

Cognitive Impairment 3 Months After Moderate and Severe Traumatic Brain Injury: A Prospective Follow-Up Study

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Objective: To explore the magnitude and frequency of cognitive impairment 3 months after moderate to severe traumatic brain injury (TBI), and to evaluate its relationship to disability at 1-year follow-up.

Design: Prospective follow-up study.

Setting: Regional level I trauma center.

Participants: Patients aged 15 to 65 years with definite TBI, defined as Glasgow Coma Scale score of 3 to 13 and injury documented by magnetic resonance imaging (n=59) or computed tomography (n=2); healthy volunteers (n=47) served as controls.

Interventions: Not applicable.

Main Outcome Measures: Neuropsychological assessment 3 months postinjury and Glasgow Outcome Scale Extended (GOSE) at 3 and 12 months postinjury.

Results: Patients with TBI performed worse than controls, most consistently in terms of information processing speed and verbal memory. However, a maximum of only 43% of patients with TBI had impaired test scores (defined as <1.5 SD below mean of normative data) on any one measure. Based on a selection of 9 tests, a 0 or 1 impaired score was seen in 46 (98%) of 47 controls, in 20 (57%) of 35 patients with moderate TBI, and in 9 (35%) of 26 patients with severe TBI. At 1 year postinjury, disability (defined as GOSE score ≤6) was present in 57% of those with 2 or more impaired test scores and in 21% of those with 0 or 1 impaired score ($P=.005$).

Conclusions: In this sample of patients with recent, definite TBI and healthy volunteers, we found that TBI affected cognition in moderate as well as severe cases. The presence of cognitive impairment was associated with future disability. However, half of the patients with moderate TBI and even one

third of those with severe TBI had a normal cognitive assessment 3 months postinjury.

Key Words: Craniocerebral trauma; Longitudinal studies; Neuropsychological tests; Neuropsychology; Prognosis; Rehabilitation.

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COGNITIVE IMPAIRMENT is a common sequela of moderate and severe TBI,¹ with effects particularly prominent in terms of information processing speed and attention,^{2,3} memory,⁴ and executive functioning.⁵ Several studies demonstrated, at various time intervals postinjury, that cognitive dysfunction mediates functional problems.⁶⁻⁸

Cognition is markedly impaired around 1 month postinjury⁹ or by resolution of PTA,^{10,11} but studies are difficult to compare because of differences regarding duration of follow-up, proportion of severe cases, and whether patients are selected from the acute care⁵ or rehabilitation setting.^{10,11} A common research design has been the comparison of mean test performances between patients with TBI and a control group. The magnitude of the effect of TBI on cognition (ie, effect size) may be expressed as Cohen's d , the standardized difference of means in 2 groups. In a meta-analysis, a large mean effect size ($d_{\text{pooled}}=.97$) of TBI across studies was found for moderate to severe TBI within the first 6 months.¹² The authors pointed out that while cases of moderate and severe TBI typically are analyzed together in neuropsychological research, they constitute a heterogeneous group. Thus, the reported effects might be overestimated for moderate TBI or underestimated for severe TBI, or both.¹²

List of Abbreviations

CCPT-II	Conners' Continuous Performance Test II
CT	computed tomography
CVLT-II	California Verbal Learning Test II
CVMT	Continuous Visual Memory Test
CWIT	Color-Word Interference Test
DAI	diffuse axonal injury
D-KEFS	Delis Kaplan Executive Function System
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale Extended
IQ	intelligence quotient
MRI	magnetic resonance imaging
PTA	posttraumatic amnesia
SDMT	Symbol Digit Modalities Test
TBI	traumatic brain injury
TCF	Taylor Complex Figure
TMT	Trail-Making Test
WAIS-III	Wechsler Adult Intelligence Scale-Third Edition

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In other studies of early cognitive outcome in TBI patient groups,^{10,11} as well as in individual clinical assessments,¹³ interpretation of neuropsychological test scores is based on comparison with normative data. In some settings, such as legal expert examinations and research, criteria defining impairment is required, but there is no such general definition.¹⁴ The issue is further complicated by the fact that healthy people perform below the normal range in some percentage of administered tests,^{14,15} and defining "impairment" remains a matter of discussion.

Taken together, there is still a need for studies exploring the extent of cognitive deficits in patients with TBI, because previous studies are heterogeneous regarding the time postinjury, the selection of patients, and the research design.

For the present study we performed neuropsychological testing 3 months postinjury as part of a large follow-up study of patients admitted with moderate or severe head injury to a regional level I trauma center. In a larger subgroup of the main cohort, we previously demonstrated that virtually all patients had parenchymal lesions detected with early MRI. DAI and contusions were frequently found, often in concert.¹⁶

The aim of the present 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 3 months and 1-year follow-up.

METHODS

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

Participants

Sixty-one patients (age range, 15–65y) admitted to the Neurosurgical Department, St Olavs Hospital, Trondheim University Hospital, Norway participated in the study. The hospital, a level I trauma center, has an ongoing database that includes all patients admitted with moderate to severe head injuries as defined by the Head Injury Severity Scale criteria.¹⁷ In this main database, 97% of admitted patients have consented to registration, and less than 2% have been lost to follow-up (ie, missing GOSE score).

For the present study, patients in the main database were invited to participate in neuropsychological testing at 3 months postinjury. Inclusion criteria were (1) the ability to cooperate during testing; (2) no ongoing substance abuse, diagnosed neurologic or psychiatric condition, or previous moderate to severe head injury according to the same criteria; and (3) fluency in the Norwegian language. The main inclusion period was from October 2004 to October 2007. During this period, 52 patients were included (appendix 1); these constitute 85% of the sample in this study. For the purpose of increasing the sample, we included 9 patients who had been injured and registered in the main database after the first inclusion period and who were evaluated at 3 months follow-up. Table 1 reports patient demographic data. The control group consisted of 47 healthy persons, matched to the total sample of patients for age, sex, and education. They were recruited via advertisements, among family and friends of patients with head injury, and among acquaintances of researchers and staff.

Injury-Related Variables

Evaluated variables included mechanism of injury, MRI findings, and GCS score (scoring procedures have been de-

scribed in an earlier publication¹⁶), with a GCS score of 9 to 13 indicating moderate TBI and a GCS score of 8 or less reflecting severe TBI.

Magnetic Resonance Imaging

MRI (1.5 Tesla) was performed at a median of 10 days postinjury (range, 1–120). The scan protocol included T1- and T2-weighted sequences, a T2*-weighted gradient echo sequence, fluid-attenuated inversion recovery sequences, and diffusion-weighted imaging. MRI parameters and procedure of evaluation have been reported previously.¹⁶

Procedures for Neuropsychological Testing and Scoring

Neuropsychological assessment was performed at a mean of 98 ± 10 (SD) days postinjury. Psychologists, 2 trained masters-level students, and 1 test technician at St Olav 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 the procedures. The students received training and could discuss issues with the psychologists.

Raw scores were converted to standard scores by use of normative data provided by the manufacturers of the tests, except for the Symbol Digit Modality Test, where a normative sample quoted by Lezak et al¹⁸ was used. For participants aged 15 years, the norms for those aged 16 years were used. Standard scores were given as T scores, scaled scores (S scores), Z scores, or percentiles. An individual's standardized test score was classified as impaired if below 1.5 SD according to the reference norms for the test (T score ≤ 34 , S score ≤ 5 , Z score ≤ -1.5 , or percentile ≤ 5). Data were also analyzed applying a cutoff criterion at 1 SD. In some cases 1 or more tests were not administered for various reasons; thus the number of patients evaluated with each test deviates from the total sample size.

Neuropsychological Measures

The 4 subtests of the Wechsler Abbreviated Scale of Intelligence¹⁹ were administered to estimate general intellectual capacity. To avoid future retest effects in a planned reassessment, we used a split-half procedure, and a raw score was estimated. The control participants were tested with all items, but their IQ scores in this study were calculated as for the patients, by use of every second item procedure. The following neuropsychological methods were used to assess different domains of cognitive function:

1. *Motor function*: Grooved Pegboard, dominant hand,²⁰ TMT, condition 5 (motor speed) from the D-KEFS.²¹
2. *Information processing*: TMT, condition 1 (visual scanning), 2 (number sequencing), and 3 (letter sequencing); CWIT, condition 1 (color naming) and 2 (word reading) from D-KEFS and SDMT, oral and written versions.²²
3. *Attention and vigilance*: CCPT-II.²³
4. *Visual learning and memory*: CVMIT,²⁴ TCF.²⁵ The TCF was not administered to controls. Raw scores for the TCF were converted to standard scores based on normative data for the Rey-Osterrieth Complex Figure.²⁶
5. *Verbal learning and memory*: CVLT-II.²⁷
6. *Working memory*: Digit Span Backwards from the WAIS-III,²⁸ Letter-Number Sequencing from WAIS-III.
7. *Executive functions*: Wisconsin Card Sorting Test computer version²⁹; Verbal Fluency Test from D-KEFS; TMT, condition 4 (letter-number switching) from D-KEFS; CWIT, condition 3 and 4 (inhibition and inhibition/switching) from D-KEFS; Tower test from D-KEFS.

Table 1: Demographic, Injury-Related, and Outcome Variables in Individuals With Moderate and Severe TBI

Variable	No. of Cases (%)	
	Main Cohort (n=52)	Patients Enrolled Later (n=9)
Age at testing; mean \pm SD (y)	30.6 \pm 14.6	26.4 \pm 12.8
Male/female	40 (77)/12 (23)	5 (56)/4 (44)
Days postinjury; mean \pm SD (range)	97.3 \pm 10.8 (75–133)	103.4 \pm 9.4 (90–122)
GCS score; median (IQR)*	9 (7–13)	7.5 (6.25–12.75)
Moderate/severe injury	32 (62)/20 (38)	3 (33)/6 (67)
Mechanism of injury		
Fall	20 (39)	1 (11)
Traffic accident	28 (54)	8 (89)
Other	4 (7)	0
MRI examination†		
No findings	1 (2)	0
Pure DAI	10 (19)	3 (38)
Cortical contusions	17 (33)	0
DAI and contusions	24 (46)	5 (56)
GOSE score at testing‡		
8	12 (23)	0
7	3 (6)	0
6	13 (25)	2 (22)
5	21 (40)	7 (78)
4	1 (2)	0
3	1 (2)	0
GOSE score at follow-up§		
8	22 (42)	2 (29)
7	11 (21)	1 (14)
6	9 (17)	3 (43)
5	10 (19)	1 (14)

NOTE. Values are number of cases (%) unless otherwise stated.

Abbreviation: IQR, interquartile range.

*Exact GCS score available in 59 cases.

†One patient not examined with MRI.

‡One patient could not be reliably assessed because of severe orthopedic injuries.

§Data not available in 2 cases.

The different subscores obtained from each test are shown in tables 2 and 3.

Global Outcome

Global functioning was assessed by the first author according to the GOSE at 3 and 12 months follow-up using a structured interview.³⁰ The scale assesses disability, participation, and symptoms after head injury. A cutoff GOSE score of 6 was chosen, indicating the presence of severe (GOSE score, 3–4) or moderate (GOSE score, 5–6) disability. However, because head injury–related complaints may be present in patients without this level of disability, to a degree that affect daily life (GOSE score, 7), we also performed some analyses using a cutoff score of 7.

Statistical Analysis

Dependent variables were checked for normality in patients with TBI and control participants by inspection of Q-Q plots. Raw scores for each test are presented as mean and SD for normally distributed data, and otherwise as median with interquartile range (25th and 75th percentile). Comparisons between patients with TBI and control participants were performed using the Student *t* test and Mann-Whitney U test, respectively. Effect sizes were calculated both as Cohen's *d* based on pooled variance (d_{pooled}) and as Glass' *d*, where the denominator is the SD of the control group (ES_{control}).³¹ For the tests where data were nonnormally distributed, standardized

effect size was estimated by dividing the difference between the median scores by the interquartile range of controls $\times .75$ (ES_{control}).³¹ Cohen defined a *d* of 0.8, 0.5, and 0.2 as reflecting large, medium, and small effect sizes, respectively.³²

Proportions were compared using the exact *z* pooled test as recommended for small counts when the expected value was less than 5 for any cell.³³ In the presence of missing data, we used available case analysis, using all cases where a variable is present.³⁴ Thus the number of cases is different for each variable. Reported *P* values are 2-sided. To adjust for multiple tests, a *P* value of .01 or less was regarded as significant when analyzing the total battery of the neuropsychological tests, and otherwise an α level of .05 was applied. Statistical analyses were performed using the statistical software SPSS for Windows, version 16.0^a with the exception of exact unconditional tests, which were performed using <http://www.stat.ncsu.edu/exact/>.

RESULTS

Demographic and injury-related characteristics of the patients and control participants are presented in tables 1 and 4.

Neuroimaging

All patients were examined by MRI except one, who had cortical contusions depicted with CT. One of the 60 patients had no lesions in the brain parenchyma when examined with MRI 21 days postinjury. This patient had a moderate injury

Table 2: Neuropsychological Test Performance in Patients and Controls

Test	n	Patients	n	Controls	P	ES _{control} [*]	d _{pooled} [†]
Motor function							
TMT; motor [‡]	61	25 (18.5–34)	47	22 (18–27.5)	.06	.42	
Grooved Pegboard; dominant hand (s)	61	72.8±18.3	47	64.0±7.3	.001	1.20	.61
Grooved Pegboard; nondominant hand (s)	60	80.5±17.8	47	70.2±8.4	<.001	1.22	.71
Information processing speed							
TMT; visual scanning [‡] (s)	61	26 (23–33)	47	20 (17–23)	<.001	1.33	
TMT; numbers [‡] (s)	61	34 (29–47)	47	24 (21–29)	<.001	1.67	
TMT; letters [‡] (s)	61	34 (28.5–49.5)	47	24 (20–30)	<.001	1.33	
CWIT; color naming (s)	59	34.8±9.3	47	29.0±4.7	<.001	1.23	.76
CWIT; word reading (s)	59	25.4±5.8	47	22.4±3.6	.002	.82	.60
SDMT; oral version	59	56.0±17.5	47	66.1±11.4	.001	.88	.67
SDMT; written version	61	45.2±13.3	47	53.5±8.0	<.001	1.04	.73
Sustained attention							
CCPT; omissions [‡]	57	3 (1–6)	47	1 (0–2)	.014	1.33	
CCPT; commissions [‡]	57	12 (9–21.5)	47	9 (5–15)	.003	.40	
CCPT; hit RT	57	378.7±82.2	47	391.7±63.8	.37		
CCPT; hit RT SE [‡]	57	5.8 (4.3–6.0)	47	5.0 (3.9–5.9)	.047	.56	
CCPT; detectability	57	.68±.39	47	.92±.43	.004	.55	.58
CCPT; hit RT by block [‡]	57	0.0 (–.01 to .01)	47	0.0 (–.01 to .02)	.60		
CCPT; hit RT by block SE [‡]	57	0.000 (–.033 to .033)	47	0.005 (–.030 to .050)	.57		
CCPT; hit RT by ISI [‡]	57	.040 (–.000 to .070)	47	.040 (–.030 to .060)	.17		
CCPT; hit RT by ISI SE	57	–.014±.09	47	.034±.12	.021	.41	.46
Visual memory							
CVMT; hits [‡]	59	38 (34–39)	47	39 (37–41)	.012	.33	
CVMT; total correct	59	73.2±9.5	47	77.0±6.3	.019	.62	.47
CVMT; false [‡]	59	16 (10–20)	47	15 (11–19.75)	.85		
CVMT; delayed	59	4.3±1.7	47	4.7±1.4	.10	.34	.32
Verbal memory							
CVLT; total recall trial 1–5	61	47.5±12.9	47	53.4±8.9	.006	.67	.52
CVLT, short-delay free recall [‡]	61	10 (8–12.5)	47	12 (11–14)	.013	.67	
CVLT, long-delay free recall [‡]	61	11 (7.5–14)	47	12 (11–14)	.007	.44	
Working memory							
Digitspan backwards	60	6.7±2.2	47	6.9±2.4	.68		
Letter-Number Sequencing	59	10.3±3.1	47	11.4±2.8	.051	.41	.39
Executive function							
WCST; total errors [‡]	59	22 (14–38)	47	14 (10–20)	.002	1.07	
WCST; perseverative responses [‡]	59	11 (7–19)	47	8 (6–11)	.010	.80	
WCST; categories achieved [‡]	59	6 (6–6)	47	6 (6–6)	.57		
Verbal Fluency; letter	60	32.4±10.8	47	39.5±11.3	.001	.63	.65
Verbal Fluency; category	60	39.5±10.1	47	52.6±10.9	<.001	1.21	1.26
Verbal Fluency; category switching; tot corr	60	12.7±2.9	47	13.8±2.8	.036	.42	.41
Verbal Fluency; category switching; tot sw	60	11.3±3.3	47	11.9±3.1	.29		
Tower; total achievement	61	17.5±3.6	47	18.0±3.6	.41		
TMT; letter-number switching [‡] (s)	61	81 (64.5–108.5)	47	61 (50–76)	<.001	1.03	
CWIT; inhibition (s)	59	58.9±18.7	47	49.8±8.0	.001	1.13	.61
CWIT; inhibition/switching [‡] (s)	59	68 (56–83)	47	54 (51–64)	<.001	1.44	

NOTE. Values are mean ± SD, median (25%–75%), or as otherwise indicated.

Abbreviations: corr, correct; ES, effect size; ISI, interstimulus interval; RT, reaction time; sw, switching; WCST, Wisconsin Card Sorting Test.

*Cohen's *d*; mean difference divided by the pooled SD.

†For tests yielding normally distributed data; Glass' *d*; ES is the standardized mean, using the SD of the control group. For the nonnormally distributed data, ES_{control} was calculated as difference between medians divided by .75 × interquartile range_{control}.

‡Data not normally distributed.

with 4 days of PTA and subarachnoid hemorrhage on the initial CT scan. Thus, all patients had definite TBI, and 69% had DAI detected with MRI.

Intellectual Abilities

When tested via *t* test, patients with TBI had significantly lower verbal, performance, and total IQ scores than control participants ($P \leq .001$). Women with TBI had significantly higher total IQ scores than men with TBI ($P = .04$) and per-

formed in a range similar to controls. Among controls, there was no difference between sexes ($P = .29$) (see table 4).

Test Performance and Effect Sizes

There were significant differences in raw scores between patients with TBI and controls in most cognitive domains (see table 2). All measures of information processing speed and verbal memory were significantly impaired in patients compared with controls. Within the remaining domains, significant

Table 3: Number and Proportion of Scores Below 1.5 SD, All Patients and Controls

Test	TBI <1.5 SD		Controls <1.5 SD		P
	Total	n (%)	Total	n (%)	
Motor function					
PEG dominant side	61	12 (20)	47	1 (2)	.007
PEG nondominant side	60	16 (27)	47	2 (4)	.52
TMT 5	61	5 (8)	47	1 (2)	.003
Information processing speed					
TMT; visual scanning	61	16 (26)	47	1 (2)	.003
TMT; numbers	61	13 (21)	47	0	.002
TMT; letters	61	14 (23)	47	2 (4)	.008
CWIT; color naming	59	17 (28)	47	2 (4)	.002
CWIT; word reading	59	12 (20)	47	2 (4)	.017
SDMT; oral version	59	16 (27)	47	0	.001
SDMT; written version	61	26 (43)	47	1 (2)	.001
Sustained attention/vigilance					
CCPT; omissions	58	8 (14)	47	3 (6)	.26
CCPT; commissions	58	5 (9)	47	1 (2)	.18
CCPT; hit RT	58	6 (10)	47	4 (9)	.78
CCPT; hit SE	58	6 (10)	47	5 (11)	.99
CCPT detect	58	0 (0)	47	1 (2)	.36
CCPT; hit RT by block	58	4 (7)	47	2 (4)	.63
CCPT; hit SE by block	58	6 (10)	47	5 (11)	.99
CCPT; hit RT SE by ISI	58	1 (2)	47	3 (6)	.26
CCPT; hit RT SE by ISI	58	3 (5)	47	5 (11)	.36
Visual memory					
CVMT; hits	59	14 (24)	47	4 (9)	.040
CVMT; false	59	20 (34)	47	14 (30)	.67
CVMT; total	59	21 (36)	47	13 (28)	.54
CVMT; delayed	59	9 (15)	47	2 (4)	.075
TCF; delayed	59	8 (14)	0	NA	ND
Verbal memory					
CVLT; total recall trial 1–5	59	9 (15)	47	1 (2)	.022
CVLT; short-delay free recall	59	15 (25)	47	1 (2)	.002
CVLT; long-delay free recall	59	17 (29)	47	3 (6)	.004
Working memory					
Letter-Number Sequencing	60	4 (7)	47	1 (2)	.36
Executive function					
WCST; total errors	59	5 (8)	47	1 (2)	.19
WCST; perseverative responses	59	5 (8)	47	2 (4)	.52
WCST; categories achieved	59	1 (2)	47	1 (2)	.96
Letter Fluency	60	10 (17)	47	1 (2)	.015
Category Fluency	60	10 (16)	47	0	.004
Category switching; total correct	60	7 (12)	47	2 (4)	.20
Category switching; total switch	60	8 (13)	47	2 (4)	.13
CWIT inhibition	59	11 (19)	47	1 (2)	.009
CWIT inhibition/switching	59	14 (23)	47	2 (4)	.006
TMT; letter-number switching	61	11 (19)	47	0	.004
Tower; total achievement	59	1 (2)	47	1 (2)	.96

Abbreviations: ISI, interstimulus interval; PEG, Grooved Pegboard; RT, reaction time; WCST, Wisconsin Card Sorting Test; NA, not applicable; ND, no data.

differences in mean performance were shown for many, but not all, of the measures. For working memory, no significant differences were found. Effect sizes, computed when the *P* value was .05 or less, were medium to large and typically larger when the variance in the control group was used for standardization.

Frequency of impairments According to Normative Data

Table 3 displays the proportions of persons scoring in the impaired range (-1.5 SD) according to normative data for each test. Across all tests, 0% to 43% of the patients with TBI had clinically impaired scores in contrast to 0% to 30% among

controls. The tests of information processing speed, motor function assessed by the Grooved Pegboard, and the delayed recall tasks of the CVLT-II had the highest proportion of impaired scores, while they at the same time yielded very few impaired scores in the control group. On several executive tasks, as well as on the working memory task and some measures of visual memory, attention, and vigilance, no significant difference in frequency of impairment was found between groups.

When 1.0 SD was used as the cutoff criteria for impairment, the proportion of patients with impairments increased. Those tests showing the greatest increase in the number of patients

Table 4: Intellectual Ability in Relation to Sex and Injury Severity

Variable	Controls (n=47)	TBI, All Patients (n=61)	Moderate TBI (n=35)	Severe TBI (n=26)	Male, TBI (n=45)	Female, TBI (n=16)
VIQ	117±13	106±17	108±12	103±21	102±16	117±14
PIQ	115±13	106±13	107±13	104±13	104±13	111±13
Total IQ*	118±12	106±16 [†]	109±12	103±20	102±15 [‡]	116±14
Age (y)	30.2±13.3	30.0±14.3	33.1±15.2	25.9±12.0	29.0±13.3	33.0±16.9
Education (y)	12.0±1.8	11.8±2.1	12.0±2.0	11.7±2.3	11.3±1.6	13.3±2.8

NOTE. Values are mean ± SD.

Abbreviations: PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient.

*Three patients had no IQ scores from Wechsler Abbreviated Scale of Intelligence.

[†]Significantly lower than in controls.

[‡]Significantly lower than in women with TBI.

designated as impaired were the SDMT written version (43%–53%), the grooved Pegboard (20%–41%), the CVLT-II delayed recall (29%–38%), and the Letter Fluency (16%–28%). The proportions of impaired persons were only modestly increased on other tests. Additionally, more healthy controls were diagnosed as impaired on other tests. This was in the range of 10% to 15% for several tests, including the CVLT-II and the Wisconsin Card Sorting Test. For SDMT and the TMT condition 2 and 4, relatively few controls (0%–4%) were impaired.

Cognitive Functioning in Subgroups of Patients According to Severity of Injury

Nine tests that are frequently used in clinical practice and that in the preceding analyses were associated with large effect sizes or good ability to discriminate patients and controls were examined further: Grooved Pegboard (dominant hand), CWIT (color naming and inhibition/switching), Verbal Fluency (letters), TMT (number sequencing and number-letter switching), SDMT (written version), CVMT (hits), and CVLT-II (delayed recall). Table 5 shows the number of impaired scores (standardized test score below 1.5 SD) out of the 9 tests. In the healthy volunteers, 98% had no more than 1 impaired score, considered as reflecting a normal performance in this sample, whereas having 2 or more impaired scores was considered cognitive impairment.

Test performances of the patients with moderate and severe TBI are shown in table 6. Mean d_{pooled} for the normally distributed tests (Grooved Pegboard [dominant hand], VF [letters], CWIT [color naming], and SDMT [written]) was 0.61 for moderate and 0.95 for severe TBI.

Of those with moderate injury, 15 (43%) demonstrated cognitive impairment, as did 17 (65%) of patients with severe TBI ($P=.09$; via exact z pooled test for comparison of proportions).

Table 5: Relative Frequency of Impaired Test Scores Out of 9 Tests According to Normative Data

No. of Low Test Scores*	Moderate TBI (n=35)	Severe TBI (n=26)	Controls (n=47)
0	13 (37)	5 (19)	35 (75)
1	7 (20)	4 (15)	11 (23)
2–3	10 (29)	10 (38)	1 (2)
4–5	5 (14)	3 (12)	0
6–7	0	1 (4)	0
8–9	0	3 (12)	0

NOTE. Values are n (%) or as otherwise indicated.

*Standardized test scores <1.5 SD.

When applying 1.0 SD as the cutoff criterion of impairment, 88% of controls had 0 or 1 impaired score; thus 12% would have been classified as cognitively impaired. Twenty-one patients (60%) with moderate injury and 19 patients (73%) with severe injury would be classified as cognitively impaired.

Functional Outcome at 3 Months Postinjury

Follow-up GOSE scores at 3 months were available for 60 patients with TBI. One individual could not be reliably assessed because of severe orthopedic injury requiring lengthy institutional rehabilitation. GOSE scores concurrent with the neuropsychological assessment were 6 or less in 45 (75%) of 60 patients with GOSE scores. Seventeen (61%) of the 28 patients with no more than 1 impaired test score and 28 (88%) of the 32 patients with 2 or more impaired test scores had concurrent GOSE scores of 6 or less.

Functional Outcome at 12 Months Postinjury

Follow-up GOSE scores at 12 months were available for 59 patients with TBI. Of these, 23 (39%) had moderate or severe disability as defined by a GOSE score of 6 or less. Six (21%) of 29 patients with a normal neuropsychological assessment at 3 months (no more than 1 impaired score) had GOSE scores of 6 or less, and in the group with cognitive impairment (≥ 2 impaired test scores), 17 (57%) of 30 had GOSE scores of 6 or less ($P=.006$).

When a cutoff criterion of a GOSE score of 7 or less was applied, 13 (45%) of those with 0 or 1 impaired score and 22 (73%) of those with 2 or more impaired test scores reported disability or head injury–related complaints at 12 months' follow-up ($P=.030$).

DISCUSSION

We studied neuropsychological test performance in patients recruited from an acute care setting, 3 months after moderate or severe TBI with parenchymal lesions detected on MRI in virtually all cases. Patients with TBI performed worse than control participants in almost all domains; this could be shown for the subpopulation of patients with moderate TBI when analyzed separately. Effect sizes were largest for tests requiring manual and processing speed. However, after moderate TBI, most patients had a normal neuropsychological assessment (no more than 1 score below 1.5 SD of normative mean). Even after severe injury, normal performances were found in one third of patients. Cognitive impairment was associated with later complaints or disability.

Effect of TBI on Cognition

In this study, many patients with definite TBI performed in the normal range of neuropsychological assessment measures

Table 6: Test Performance in Relation to Injury Severity, Moderate and Severe TBI Compared With Control Subjects

Test	Moderate TBI (n=35)	P	ES _{control} [†]	d _{pooled} [*]	Severe TBI (n=26)	P	ES _{control} [†]	d _{pooled} [*]
Motor function								
Grooved Pegboard; dominant hand (s)	68.9±11.7	.032	.68	.52	78.0±23.7	.007	1.91	.92
Information processing speed								
TMT; numbers [‡] (s)	34 (29–40)	<.001	1.67		35 (27.5–51)	<.001	1.83	
CWIT; color naming (s)	33.2±8.6	.013	.90	.69	36.9±1.0	.001	1.68	1.12
SMDT; written version	47.4±11.7	.011	.75	.62	42.2±15.0	.001	1.41	1.03
Visual memory								
CMVT; hits [‡]	39 (36–40)	.270	0		36 (31–39)	.001	1.00	
Verbal memory								
CVLT, long-delay free recall [‡]	11 (8–14)	.040	.44		11 (3.75–14.0)	.013	.44	
Executive function								
Verbal Fluency; letter	33.3±10.6	.010	.58	.59	31.8±11.3	.005	.71	.71
TMT; letter-number switching [‡] (s)	82 (65–105)	<.001	1.03		81.5 (63.25–127.5)	.003	1.11	
CWIT; inhibition/switching [‡] (s)	65 (54.75–78.5)	.004	1.13		72 (60–89)	<.001	1.85	

NOTE. Values are mean ± SD, median (25%–75%), or as otherwise indicated.

Abbreviation: ES, effect size.

*Cohen's *d*; mean difference divided by the pooled SD.

[†]For tests yielding normally distributed data; Glass' *d*; ES is the standardized mean, using the SD of the control group. For the nonnormally distributed data, ES_{control} was calculated as difference between medians divided by .75 × interquartile range_{control}.

[‡]Data not normally distributed.

as early as 3 months postinjury. This was unexpected, and we regard this as a novel finding in contrast with some previous studies. Novack et al³⁵ found more pronounced cognitive decline in a sample of 72 patients who were tested 6 months postinjury. Their cohort included a higher proportion of patients with severe TBI who were recruited from a rehabilitation setting. Boake et al¹⁰ and Kreutzer et al¹¹ studied patients shortly after resolution of PTA; the mean days postinjury were 42 and 50, respectively. Both research groups found a higher proportion of impaired test scores compared with normative data. The difference between these studies and ours is most likely because their patients were tested earlier than ours, and their sample was drawn from the rehabilitation setting and likely included more severe cases.³⁶

We do not, however, consider our sample to be biased by systematic exclusion or loss of severe cases. On the contrary, patients who refused testing more often had moderate TBI than those who participated, and the 9 patients who were included after the main inclusion period had severe injuries.

We used 1.5 SD as the cutoff level for evaluation of the standardized scores, which corresponds to a 5% rate of impairment in healthy persons. The control group performed fairly well, in line with this expectation, and thus the tests demonstrated high specificity to TBI with this definition of impairment.

Applying 1.0 SD as a cutoff did not lead to better discrimination between patients and controls. That was to be expected because even when effect sizes are large, overlap between groups is considerable.³⁷ Hence, there is a need for new test paradigms or other methods of examinations with higher discriminative abilities. Reitan and Wolfson³⁸ argued that typical neuropsychological tests with continuous score distribution should be supplemented by tests identifying specific deficits as present or absent, yielding a dichotomous distribution. They presented promising results with few false-negative tests in a sample of patients with mixed brain injuries, by use of tests designed to identify neurologic deficits. However, the applicability of this technique in patients with TBI is unknown.

Alternatively, a substantial proportion of the patients with TBI might actually have recovered their cognitive capacity at

this early stage, a phenomenon patients demonstrated in mild TBI.^{12,39} Still, 65% of the patients with 0 or 1 impaired score had a concurrent GOSE score of 6 or less, indicating that head injury-related disability was present. If cognitive dysfunction mediates the functional problems, which has been previously demonstrated,^{6,7} this supports the concern for low ecologic validity of common neuropsychological tests.⁴⁰ On the other hand, injury-related factors other than impaired cognition, such as pain or affective symptoms, might also contribute to their functional decline. Furthermore, GOSE scores of 7 and 8 are partly based on self-report, and may be less reliable than neuropsychological test scores.

Test Performance in Moderate TBI

Patients with moderate TBI had significantly lower test scores than controls. Dikmen et al¹ reviewed cognitive outcome more than 6 months postinjury and concluded that the evidence of cognitive dysfunction after moderate TBI was "limited and suggestive." In the present study, we demonstrated that moderate TBI clearly affects cognition 3 months postinjury, and future studies are needed to explore the cognitive outcome in moderate TBI later in recovery. We included patients with GCS scores of 13, a score defining mild TBI in some previous studies. However, all but 1 of these patients had a PTA duration of greater than 24 hours, and thus would have been classified as having moderate TBI according to several recommendations.^{41,42} Furthermore, there is an increasing trend to classify patients with GCS scores of 13 as having moderate TBI.⁴³

Test Performance in Relation to MRI Findings

DAI was found in 69% of TBI cases included in this study. DAI has previously been related to impairments of information processing speed,⁴⁴ executive functions, and verbal memory.^{45,46} However, in some of these studies the diagnosis of DAI was based on CT finding, which is not optimal,^{44,45} or cases of DAI were not compared with cases without DAI.⁴⁶ The findings in our study support the hypothesis that DAI may be an important explanation for the large effects on measures of

speed found in this study. Few patients had no evidence of DAI in our study, and variances in test performance were large. Thus, power was not sufficient to compare cases with and without DAI. Hopefully, this will be explored in a future, larger study.

Test Performance in Relation to Cognitive Domains and Evaluation of Measures

Tests measuring processing speed, like the TMT, SDMT, and CWIT, showed the largest effect sizes. Impairments demonstrated by these tests were specific to TBI, as 20% to 30% of the individuals with TBI, but very few control participants, performed in the impaired range. The most sensitive test was SDMT. However, even for this test, reported to be very sensitive to brain insults,¹³ the percentage of patients with TBI with test performance below 1.5 SD was only 30% and 43% for the oral and written version, respectively.

The measures of working memory (Digit Span Backwards and letter-number sequencing) were surprisingly insensitive to TBI. It is possible that these tests measure aspects of working memory that are only mildly affected by TBI, and that tests requiring more simultaneous processing, such as the n-back paradigms,⁴⁷ might be more useful in future studies of working memory deficits after TBI.

For visual memory, measured as CVMT total score, we found very similar results in both groups. This was due to a higher rate of false positives among control participants than reported in the normative sample.²⁴ Given the generally strong abilities of our control group, this is difficult to explain. In a study of criterion validity of the CVMT in moderate to severe TBI, the authors concluded that the CVMT was clinically useful, but they did not make any comparisons with normative data.⁴⁸

The CCPT-II also poorly discriminated between patients with TBI and control participants. Other continuous performance test measures have been found to be sensitive to dysfunction of the attention system.⁴⁹ Thus, it is possible that CCPT-II is less useful than other continuous performance tests in patients with TBI. However, our finding may also support previous research demonstrating relatively preserved vigilance after TBI.⁵⁰

Cognitive Functioning in Relation to 1-Year Functional Outcome

We found a higher frequency of disability 1 year postinjury in patients with cognitive impairment diagnosed 3 months postinjury; we thus confirmed that cognitive impairments in the early phase can be considered a risk factor for future disability.⁵¹ On the other hand, a significant proportion, 43%, of those with a normal early assessment experienced later complaints as defined by a GOSE score of 7 or less, and we consider this an interesting finding.

Study Limitations

The whole sample was not derived consecutively during one study period, as 15% of the patients were injured after the main inclusion period. Secondly, the neuropsychological test performances in our patients with severe TBI should not be generalized to all patients with severe TBI, but can only be applied to those who are able to cooperate with testing. All the patients with severe TBI in this study experienced a favorable outcome, with a GOSE score greater than 4 at 12 months' follow-up. The patients who were unable to cooperate with testing, however, represented a subgroup with very severe injury and poor outcome, and who even at 12 months postinjury were unable to complete a standardized neuropsychological assessment.

Patients with TBI had significantly lower IQ scores than the control participants. This may demonstrate an adverse effect of TBI, as previously described.⁵² However, the high IQ scores among women with TBI argue against this as the sole explanation, and most likely there were some underlying preinjury differences between patients and controls. Recruitment of a control group has been challenged in TBI research,^{1,12} but there is no general agreement on the method of choice. We consider a possible preinjury difference between men and women patients with TBI an interesting finding, as this could confound possible sex differences regarding effects of TBI.

We could have included measures of symptom validity, because many individuals with TBI were injured in traffic accidents and will eventually be involved in litigation. Poor effort, however, would presumably have indicated a falsely high rather than low sensitivity of the tests.

Finally, no systematic masking of the outcome assessor was applied, although test scores were not at hand during the GOSE scoring, and the categorization into impaired or normal was not yet performed.

CONCLUSIONS

Patients with moderate and severe levels of TBI were cognitively impaired compared with a healthy control group, and cognitive impairment at 3 months was associated with later disability. We demonstrated a fair specificity of impairment below 1.5 SD, as this was seldom found in the control group. On the other hand, the sensitivity to TBI of a conventional assessment was lower than expected. From a clinical perspective, we consider this an important and novel finding. A seemingly normal assessment was common in patients with recent TBI confirmed by MRI findings, despite the presence of concurrent disability in the majority of these patients. Patients' subjective report of complaints affecting daily life at 1-year follow-up was also considerable.

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APPENDIX 1. EXPLANATION OF HOW PATIENTS WERE SELECTED FOR NEUROPSYCHOLOGICAL ASSESSMENT

Population

- Of 172 patients admitted, 169 consented to follow-up.
- Of these, 115 persons were 15–65 years of age.

Reasons for exclusion

- 16 persons died.
- 17 persons had preinjury morbidity.
- 1 person developed a chronic subdural hemorrhage requiring surgery at 3 months.
- 2 persons were not fluent in Norwegian language.
- 12 persons could not cooperate; of these:
 - 7 had been in vegetative state 4 weeks postinjury.
 - 3 had been minimally conscious at 4 weeks postinjury.
 - 2 had been in PTA at 4 weeks postinjury.
 - All had poor outcome at 12 months.
 - Only 1 could be tested by 12 months.
- 14 persons rejected testing at the study hospital; of these:
 - 11 had a moderate TBI; 3 had severe TBI.
 - 11 had a good recovery at 12 months' follow-up.

- 3 had moderate disability at 12 months' follow-up.

Lost to follow-up

1 person was lost to follow-up.

52 persons included from the main cohort

Convenience sample

9 persons in the main database, tested at 3 months in 2008 and 2009

Final study sample of 61 individuals with TBI

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