studies.(117,

152) However, differential rates of recovery in visual memory were observed after moderate and severe TBI, which is in contrast to previous findings in studies that employed different tests to assess visual memory.(152) While the improvement in visual memory reflects true recovery to some degree,(284) the participants with moderate TBI improved from just below the normative average to just above the normative average. Our findings warrant further exploration in future studies, including the use of other tests.

Only individuals with severe TBI exhibited improvement of executive function, even though both groups had reduced executive function at 12 months post-injury. It is possible that individuals with moderate TBI had recovered most of their executive function within the first 3 months post-injury, supporting the observation that that untimed executive function recovers within the first 5 months post-injury.(117) However, the executive function remained worse among participants with moderate TBI than among controls 12 months post-injury. This finding may suggest that the neuropathological processes and the localization of brain damage frequently associated with TBI may play a significant role in cognitive impairment, even after moderate TBI.

5.2.2 Impairment or normality?

The differences detected between the groups (as discussed above in Section 5.2.1) may reflect a shift in the entire distribution of neuropsychological test performance among participants with TBI compared with healthy controls. Overlap in distribution of scores between groups may be observed even for large effect sizes,(247) although this relies on assumptions of normal distribution and equal variance between the groups. On the other hand, it has been argued that group averages or meta-analyses may obscure subgroups that present more pronounced cognitive dysfunction than the rest of the group (272, 297) – often referred to as “the miserable minority”.(298) While the term “miserable minority” was developed within the field of mild TBI, it might also apply to moderate TBI. Figure 11 illustrates these two approaches to understanding cognitive impairment after TBI.

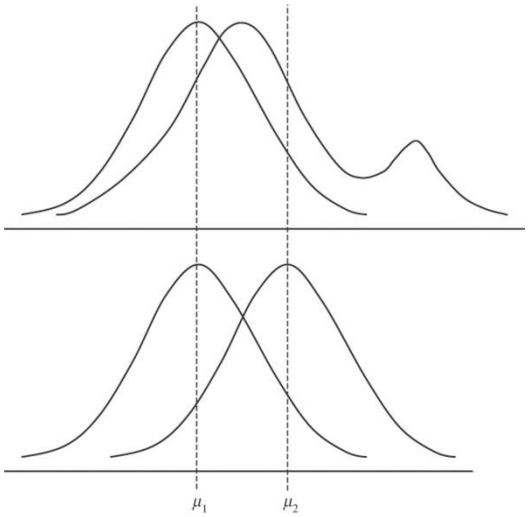

Figure 11
Hypothetical scenarios of distributions that mathematically would yield the same effect size. The secondary peak in the top distribution could represent the nested effect of a sub-group that had residual effects of TBI. μ_1 represent the population mean for persons *without* TBI, and μ_2 represent the population mean for persons *with* TBI. Lower scores is distributed toward the right end of the X-axis. Adapted with permission from Pertab et al (2009).(297)

In Study 1, 43% of participants with moderate TBI and 65% of participants with severe TBI were classified with cognitive impairment 3 months post-injury. This finding was in contrast to several other studies that reported more pronounced cognitive impairment, but with recruitment from rehabilitation setting and a greater proportion of severe TBI(118) or assessment at an earlier time point after the injury.(124, 299) Furthermore, at 3 months post-injury, 67% of the distribution of test scores for individuals with moderate TBI and controls overlapped in our study, compared with only an estimated 45% reported in a study reviewing cognitive impairment <6 months post-injury.(214) The authors of the latter study also reported 52% overlap at 24 months post-injury (214); however, moderate and severe TBI were not analysed separately. Although differently analyzed, we also observed that at 12 months post-injury individuals with moderate TBI performed in the normal range in all domains when compared with norms, and performed similarly to healthy controls regarding all cognitive domains except executive function. These findings lend strength to the concerns regarding overestimating cognitive impairments for individuals with moderate TBI.(214) Our results imply that more than one-half of individuals with moderate TBI would be classified with "normal" cognitive

performance. However, it may be argued that moderate TBI affects cognitive function differentially, and that there is a subgroup of individuals with TBI who are more vulnerable to sustaining chronic cognitive impairment, as illustrated in the upper distribution in Figure 11. Although the existence of such a subgroup has been challenged,(300) the debate still continues.(301)

Nevertheless, to define impairment is challenging (see discussion in Section 5.1.1). As observed in Study 2, only comparisons with the control group revealed reduced executive function among individuals with moderate and severe TBI at 12 months post-injury. In addition, a greater proportion of individuals with moderate TBI had low scores on tests measuring executive function and processing speed compared with controls. Therefore, classifying performance on neuropsychological tests only according to Anglo-American norms may have affected the proportion denoted as impaired. In addition, not classifying performance as impaired does not necessarily imply normality. For example, individuals with high intellectual ability may not be classified as impaired using only standard normative samples, despite reduced cognitive functioning compared with their cognitive capacity prior to the injury.(130-132) Taken together, this illustrates that comparisons to norms must be interpreted with caution.(84) If cut-off scores are used to indicate impairment, the scores should be adjusted for each patient's level of intelligence – as is commonly done in clinical neuropsychological assessments. Unfortunately, our estimate of intelligence was not optimal, which hampered adjustment for such estimates. Nevertheless, our study has highlighted the importance of addressing the degree and characteristics of cognitive impairments after moderate TBI, specifically.

5.2.3 Self-reported cognitive, emotional and behavioural function 2-5 years post-injury

Participants with moderate and severe TBI reported greater perceived overall executive problems than healthy controls. This finding was evident both in terms of group differences and regarding the frequency with which individuals reported problems in the clinical range, corroborating previous studies in TBI populations.(138) In particular, perceived problems with attentional control and monitoring ongoing operations were frequently reported, supporting previous studies

that assessed populations with other neurological deficits.(140, 302, 303) Problem solving, initiation, and task monitoring were not perceived as problematic among individuals with TBI in our study. This is in contrast to a study comprising moderate and severe TBI survivors in which these functions were perceived as most problematic.(138) However, the latter study included a greater proportion of individuals with severe TBI and lacked a control group, which makes these findings difficult to compare.(138)

In particular, we observed that participants with TBI experienced more problems with inhibition, mental flexibility, and emotional regulation. In addition, our results demonstrated greater perceived problems with emotional regulation among respondents with TBI than healthy controls. Particularly excessive mood swings were common, which reportedly indicates an increased risk of psychiatric diagnoses.(241) Controlling emotional and behavioural expression may be important for social and occupational functioning. Our respondents with TBI did not report more withdrawal or problems with social relations, although these features have been observed in other studies.(158, 304) The substantial proportion of moderate TBI in our study may reduce the risk of underreporting problems due to reduced self-awareness,(180) lending strength to our finding. Interestingly, we did not find an association between their experiences of their own cognitive, emotional, and behavioural function and occupational status.

Individuals with TBI reported a high burden of internalizing problems, and more often reported feeling sad or depressed, which corroborates previous studies.(159, 198, 207) The main concerns for participants with TBI were related to perceived negative self-image, indicating that addressing positive re-appraisal of the self-image is important in post-TBI rehabilitation. The individuals with TBI also reported more problems with externalizing and aggressive behaviour than healthy controls, which is consistent with the literature reviewing long-term psychiatric outcomes after TBI.(157, 160) In our study, individuals with TBI did not report more rule-breaking behaviour (lack of empathy, substance abuse, and law-breaking behaviour) or intrusive behaviour, which suggests that the aggression scale encompasses the most prominent post-TBI behavioural problems. The aggression scale on the ASR consists

of several items related to behavioural control, and we speculate that executive problems (e.g., impaired inhibition and reduced task monitoring/switching) (109) may mediate the behavioural and emotional problems experienced by individuals after TBI.(157) Our results suggests that the ASR may prove to be valuable as a tool during post-TBI clinical assessment, but that a single mean composite profile does not typify the emotional and behavioural sequelae reported in the TBI population.(159, 198)

Finally, we found that group differences did not always indicate symptoms above the clinical cut-off, which is in line with previous studies.(159, 162) The challenges visited by exploring the prevalence of ratings above a clinical cut-off mirror observations made with regard to the application of cut-off points and impairment on performance-based neuropsychological tests discussed in Section 5.2.2. Nevertheless, particular concern is raised by the lack of Norwegian or Scandinavian norms. Scandinavian norms have been developed for the children's version of the ASEBA (CBCL), demonstrating significant differences in responses between Anglo-American and Scandinavian samples.(305) The diagnostic approach of assessing neuropsychiatric problems with structured diagnostic interviews is considered the "gold standard". However, we believe that self-report questionnaires yield important insight into how life after TBI is experienced by the individual, and have demonstrated that subclinical problems are commonly experienced and may add to the total symptom burden for individuals with TBI

5.2.4 Predictors of outcome – the biopsychosocial model

In accordance with the biopsychosocial model outlined in Section 1.5,(204) our study demonstrated the consequences of moderate and severe TBI regarding all aspects of functioning: biological, psychological, and social changes. Monitoring the clinical course for individuals with TBI on a long-term basis is complex. As our results indicated, cognitive, emotional, and behavioural outcomes may have distinct pathways and associated risk factors. In addition, the outcomes are interrelated to some extent. This must be kept in mind in the following sections.

5.2.4.1 DAI – a possible biological risk factor for reduced self-reported cognitive, emotional, and behavioural function

Extending previous studies, our results suggest that DAI plays a role in the development of perceived internalizing problems (e.g., anxiety and depression) and behaviour regulation. This association persisted even after adjusting for early self-reported depressive symptoms, which the present study is the first to demonstrate. DAI often causes widespread damage in the fronto-temporal and subcortical structures (8) that also affects subcortical structures with frontal projections,(149, 156) areas that are associated with executive functions.(111) However, both focal and diffuse damage affects the neural pathways necessary for optimal function.(93) Furthermore, the group without DAI in our study was small, and only comprised individuals with moderate TBI. In addition, age at injury and length of education may have a confounding effect on the association observed with regard to self-reported behaviour regulation. Nevertheless, other measures of injury severity, such as GCS score and duration of PTA, appeared not to be associated with later self-reported problems, and the assessment of the predictive role of PTA extends existing knowledge. Taken together, we may speculate that the pathophysiological processes associated with DAI have a distinct effect on later perceived problems with emotional and behavioural regulation as long as 2-5 years after injury.

5.2.4.2 Symptoms of depression – double vulnerability?

Self-reported symptoms of depression within the first year post-injury predicted later perceived overall problems with goal-directed cognitive and behavioural regulation, in addition to externalizing and internalizing problems. Although the participants had no previous psychiatric disorder, pre-injury subclinical symptoms cannot be ruled out. However, our results suggest that the depressive symptoms developed secondary to the TBI. In particular, individuals who reported depressive symptoms at 1 year post-injury had a high risk of experiencing later cognitive and emotional problems. This finding is consistent with studies showing that emotional distress affects the extent of self-reported cognitive problems.(140, 306) However, the damage to neural circuits involving cortical, subcortical, and limbic structures that is often observed after DAI may cause changes to neural circuitries and neurotransmitter systems involved in emotional regulation, thereby also affecting the development of

secondary mood disorders.(167) However, depressive symptoms may also be the result of psychological vulnerability, self-awareness of disability, psychological response to the injury, and social disruption.(171, 207) One study in particular found that the person's perception of the severity of their cognitive impairment shortly after the TBI was associated with later symptoms of depression.(200) Taken together, the results indicate that individuals with TBI may be doubly vulnerable to developing secondary symptoms of depression after moderate and severe TBI.

5.2.4.3 Age and education

Younger age at injury and early symptoms of depression predicted more self-reported externalizing problems 2-5 years post-injury, consistent with previous studies.(164, 198) However, other reports have indicated that more years of education and higher socioeconomic status are associated with lesser endorsement of emotional and behavioural problems,(198) which was not confirmed in our study. Good access to health services regardless of socioeconomic background and the community welfare system in Norway may contribute to this finding. In addition, the elevated aggressive behaviour in participants who were younger at the time of injury could be explained by increased vulnerability to injury in developing brain areas.(19) The frontal lobe is still maturing during adolescence and young adulthood, rendering functions located therein (e.g., emotional and behavioural regulation) at increased risk following injury.(113, 307) Furthermore, age was not associated with symptoms of depression, anxiety, or somatic complaints among individuals with TBI. This suggests the presence of distinct pathways and risk factors in the development of depression and anxiety as opposed to aggression, as others have also indicated.(198)

5.2.4.4 Neuropsychological test performance and self-reported function

Reduced attention and reduced working memory were among the most prominent problems reported by the participants with TBI in Study 3. However, performance-based neuropsychological tests of attention and working memory did not discriminate well between individuals with TBI and controls at 3 or 12 months post-injury. It is possible that the selected Continuous Performance Tests (CPTs) were less useful in assessing attention among individuals with TBI. Nevertheless, other CPT paradigms have been found to be sensitive to dysfunction of the attention

system caused by acquired brain injury or in conjunction with any specific disorder.(308) However, our finding may also support previous research demonstrating relatively preserved vigilance after TBI.(309) In addition, the tests assessing working memory in our study may measure aspects that are only mildly affected by TBI, and tests requiring more simultaneous processing, such as the n-back paradigms,(310) might be more useful in future studies of working memory deficits after TBI. However, our findings may also illustrate the problematic association between performance-based measures and self-report instruments.

In Study 3, we observed no association between performance-based measures of cognitive function 3 months post-injury and self-reported executive function. This finding was in contrast to other studies that have demonstrated associations between performance-based and self-reported measures of task monitoring and switching.(138, 140) The lack of convergence among the data may be explained by the time interval between the assessments or by different modes of measurement.(113) It has been argued that performance-based measures of executive function provide insight into the efficiency of processing, while rating scales of executive function provide information about success in rational goal pursuit in everyday life.(114) Another explanation is that self-reported cognitive complaints are affected by emotional symptoms,(140, 194, 195) while performance-based measures of executive function are more closely linked to neural damage after TBI.(83, 139, 140, 195) It is also possible that the assessment methods are complementary and reflect different neural networks.(140) Furthermore, as we observed in Study 1, a proportion of those with a normal neuropsychological assessment at 3 months post-injury nevertheless went on to report later complaints with respect to global outcome. However, the upper range of the GOSE relies on self-reporting, and in accordance with Figure 3, neuropsychological performance explains only a part of self-reported responses.(207)

5.2.4.5 The significance of executive function

Regardless of injury severity, executive function was important to patients ability to resume independent living, employment, and leisure activities, as evaluated by global outcome. This association was evident even after adjustment for age and injury

severity (duration of PTA), a finding that extends previous literature. Although it has been argued that neuropsychological tests of executive function do not encompass all aspects of executive function and lack ecological validity, our findings indicate that there is at least some association between such tests and concurrent global function. Furthermore, reviews have pointed out that executive function in particular has been the most reliable neuropsychological indicator of reduced global function.(65, 154) Our results support the view that patients' problems with employment, social relationships, leisure activities, and independent living might be specifically related to executive dysfunction.(65, 149)

5.3 Clinical implications and future perspectives

A full recovery is the initial goal for everyone sustaining a TBI. However, predicting the course of recovery and how the individual will experience life after TBI is complex and difficult. This was particularly true for the milder injuries and outcomes in the upper ranges. Additional research on outcome, specifically after moderate TBI, is warranted, as cognitive impairment after moderate TBI appears to be overestimated. Furthermore, the observation that above average performance is not uncommon after TBI may indicate that TBI affects specific cognitive functions in the individual, and may provide clues to cognitive compensation strategies for patients during the rehabilitation process. This study is one of the few studies that address good or preserved cognitive abilities after TBI, and cognitive strengths are important to consider during the rehabilitation process. Exploration of the existence of a "miserable" proportion of persons with TBI that experience more severe cognitive dysfunction after moderate TBI is also needed. If such a subgroup is confirmed, attempts to detect risk factors specifically for this subgroup would be important, and would provide the necessary groundwork for additional clinical management and rehabilitation of individuals with moderate TBI.

Our study further underscores the clinical importance of early MRI to detect DAI using standard procedures that are easily implemented in the clinic. DAI appears to be an early indicator for later symptoms of internalizing problems, such as depression and anxiety. Owing to the heterogeneous nature of TBI,(4) future prospective studies with large samples that distinguish focal damage from DAI are

necessary for understanding the neural underpinnings of self-reported executive, emotional, and behavioural problems. Studies of the longitudinal evolution of MRI characteristics in association with performance-based neuropsychological tests and self-reported function may provide additional insight into the course and consequences of the neuropathological processes. Although beyond the scope of this thesis, we have observed that apparent diffusion coefficient (ADC) values on MRI were associated with both global outcome and the ability to perform speeded, complex sensory-motor action.(311) Our research group has also found that increased brain activations in individuals with TBI on fMRI had a dose-dependent, linear, positive relationship to injury severity and were negatively correlated with self-reported executive problems in daily life situations.(312) Exploring relations between the evolution of cerebral volumes in targeted brain regions and cognitive and emotional function are still in the planning stages.

Based on our findings, we recommend scheduled assessments at several time points during the subacute and chronic phases up to 2-5 years after sustaining moderate or severe TBI. These checkpoints would allow for psycho-educative intervention with possible consequences for all persons with TBI. In addition, screening for cognitive dysfunction, symptoms of emotional or behavioural problems, as well as other risk factors for reduced function and outcome on a long-term basis would be possible. Reduced executive function appears to be a particularly important factor in long-term outcome, and is essential for the clinician to recognize and target in rehabilitation plans. Furthermore, there is need for a more uniform definition of impairment that corrects for the differential sensitivity and specificity of the neuropsychological tests. In addition, algorithms for correcting IQ estimates should be routinely implemented in future studies, as illustrated by the work of Iverson et al.(128) Although the psychometric properties of some of the neuropsychological tests have been explored,(125, 126) our study illustrated the continued need for the development of Scandinavian norms - for both the neuropsychological tests and the questionnaires applied in our study. In addition, future studies of preserved abilities among individuals with TBI are warranted, as this could provide clues to compensatory strategies for rehabilitation after TBI. Our results also indicate a further need for

validation of both performance-based and self-report measures of executive function, in relation to each other and to other measures of outcome.

Furthermore, our findings suggest that depressive symptoms should be routinely assessed during rehabilitation, as they appear to be an important warning of future emotional problems. Adaptive problems in everyday life owing to impairments after TBI in combination with the negative thinking that is typically experienced during depression (162) may result in a negative spiral, leading to the increase in self-reported depressive symptoms that we observed in our study. Inclusion of structured diagnostic interviews and personality inventories in studies of predictive factors of self-reported cognitive and emotional function may add to the existing knowledge of emotional and behavioural outcomes after TBI.

5.4 Ethical reflections – should this study have been done?

At injury and during the acute phase, individuals sustaining TBI and their families are in distress. It may be argued that being asked to participate in research might add to the burden. Furthermore, individuals with TBI are considered a vulnerable population owing to their reduced cognitive function. In cases of significant cognitive impairment, close relatives provided consent on behalf of the injured individual, which may be considered problematic. However, much work was done to ensure that consent was based on good information about the purpose of the study (orally and in writing), and that the participants were able to withdraw from the study at any point. Particular care was taken when securing consent from potential participants younger than 16 years of age.

The study did not include any painful or invasive methods, and employed only methods that were part of the ordinary clinical management of persons with TBI at the study. The procedures initiated by the research protocol did however represent improvements in clinical management and patient education. Specifically, the implementation of scheduled follow-up at several time points represented an improvement, and allowed us to monitor individuals at risk and uncover secondary problems caused by the TBI. In particular, detecting clinically significant symptoms of mental health problems at long-term follow-up gave us the opportunity to offer referrals for psychiatric evaluation and treatment, which is a distinct improvement.

6.0 Summary and conclusions

Returning to Johnny and Nina, who were introduced in the beginning of this thesis, the results from this study indicate that their future would most likely be summarized like this:

Nina, who survived a moderate TBI, recovered from PTA 1 day after the injury. Although some cognitive problems were detected at 3 months post-injury, she performed above the normative average on most neuropsychological tests at 12 months post-injury. The only exception was tests of executive function, in which average performance was observed. She returned to full-time work within the first 6 months after the TBI. Although she reported feeling more exhausted than before, others had not noticed her fatigue. She also reports some symptoms of fatigue, low self-esteem, and problems with headaches at 12 months post-injury. During the next few years, she is at risk of developing additional symptoms of depression, accompanied by problems with attention, mood swings, and sadness.

Johnny, who survived a severe TBI with additional complications during medical treatment, experienced altered consciousness for months after the injury. One year later, reduced processing speed, memory problems, and executive dysfunction that affect his everyday life still persist. To be able to complete his education as a carpenter, he will need integrated service from health personnel, community services, and special education programmes. However, due to the continued problems caused by the limb fractures, evaluation of a different occupation may be needed in the future. In the long term, he most likely will experience problems with attention, working memory, rigidity, regulating emotions, and aggression. There is still some risk of developing secondary depression and rule-breaking behaviour, as well as becoming unemployed.

Our studies have produced new and important knowledge about the differential patterns of cognitive function and recovery within the first year after moderate and severe TBI. The study has also provided information about a broad spectrum of long-term perceived outcomes after moderate and severe TBI, resulting in profiles of self-reported cognitive, emotional, and behavioural function 2-5 year post-injury. In addition, the results have extended previous knowledge about predictors and

correlates to long-term self-reported cognitive, emotional, and behavioural problems after TBI.

The following points summarize our main findings:

- Cognitive function was affected by both moderate and severe TBI at 3 and 12 months post-injury, and was associated with global outcome at 12 months post-injury.

- While executive function among individuals with moderate TBI was reduced compared with healthy controls, individuals with severe TBI exhibited reduced motor function, processing speed, verbal memory, and executive function at 12 months post-injury.

- Individuals with moderate and severe TBI also differed with regard to which cognitive functions improved from 3 to 12 months post-injury; only processing speed and visual memory improved for both groups during this interval.

- A proportion of individuals with moderate TBI exhibited normal performance on most neuropsychological tests at both 3 and 12 months post-injury — a finding that lends strength to the concerns regarding the overestimation of cognitive problems after moderate TBI. However, compared with healthy controls, individuals with moderate TBI had more low scores on tests measuring executive function and processing speed at 12 months post-injury.

- Regardless of injury severity, executive function appeared to be important to patients' ability to resume independent living, employment, and leisure activities, as evaluated by global outcome.

- Persons with moderate and severe TBI reported more pronounced difficulties in aspects of executive function related to attentional control, working memory, and emotional regulation, as well as emotional and behavioural

problems related to symptoms of depression, anxiety, and aggressive behaviour, at 2-5 years post-injury compared to healthy controls.

- Reported symptoms of depression during the first year after injury and the detection of DAI on early MRI were important predictors of later self-reported executive, emotional, and behavioural problems.

- Our findings indicate interplay between demographic, neuropathological, and psychological factors during the development of self-reported executive, emotional, and behavioural problems for years after TBI. As such, outcomes after moderate and severe TBI are best understood within the framework of a biopsychosocial model.

- Based on our results, early neuroimaging examinations and psychological evaluations screening for symptoms of depression may provide clues as to which patients might be at risk of developing later problems, and may assist in clinical decision-making regarding long-term follow-up.

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