ORIGINAL RESEARCH

Cognitive Reserve Moderates Cognitive Outcome After Mild Traumatic Brain Injury

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Abstract

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

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

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

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

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

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

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

Methods

Participants

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

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

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

Procedure and clinical variables

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

Cognitive assessment

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

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

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

List of abbreviations:

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

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

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

Abbreviations: CT, computed tomography; IQR, interquartile range; GCS, Glasgow Coma Scale; LOC, loss of consciousness; PTA, posttraumatic amnesia.
* Kruskal-Wallis test/Mann-Whitney *U* test.
† Pearson χ² test.
‡ One-way analysis of covariance with age as a covariate.
§ Raw scores converted to T score using the Wechsler Abbreviated Scale of Intelligence manual for easier interpretation. *P*-value from a 1-way analysis of variance is shown. The published normative reference values have a mean of 50 and an SD of 10.
‖ Sharp injuries, such as cuts, are included here for TC.
¶ *P*<.05.

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

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

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

NOTE. The published normative reference values have a mean ± SD of 50±10.

Abbreviations: AVLT, Auditory Verbal Learning Test; NA, not applicable.

* Group effect Kruskal-Wallis test. Unadjusted and Bonferroni adjusted (original P value multiplied with 5) are shown.

[†] No. of recalled words in trial 1-5.

[‡] Analyzed with linear mixed model (fig 1).

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

Estimation of premorbid intelligence and cognitive reserve

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

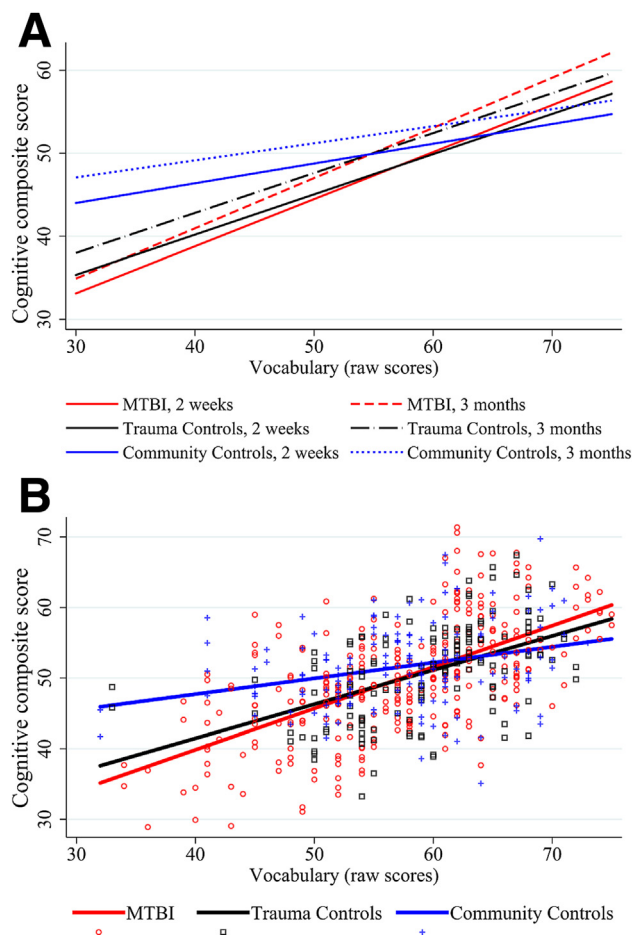## Postconcussion symptom measure

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

Statistical analyses

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

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

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

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

Results

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

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

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

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

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

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

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

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

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

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

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

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

Neither the 3-way interaction term group (PCS+, PCS−)× time×vocabulary nor any of the 2-way interactions were statistically significant, and they were omitted from the model. In figure 2, the time×group interaction is shown for illustrative purposes. With all the interaction terms omitted and with age, sex and vocabulary scores controlled for, the PCS+ and PCS− groups had almost identical cognitive composite scores (mean difference, 0.16; 95% CI, −2.33 to 2.65; $P=.901$). The intraclass correlation for this model was 0.83, the estimated variance of the random intercept was 32.0, and the variance of the within-subject residuals

was 6.5. When vocabulary scores were not controlled for, there was still no significant difference in the cognitive composite scores between the groups (mean difference, −2.02; 95% CI, −5.12 to 1.07; $P=.200$).

Raw scores vs normative scores for the Vocabulary test

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

Discussion

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

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

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

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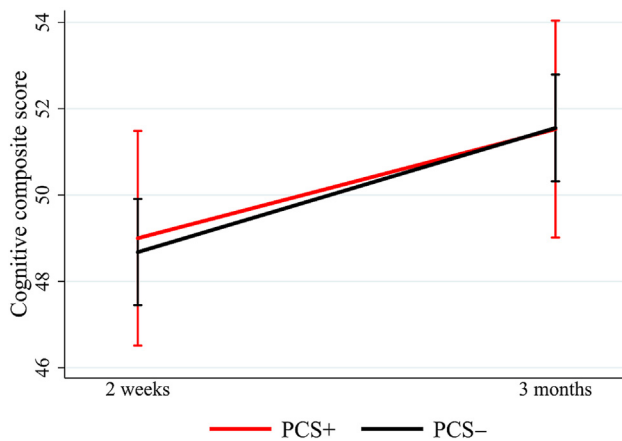[‖] Analyzed with linear mixed model (fig 2).
[¶] 27 patients with PCS completed the 3-month assessment.
[#] 126 patients without PCS completed the 3-month assessment.
** $P<.05$.

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

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

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

The TC group did not differ significantly from either the MTBI group or the CC group regarding the effect of cognitive reserve on cognition. It is therefore not possible to conclude firmly whether the effect of cognitive reserve is specific for MTBI (ie, compared with trauma in general). In fact, even though the estimate (ie, the effect of cognitive reserve on cognition) was largest in the MTBI group, the estimates for the MTBI group and the TC group differed less than the estimates for the TC group and the CC

group. In MTBI research, it is common to observe greater similarities between patients with MTBI and TCs than between patients with MTBI and healthy controls without MTBI. This has been reported for cognition[45] and abnormalities in white matter.[46,47] The mechanisms behind this are largely unknown and need further investigation.

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

Study limitations

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

Conclusions

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

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

Supplier

a. Stata 15.1; StataCorp LLC.

Keywords

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

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