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ORIGINAL ARTICLE

Differentiated patterns of cognitive impairment 12 months after severe and moderate traumatic brain injury

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Abstract

Objective: To assess cognitive function at 12 months after moderate and severe traumatic brain injury (TBI) separately, as well as improvement from 3 to 12 months and relationship to global outcome.
Methods: Cognitive function among patients with moderate ($n = 30$, Glasgow Coma Scale score (GCS) 9–3) and severe traumatic brain injury ($n = 20$, GCS score ≤ 8), recruited from an unselected neurosurgical cohort, all with MRI performed in the early phase were assessed with a neuropsychological test battery and Glasgow Outcome Scale Extended. Healthy volunteers ($n = 47$) matched for age, gender and years of education served as controls.
Results: Executive function was reduced at 12-months post-injury in patients with both moderate and severe TBI. However, motor function, processing speed and memory were reduced only among patients with severe TBI. Both patients with moderate and severe TBI improved their processing speed and visual memory. Patients with moderate TBI also improved motor function, while patients with severe TBI also improved executive function.
Conclusion: Differentiating between patients with moderate and severe TBI yields a more accurate description of cognitive deficits and their improvement over time. Further, executive dysfunction and attention problems affected the ability to resume independent living and employment regardless of injury severity and age.

Keywords

Craniocerebral trauma, deficits, executive function, longitudinal studies, memory deficits, neurobehavioural signs and symptoms, outcome assessment

History

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Abbreviations: DAI, diffuse axonal injury; GCS, Glasgow Coma Scale; GOSE, Glasgow Outcome Scale Extended; HISS, Head Injury Severity Scale; IQ, Intelligence Quotient; MRI, Magnetic Resonance Imaging; PTA, post-traumatic amnesia; TBI, traumatic brain injury.

Introduction

Survivors after moderate and severe traumatic brain injury (TBI) often suffer from impairments across a range of cognitive abilities, including executive functions, processing speed, memory and attention [1–4]. Such impairments are often hidden disabilities and are not always well understood by family, friends, teachers or employers. When reporting cognitive outcomes after TBI, many studies have not differentiated between moderate and severe TBI despite the fact that patients with TBI comprise a heterogeneous group [2]. Therefore, these studies may have over-estimated impairments for moderate TBI and under-estimated them for severe TBI [3, 4]. 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 [1]. Some studies have shown that patients with moderate TBI perform significantly better than those with severe TBI on tests of memory [5–7] and executive function at 1-year post-injury [8]. However, some of these studies have assessed outcome with different neuropsychological tests and used differing comparison groups (norms, control groups, patients with mild or severe TBI). This makes comparisons across studies difficult.

Patients with moderate and severe TBI might also differ regarding their rates of improvement over time. Dikmen et al. [9] observed greater improvement from 1 to 12 months post-injury among patients with longer duration of coma, but few other studies have compared improvement trajectories for patients grouped according to injury severity. Further, the cognitive domains have dissimilar recovery trajectories [10–14]. Christensen et al. [10] also found that recovery varied

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according to time post-injury; where the most accelerated recovery took place during the first 6 months post-injury, with more attenuated recovery after that. Further, most previous prospective longitudinal studies examining these issues have used only a few tests [15].

Cognitive dysfunction observed after TBI may also affect the ability to resume leisure activities and employment, cause problems with independent living and impair social relationships [16–18], all of which may be termed global outcomes [19]. Global outcome has been observed to be associated with concurrent neuropsychological function [19, 20]. While strong association has been found with executive function, the evidence so far remains inconclusive with regard to other cognitive domains [21, 22].

Using a selected sample of tests, the authors have previously reported that, in a sample of patients with definite brain injury on MRI in the acute phase, 43% of the patients with moderate TBI had cognitive impairment according to norms on nine selected sensitive tests, while 65% of the patients with severe TBI performed had the same level of impairment [23]. Hence, the aims of this prospective study were to assess cognitive function 12 months after TBI in approximately the same, unselected cohort of patients with moderate and severe TBI with definite findings on MR-images in the acute phase and to describe improvement from 3 to 12 months. Some studies have pointed out the necessity of using a broad battery of neuropsychological test when assessing cognitive function and improvement after TBI [9, 10] and this study has attemted to address this. In particular, the aim was to differentiate between patients with moderate and severe TBI to see whether this gives a more accurate description of the cognitive function [4]. Another aim was to explore whether performances on neuropsychological tests at 12 months were associated with concurrent measures of global function.

Methods

Study design and participants

This prospective follow-up study was undertaken at a level I trauma centre, St. Olavs Hospital, Trondheim University Hospital, Norway. The hospital has a database that includes all patients admitted to the Neurosurgical Department with moderate-to-severe head injuries, as defined by the Head Injury Severity Scale (HISS) criteria [24]. The inclusion period for the present study was from October 2004 to October 2007. Survivors in the main database between age 15–65 years were invited to participate in neuropsychological testing at 3 and 12 months post-injury if they met the following inclusion criteria successively: (1) no ongoing or pre-injury substance abuse, diagnosed neurological or psychiatric condition or previous moderate-to-severe head injury according to the same criteria, (2) the ability to co-operate during testing (without disorders of consciousness) and (3) fluency in the Norwegian language. Flow-chart and additional descriptions of non-participants between 15–65 years are included in the Appendix.

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 they could not be reached (17 with moderate TBI and three with severe TBI). Thus, the final sample population consisted of 50 patients (30 with moderate and 20 with severe TBI; 71% of the eligible patients) tested at both 3 and 12 months post-injury. Healthy controls were recruited among family and friends of the patients with TBI and otherwise through advertisements and among acquaintances of researchers and staff. The control group consisted of 47 healthy persons without previous TBI, matched to the total sample of patients for age, sex and education.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Social Science Data Services (NSD). Written consent was obtained from patients and from parents of individuals younger than 16 years.

Education and pre-injury function

Pre-injury variables were years of education and an estimated mean of marks from school attendance prior to the injury based on information provided in interviews at the time of testing. A 6-interval scale was used, rated from low (0) to high (6) level of performance.

Injury-related variables

Injury-related variables were mechanism of injury, lowest observed Glasgow Coma Scale (GCS) score (recorded at or after admittance or before intubation in cases of pre-hospital intubation) [25], magnetic resonance imaging (MRI) findings and duration of post-traumatic amnesia (PTA). MR imaging (1.5 Tesla) was performed at median 10 days post-injury (range = 1–120). The scan protocol included T1 and T2-weighted sequences, a T2-weighted gradient echo sequence (T2*), fluid-attenuated inversion recovery (FLAIR) sequences and diffusion-weighted imaging (DWI). MRI parameters and procedure of evaluation have been reported previously [26]. MRI findings were categorized as cortical contusions, diffuse axonal injury (pure DAI) and contusions and DAI in combination. Diffuse axonal injury (DAI) was defined as the presence of lesions in lobar white matter, corpus callosum or brainstem. These were identified either as hyper-intensities in the FLAIR sequence or DWI or as microhaemorrhages in the T2* sequence. A GCS score of 9–13 was classified as moderate TBI and a GCS score of $\leq$ 8 as severe TBI according to the Head Injury Severity Scale [24, 26].

Global outcome

Global outcome (i.e. ability to resume independent living, employment and leisure activities) was assessed by the Glasgow Outcome Scale Extended (GOSE) at 3 and 12 months follow-up [27]. The scale rates global outcome from 1–6 as severe/moderate disability, 7 as lower good recovery and 8 as upper good recovery.

Neuropsychological assessment

Neuropsychological assessment was performed at mean 98 ($\pm$11) and 379 ($\pm$45) days post-injury. Clinical psychologists

(neuropsychologists), two trained psychology students and one experienced test technician at St. Olavs University Hospital performed all testing. 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, all test-protocols with results were reviewed by the first author.

The Vocabulary and Matrix Reasoning sub-tests of the Wechsler Abbreviated Scale of Intelligence (WASI) [28] were administered at 3 months post-injury to estimate current general intellectual capacity (intelligence quotient (IQ)). A split-half procedure (using every second item; 1, 3, 5, etc, or 2, 4, 6 to estimate a raw score) was used to avoid re-test effects at reassessment. 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.

The neuropsychological tests selected are listed in Table I. They were grouped into different domains of cognitive function; motor function [29], processing speed [30, 31], working memory [32], attention [33], visual memory [34, 35], verbal memory [36] and executive function [30, 37]. The tests have demonstrated adequate validity and reliability [3] and many have been recommended by Wilde et al. [38] as common outcome measures after TBI.

To minimize practice effects, parallel versions for the neuropsychological tests were administered at 12 months when available [30, 36]. In some cases, one or more tests were not administered for various reasons; thus, the number of patients evaluated with each test deviates from the total sample size.

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 [3] was used. Standardized scores on the individual neuropsychological tests were grouped into composite scores for each cognitive domain.

Statistical analyses

Dependent variables were checked for normality by use of the Shapiro-Wilks test and inspection of Q-Q plots. Demographic characteristics, injury severity characteristics, different cognitive domains and each test are presented as mean (± SD) for normally distributed data and otherwise as median with interquartile range (IQR, 25th and 75th percentile). Statistical analyses were performed with SPSS 18.0.

In the presence of missing data, available case analysis was used, utilizing all cases for which a variable is present. Thus, the number of cases differs for each variable. Reported *p*-values are two-sided and a α-level of 0.05 was applied.

Analyses of variance (ANOVA) were used for between-group comparisons (controls, moderate 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 *a-priori* determined composite scores [39]. Non-parametric tests (i.e. Kruskal-Wallis test, Mann-Whitney U-test, chi-squared) were used for between-group comparisons when data were not

Table I. Neuropsychological tests used to assess different domains of cognitive function.

Neuropsychological tests			Reference
Motor function			
Grooved Pegboard			[29]
	Dominant hand		
	Non-dominant hand		
Information processing speed			
Delis Kaplan Executive Function System:	(D-KEFS)		[30]
Trail Making Test	Condition 2 (number sequencing)	(TMT)	
	Condition 3 (letter sequencing)		
Colour-Word Interference Test	Condition 1 (color naming)	(CWIT)	
	Condition 2 (word reading)		
Symbol Digit Modality Test	Oral version	(SDMT)	[31]
	Written version		
Working Memory			
Wechsler Adult Intelligence Scale–Third edition	(WAIS-III)		[32]
	Digit Span		
	Letter-Number Sequencing		
Attention			
Conners' Continuous Performance Test II	(CCPT-II)		[33]
Visual memory			
Continuous Visual Memory Test	(CVMT)		[34]
Rey-Osterrieth Complex Figure Test[a]	(ROCF)		[35]
Verbal memory			
California Verbal Learning Test-II	(CVLT-II)		[36]
Executive function			
Category Test computer version[b]			[37]
Verbal Fluency Test (D-KEFS)	Condition 1 (letter fluency)		[30]
	Condition 3 (category change)		
TMT (D-KEFS)	Condition 4 (Number-Letter Sequencing)		
CWIT (D-KEFS)	Condition 3 (Inhibition)		
	Condition 4 (Inhibition/Switching)		
Tower Test (D-KEFS)			

[a]ROCF was not administered at 3 months and is not included in analyses comparing cognitive function at 3 and 12 months post-injury.
[b]Category test was not administered at 3 months and is not included in analyses comparing cognitive function at 3 and 12 months post-injury.

normally distributed. When comparing the number of scores above or below average only p-values ≤ 0.01 are reported to adjust for multiple comparisons. Paired samples t-tests were used to analyse differences in performance at 3 and 12 months after injury. Effect sizes were calculated as Cohen's d based on pooled variance (d_{pooled}) [40]. Cohen [41] defined a d of 0.8, 0.5 and 0.2 as reflecting large, medium and small effect sizes, respectively. Where relevant, 95% confidence intervals (95% CI) are reported.

Proportions were compared using the Newcombe confidence interval [42] and the unconditional z-pooled test, as recommended by Lydersen et al. [43].

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. duration of post-traumatic amnesia (PTA) and age at injury). Simple linear regression analyses were used to examine whether demographic, pre-injury characteristics or injury-related measures influenced the magnitude of the improvement in cognitive function between 3 and 12 months post-injury.

Results

Pre-injury characteristics, demographic characteristics and other injury-related variables are presented in Table II. Patients with moderate and severe TBI did not differ regarding distribution of sex, age at injury, age at testing, number of days between injury and testing, years of education or pre-injury academic grades. All but one patient had definite lesions in the brain parenchyma in the early MRI. However, this moderate TBI patient had 4 days PTA and traumatic subarachnoid haemorrhage on the initial CT scan. Of all patients, 67% had diffuse axonal injury (53.3% of moderate TBI and 85% of severe TBI). Patients with moderate TBI had significantly shorter PTA duration than patients with severe TBI. Both patients with moderate TBI [mean (SD) = 119 (11) vs. 110 (11), $p = 0.023$] and severe TBI [mean (SD) = 119 (11) vs. 105 (18), $p = 0.001$] exhibited significantly lower estimated IQ than healthy controls. The patient groups did not differ in their intellectual capacity.

Cognitive function at 12 months post-TBI

Patients with moderate TBI performed significantly worse than controls only on the executive function domain (Table III) and patients with severe TBI performed worse than controls on the motor function, processing speed, verbal memory and executive function domains, with effect sizes ranging from 0.76–1.06.

Since comparing only group averages might mask the greater variance in performances among patients with TBI, performances were categorized regarding *each* of the 36 sub-scores from the 12 neuropsychological tests into low performance, average performance and high performance,

Table II. Demographics and injury severity characteristics of study participants with moderate or severe traumatic brain injury (TBI). Central tendency and variance are presented as mean and standard deviation (SD).

Variable	*n*	Moderate TBI		*n*	Severe TBI		*n*	Controls		*p*-value
Demographics										
Male sex[a]	30	20	(67)	20	17	(85)	47	36	(77)	0.324[c]
Days post-injury 1st test[a]	30	94.5	(11)	20	103	(19.25)				0.276[d]
Days post-injury 2nd test[a]	30	367	(15)	20	372	(13)				0.238[d]
Age at injury	30	33.10	(15.67)	20	27.40	(13.15)				0.142[d]
Age at test	30	34.13	(15.66)	20	28.45	(13.11)	47	30	(13)	0.313[c]
Years education	30	11.8	(2.2)	20	11.7	(2.0)	47	12.1	(1.9)	0.655[c]
Pre-injury grades	28	3.3	(1.4)	20	2.9	(1.3)				0.290[e]
Estimated IQ	29	110	(11)	19	105	(18)	47	119	(11)	<0.001[c]
Injury mechanisms	30			20						0.402[e]
Fall[b]		11	(36.7)		9	(45)				
Traffic accident[b]		15	(50)		11	(55)				
Other[b]		4	(13.3)		0	(0)				
TBI severity characteristics										
GCS score (median)	29	12		19	6					
PTA < 1 week[b]	30	19	(63.3)	19	6	(31.6)				0.030[e]
PTA 0–1 week[b]	30	19	(63.3)	19	6	(31.6)				0.055[e]
PTA 1–2 weeks[b]		5	(16.7)		3	(15.8)				
PTA 2–3 weeks[b]		3	(10.0)		3	(15.8)				
PTA 3–4 weeks[b]		3	(10.0)		3	(15.8)				
PTA more than 4 weeks[b]		0	(0.0)		4	(21.1)				
MRI findings	29			20						
No findings[b]		1	(3.1)		0					
Pure DAI[b]		6	(20)		5	(25)				
Cortical contusions[b]		13	(43.3)		3	(15)				
Cortical contusions/DAI[b]		10	(33.3)		12	(60)				
Presence of DAI[b]		16	(53.3)		17	(85.0)				0.022[f]

SD, standard deviation; IQR, inter quartile range; GCS, Glasgow Coma Scale; PTA, post-traumatic amnesia; DAI, diffuse axonal injury.
[a]Median (IQR).
[b]no. of cases (%).
[c]Analysis of Variance (ANOVA).
[d]Mann-Whitney U-test.
[e]Pearson's Chi-squared test.
[f]Unconditional z-pooled test.

Table III. Neuropsychological test performance at 12 months post-injury collapsed into composite scores (*T*-scores) for patients with moderate and severe TBI compared with controls.

	Controls (C)			Moderate TBI (M)			Severe TBI (S)					
Test; mean (SD)	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	ANOVA *p*	Post-hoc tests (Scheffe)	Effect-size Cohen's *d*
Motor function	47	48.59	(7.69)	30	46.80	(9.33)	20	41.30	(10.37)	0.010	C vs. M: $p = 0.688$	0.21
											C vs. S: $p = 0.010$	0.80
											M vs. S: $p = 0.102$	0.56
Information processing speed	47	52.83	(5.28)	30	48.73	(10.76)	19	43.56	(11.98)	0.001	C vs. M: $p = 0.145$	0.48
											C vs. S: $p = 0.001$	1.00
											M vs. S: $p = 0.141$	0.45
Attention	47	50.92	(4.92)	29	49.52	(4.16)	19	48.09	(8.50)	0.164	C vs. M: $p = 0.569$	0.31
											C vs. S: $p = 0.183$	0.41
											M vs. S: $p = 0.691$	0.21
Working memory	47	50.48	(9.18)	29	49.12	(9.67)	20	48.83	(10.20)	0.746	C vs. M: $p = 0.834$	0.14
											C vs. S: $p = 0.811$	0.17
											M vs. S: $p = 0.994$	0.03
Verbal memory	47	52.46	(7.21)	30	49.86	(10.59)	20	44.70	(12.55)	0.012	C vs. M: $p = 0.511$	0.29
											C vs. S: $p = 0.012$	0.76
											M vs. S: $p = 0.182$	0.44
Visual memory	47	48.59	(9.63)	28	54.94	(10.71)	17	47.10	(13.75)	0.024	C vs. M: $p = 0.055$	0.62
											C vs. S: $p = 0.889$	0.12
											M vs. S: $p = 0.068$	0.64
Executive function	46	53.38	(5.32)	25	48.78	(6.29)	18	46.08	(8.12)	< 0.001	C vs. M: $p = 0.006$	0.79
											C vs. S: $p < 0.001$	1.06
											M vs. S: $p = 0.103$	0.37

using thresholds at 1.5 SD below or above the normative mean. Across all tests, patients with severe TBI had a significantly higher number of sub-scores in the low performance category than controls (Table IV). Although the difference between patients with moderate TBI and the other groups did not reach significance, a larger amount of low scores was found within the cognitive domains processing speed and executive function, but not in other domains. The groups did not differ with regard to the amount of high performances.

Improvement in cognitive function from 3 to 12 months after TBI

Patients with moderate TBI had improved significantly on the domains motor function, processing speed and visual memory (Table V). They performed significantly worse on the domain verbal memory. Patients with severe TBI improved significantly regarding the processing speed, visual memory and executive function domains. Recovery was most pronounced in the visual memory domain for both groups. Patients with severe TBI exhibited particularly poor performance in this domain at 3 months post-injury.

Association with global outcome (GOSE) at 12 months post-injury

Among patients with moderate TBI, 33% had GOSE scores $\leq$ 6 (severe-to-moderate disability), 20% had a GOSE score of 7 (lower good recovery) and 46% had a GOSE score of 8 (upper good recovery). Among patients with severe TBI, 45% had GOSE scores $\leq$ 6, 30% had a GOSE score of 7 and 25% had a GOSE score of 8. Younger age at injury and duration of PTA $\leq$ 1 week were associated with higher GOSE score (Table VI). Better concurrent processing speed, attention, verbal memory, visual memory and executive function were all associated with higher GOSE score in univariable analysis. Only executive function and attention were associated with global outcome when adjusting for age at injury and duration of PTA.

Discussion

This prospective study assessed cognitive function at 12 months after TBI and recovery from 3 months post-injury separately for moderate and severe patients with definitive lesions in the brain parenchyma shown by MRI in the early phase. One year after injury, patients with moderate TBI exhibited reduced executive function compared with controls, while patients with severe TBI exhibited reduced motor function, processing speed, verbal memory and executive function. Both patient groups improved their visual memory and processing speed between 3 and 12 months post-injury. However, motor function only improved among patients with moderate TBI, while executive function only improved among patients with severe TBI. Executive functioning and attention at 12 months were associated with concurrent global outcome when adjusted for age at injury and injury severity.

When compared with healthy controls, it was demonstrated that the patients with moderate TBI performed worse on executive function measures. This is in agreement with findings in some other studies where fluency and flexibility in problem-solving (executive function) were reduced after moderate TBI [5, 8]. Reduced speed of information processing is often regarded as a main contributor to cognitive deficits in TBI, across injury severities [44, 45]. In this sample group averages showed no significant difference in processing speed between moderate TBI and controls. However, as shown in Table III, the effect size approached moderate range (0.48) and there were a significantly larger proportion of patients with moderate TBI scoring in the low range compared to controls, as shown in Table IV. These observations may indicate different sensitivity among the tests measuring processing speed. Alternatively, electrophysiological methods (e.g. event-related potential (ERP)

Table IV. Frequency of below average, average and above average performances on sub-scores of neuropsychological tests using threshold of 1.5 SD for controls (C) and patients with moderate (M) and severe (S) TBI.

	Controls (C)				Moderate TBI (M)				Severe TBI (S)				Mann Whitney
Cognitive domains	*M*	SD	n^a	$(\%)^b$	*M*	SD	n^a	$(\%)^b$	*M*	SD	n^a	$(\%)^b$	*p*-value
Across all tests													
Low scores	4.57	(2.42)	47	(100)	6.40	(4.45)	30	(100)	8.85	(6.71)	20	(100)	C vs. M: $p = 0.133$ C vs. S: $p = 0.010$ M vs. S: $p = 0.257$
High scores	2.60	(2.47)	37	(79.7)	2.87	(3.10)	25	(83.3)	2.85	(3.59)	13	(65)	C vs. M: $p = 0.886$ C vs. S: $p = 0.813$ M vs. S: $p = 0.710$
Motor function													
Low scores	0.06	(0.25)	3	(6.4)	0.27	(0.58)	6	(20.0)	0.40	(0.68)	6	(30.0)	C vs. M: $p = 0.063$ C vs. S: $p = 0.008$ M vs. S: $p = 0.426$
High scores	0.06	(0.25)	3	(6.4)	0.03	(0.18)	1	(3.3)	0.00	(0.00)	0	(0.0)	C vs. M: $p = 0.559$ C vs. S: $p = 0.251$ M vs. S: $p = 0.414$
Processing speed													
Low	0.19	(0.54)	6	(12.8)	0.93	(1.36)	22	(40.0)	1.40	(1.67)	11	(55.0)	C vs. M: $p = 0.004$ C vs. S: $p < 0.001$ M vs. S: $p = 0.279$
High	0.47	(0.75)	14	(31.9)	0.40	(0.86)	6	(20.0)	0.80	(0.80)	3	(15.0)	C vs. M: $p = 0.392$ C vs. S: $p = 0.208$ M vs. S: $p = 0.657$
Attention													
Low scores	0.74	(1.66)	12	(25.5)	0.90	(1.12)	15	(50.0)	1.25	(2.15)	9	(45.0)	C vs. M: $p = 0.065$ C vs. S: $p = 0.146$ M vs. S: $p = 0.821$
High scores	0.38	(0.74)	12	(25.5)	0.23	(0.73)	3	(10.0)	0.55	(0.94)	6	(30.0)	C vs. M: $p = 0.138$ C vs. S: $p = 0.591$ M vs. S: $p = 0.094$
Working memory													
Low scores	2.00	(0.00)	47	(100)	1.97	(0.18)	30	(100)	2.00	(0.00)	20	(100)	C vs. M: $p = 0.211$ C vs. S: $p = 1.000$ M vs. S: $p = 1.000$
High scores	0.00	(0.00)	0	(0)	0.00	(0.00)	0	(0)	0.00	(0.00)	0	(0)	C vs. M: $p = 1.000$ C vs. S: $p = 1.000$ M vs. S: $p = 0.414$
Verbal memory													
Low scores	0.47	(1.07)	7	(14.9)	0.47	(1.07)	7	(23.3)	1.25	(1.59)	9	(45.0)	C vs. M: $p = 0.312$ C vs. S: $p = 0.002$ M vs. S: $p = 0.065$
High scores	0.20	(0.76)	7	(14.9)	0.20	(0.76)	2	(6.7)	0.15	(0.37)	3	(15.0)	C vs. M: $p = 0.339$ C vs. S: $p = 0.982$ M vs. S: $p = 0.403$
Visual memory													
Low scores	0.33	(0.76)	19	(40.4)	0.33	(0.76)	6	(20.0)	0.70	(1.13)	8	(40.0)	C vs. M: $p = 0.080$ C vs. S: $p = 0.994$ M vs. S: $p = 0.139$
High scores	0.73	(0.98)	8	(17.0)	0.73	(0.98)	12	(40.0)	0.25	(0.64)	3	(15.0)	C vs. M: $p = 0.857$ C vs. S: $p = 0.889$ M vs. S: $p = 0.057$
Executive function													
Low scores	0.97	(1.25)	8	(17)	0.97	(1.25)	15	(50.0)	1.10	(1.29)	10	(50.0)	C vs. M: $p = 0.002$ C vs. S: $p = 0.002$ M vs. S: $p = 0.749$
High scores	0.37	(0.49)	20	(42.6)	0.37	(0.49)	11	(36.7)	0.45	(1.00)	4	(20.0)	C vs. M: $p = 0.277$ C vs. S: $p = 0.131$ M vs. S: $p = 0.408$

[a]Frequency of patients with one or more sub-scores ± 1.5 SD.
[b]Proportion of patients with one or more sub-scores ± 1.5 SD.

paradigms) may offer more sensitive methods of assessing information processing in these patients, measures independent of behavioural performance [46, 47]. The clinical implication of this is that, when assessing cognitive function in especially patients with moderate injuries, the clinician needs to carefully evaluate the sensitivity of the tests in order to pick up reduced processing speed in this patient group.

Looking only at the group averages it seemed that patients with moderate TBI in general performed in the average range at 12 months post-injury, which was in line with what was found by 3 months [23], although differently analysed. They further performed similarly to healthy controls regarding the other cognitive domains at 12 months post-injury, in contrast to previous studies reporting memory problems among

Table V. Improvement in neuropsychological function collapsed into composite scores (*T*-scores) for patients with moderate and severe TBI from 3 to 12 months post-injury.

Cognitive function	*n*	3 months		12 months		Paired differences			
		M	(SD)	*M*	(SD)	*M*	(SD)	*p*-value	95% CI
Moderate TBI									
Motor function	30	44.63	(10.76)	46.80	(9.33)	2.16	(5.40)	0.036	0.15 to 4.18
Information processing speed	28	46.00	(11.11)	49.66	(10.49)	3.67	(5.26)	0.001	1.62 to 5.70
Attention	29	48.97	(5.24)	49.52	(4.16)	0.55	(6.33)	0.646	−1.86 to 2.95
Working memory	28	47.91	(6.97)	49.75	(9.23)	1.84	(5.63)	0.095	−0.34 to 4.02
Verbal memory	30	52.71	(8.17)	49.85	(10.58)	−2.85	(7.15)	0.037	−5.52 to −0.18
Visual memory	30	45.79	(10.18)	53.98	(9.40)	8.20	(6.95)	< 0.001	5.60 to 10.79
Executive function	28	49.09	(6.40)	50.23	(6.49)	1.14	(4.36)	0.177	−0.55 to 2.83
Severe TBI									
Motor function	19	38.95	(10.04)	41.30	(10.37)	3.42	(9.08)	0.118	−0.96 to 7.80
Information processing speed	18	39.73	(12.30)	43.56	(11.98)	4.19	(5.10)	0.003	1.66 to 6.73
Attention	17	50.07	(5.75)	48.98	(7.96)	−1.09	(5.61)	0.435	−3.98 to 1.80
Working memory	20	48.48	(11.85)	48.83	(10.20)	0.35	(5.53)	0.780	−2.24 to 2.94
Verbal memory	20	47.81	(12.47)	44.70	(12.55)	−3.11	(7.35)	0.074	−6.55 to 0.32
Visual memory	17	27.70	(18.19)	48.33	(12.54)	20.68	(10.54)	< 0.001	15.26 to 26.10
Executive function	19	44.80	(10.05)	46.91	(8.46)	2.35	(3.91)	0.018	0.46 to 4.23

Table VI. Association between global outcome (assessed by Glasgow Outcome Scale-Extended score) and concurrent measures of neuropsychological tests, age at injury and length of post-traumatic amnesia (PTA).

		Unadjusted odds ratio (OR) for better global outcome			Adjusted odds ratio (OR) for better global outcome[b]		
Independent variable	*n*	Estimate	95% CI	*p*-value	Estimate	95% CI	*p*-value
Age at injury	50	0.95	0.92–0.99	0.001			
PTA <1 week	50	7.49	2.39–23.47	0.011			
Motor function[a]	50	1.40	0.84–2.34	0.199	1.09	0.61–1.95	0.766
Information processing speed[a]	50	2.18	1.30–3.66	0.003	1.63	0.90–2.96	0.107
Attention[a]	50	3.30	1.26–8.64	0.015	2.90	1.06–7.94	0.038
Working memory[a]	50	1.54	0.89–2.66	0.121	1.24	0.69–2.21	0.473
Verbal memory[a]	50	1.71	1.07–2.72	0.024	1.11	0.67–1.84	0.687
Visual memory[a]	50	1.97	1.20–3.24	0.008	1.64	0.96–2.82	0.071
Executive function[a]	50	5.17	2.02–13.23	0.001	3.78	1.34–10.69	0.012

[a]Pr 1 standard deviation (SD) increase.
[b]Adjusted for duration of PTA and age at injury.

patients with moderate TBI compared with controls [5, 48]. The relatively good performance among patients with moderate TBI in this study compared to previous observations might first be explained by that TBI with a GCS score of 13 was defined as moderate according to HISS. However, all but one of these experienced PTA for > 24 hours, which also is a criterion often used to classify TBI as moderate as opposed to mild [49]. Also, more than half of the patients had visible DAI lesions and three quarters had cortical contusions in the early MRI. Moreover, this study recruited prospectively from the acute setting, in contrast to Novack et al. [5], who recruited their study cohort from inpatient rehabilitation services which have been shown to introduce a bias toward moderate TBI with more severe injuries [50]. Further, other studies have assessed cognitive function using differing neuropsychological test [51], which makes comparisons across tests difficult [38]. The present study is one of very few recent studies to address the degree of cognitive impairments after moderate TBI, specifically.

Patients with severe TBI exhibited reduced function in most cognitive domains, with generally large effect sizes, which has also been observed in several other studies [1, 3, 5, 44]. However, in contrast to some other studies [9, 19], the present study did not demonstrate reduced function with regard to attention and working memory in either patient group. As has previously been discussed [23], the tests used might not be optimal for assessing these functions, even though these tests have been recommended as common outcome measures [38].

The groups did not differ in the amount of high scores (above average)—despite the larger amount of low scores (below average) among patients with severe TBI. This may indicate that the injury affects specific cognitive functions and the other functions are spared. Further, it has been demonstrated that above average performances are not uncommon after TBI and may provide clues to cognitive compensation strategies for the patients in the rehabilitation process. This study is one of the few studies addressing good or preserved cognitive abilities after TBI and cognitive strengths are important to take into account in the rehabilitation process.

Further, it was also observed that the use of norms derived from Anglo-American samples in a Norwegian sample increased the risk of biased results and only the use of a control group revealed the patients' reduced executive function. Previous studies have demonstrated that patients with high intellectual ability may not be classified as impaired using only standard normative samples, despite reduced cognitive functioning compared to their cognitive capacity

prior to the injury [48, 52, 53]. Taken together this illustrates that comparisons to norms must be interpreted with caution [9] and that, if using cut-off scores to indicate impairment, the scores should be adjusted for the patients level of intelligence.

Visual memory was the cognitive domain with the most prominent improvement from 3 to 12 months post-injury, especially among patients with severe TBI, which supports earlier findings [54]. Christensen et al. [10] also observed a tendency toward a more protracted recovery trajectory for visual memory, with more improvement taking place also between 6 and 12 months post-injury. The large improvement may be because the function at 3 months was lower than that observed for other cognitive domains. However, the large improvement also raises the question of test–re-test effects. While the test–re-test stability reported in the test manual of the Continuous Visual Memory Test [54] was good, stability coefficients from larger samples ($n = 40$) have reported coefficients in the moderate range [55]. Still, it is not found plausible that the great improvement among patients with severe TBI resulted entirely from test–re-test effects. This finding warrants further exploration in future studies, using also other tests.

Both patient groups improved their processing speed from 3 to 12 months post-injury, as reported in previous studies. [10, 15, 56]. Only patients with severe TBI exhibited improvement regarding measures of executive function. However, both patient groups had reduced executive function at 12 months post-injury. One possible explanation could be that patients with moderate TBI had recovered most of their executive function before the first assessment, which is in accordance with Christensen et al. [10] who observed that untimed executive function in particular exhibited steeper recovery prior to 5 months post-injury than from 5 to 12 months post-injury. Further, the patients with moderate TBI worsened their verbal memory from 3 to 12 months post-injury. However, the manual reports less robust reliability between the standard and alternate versions [36] and unintended dissimilarities in the parallel versions in the Norwegian translation of CVLT-II might also contribute to this finding.

Executive function and attention were associated with concurrent global outcomes. This association was evident even when adjusting for age and injury severity (duration of PTA) and the association between PTA duration and global outcome observed in this study support previous findings [19, 21, 57]. Notably, the executive function domain was also the cognitive domain in which both patient groups performed worse than controls. Although it has been argued that neuropsychological tests of executive function do not encompass all aspects of executive function and lack ecological validity, these 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 [21, 55]. The findings are in agreement with this and support the view that patients' problems with employment, social relationships, leisure activities and independent living [19] might be specifically related to dysfunctional executive abilities. This also implies that compensating for difficulties with solving everyday problems adapt to changing situations and inhibition is important to enable the patients to cope with the demands of the society.

Concurrent processing speed, verbal memory and visual memory were also associated with global functioning, although not when adjusting for age and injury severity. Other studies have reported a relationship between global outcomes and other concurrent cognitive functions, such as processing speed and memory function [19, 20, 58, 59]. These studies did not adjust for injury severity or pre-injury factors and follow-up ranged from 3 to 10 years post-injury. They also found that the prognostic value of these concurrent neuropsychological outcomes was limited [58].

Study limitations

The major limitation in this longitudinal prospective study is its relatively small sample size in the sub-group analyses. In addition, this study used a large and comprehensive battery of neuropsychological tests, which makes it possible to assess many aspects of cognitive function, but also increases the risk of finding higher rates of abnormal test performances due to chance [60]. To counter this risk, this study has adjusted for multiple measurements using the Scheffé Post-hoc tests [39, 61]. Furthermore, the control group was assessed only once, which made it difficult to estimate test–re-test effects. However, this study tried to minimize test–re-test effects using available parallel versions and comparable tests and the assessment intervals were 9-months. To reduce the impact of confounding factors, the control group was matched to the patient groups for age, sex and length of education. As no free standing measure of symptom validity was included in the test protocol, the possibility of malingering or other factors reducing test validity could not be entirely excluded. However, all neuropsychological testing was done in a clinical setting and no patients were in a litigation process or seeking economic compensation at time of assessment, reducing the risk of malingering.

Conclusion

In this longitudinal study with MRI in the early phase, it was found that differentiating between patients with moderate and severe TBI revealed important differences in the degree of cognitive impairment 12 months after the injury and yielded a more accurate description of cognitive deficits and their improvement over time. Patients with severe TBI exhibited reduced function in several cognitive domains, both compared to norms and the control group. While executive function among patients with moderate TBI was reduced compared with healthy controls, they performed in the normal range in all domains when compared to norms—a finding that lends strength to the concerns regarding over-estimating the cognitive problems after moderate TBI. However, they nevertheless had more low scores on tests measuring executive function and processing speed, which highlight the importance of test sensitivity when assessing cognitive impairment in this group. The groups also differed in which cognitive functions improved from 3 to 12 months post-injury, with only processing speed and visual memory improving for both groups. Regardless of injury severity, executive function

appears to be important for the patients in resuming independent living, employment and leisure activities, as evaluated by global outcome. Hence, it is essential for the clinician to recognize and target the importance of executive function in rehabilitation plans.

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Declaration of interest

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Appendix

Table A1. Appendix: Description of non-participants between 15–65 years.

					HISS (*n*)		PTA (*n*)			MRI-findings (*n*)			
Exclusion criteria		*n*	Sex Male/ Female, *n*	Age, *M* (SD)	Moderate	Severe	<1 week	>1 week	Unknown	DAI	Cont	DAI + Cont	Unknown
Pre-injury condition:	Neurological disease or injury	6	5/1	48.7	3	3	2	3	1	2	3	1	0
	Drug abuse	3	3/0	27.7	2	1	2	1	0	1	1	1	0
	Alcohol abuse	6	6/0	54.8	3	3	2	1	3	0	2	0	4
	Psychiatric condition	3	2/1	35.3	1	2	0	1	2	1	0	1	1
Unable to co-operate		9	8/1		0	9	0	9	0				
Lost to follow-up	Rejected participation	10	5/5	35.7	9	1	4	2	4	1	3	3	3
	Long geographical distances	10	8/2	33.3	8	2	5	1	4	2	1	2	5

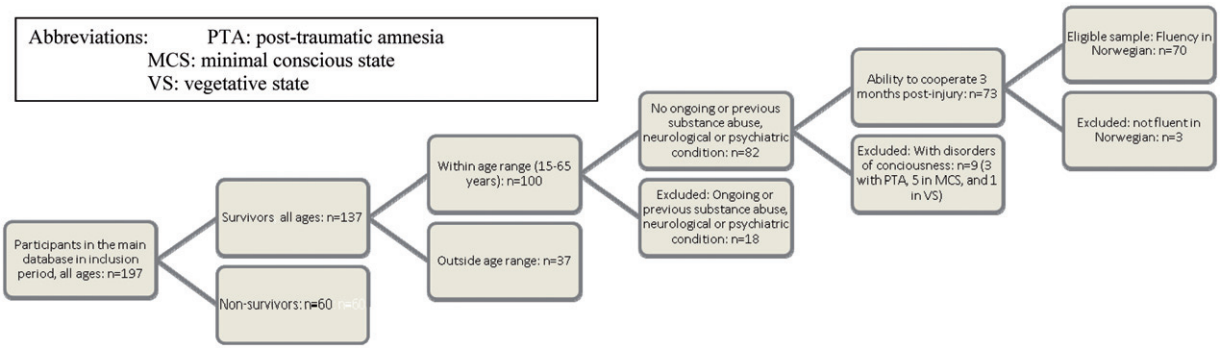

Figure A1. Flow-chart displaying the selection of eligible patients in the study.