

ORIGINAL ARTICLE

Postrecovery Cognitive Decline in Adults With Traumatic Brain Injury

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ABSTRACT. Till C, Colella B, Verwegen J, Green RE. Postrecovery cognitive decline in adults with traumatic brain injury. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S25-34.

Objective: To assess prospectively the degree of postrecovery long-term cognitive decline after moderate to severe traumatic brain injury (TBI).

Design: Observational cohort.

Setting: Inpatient rehabilitation hospital.

Participants: Adults (N=33) with moderate and severe TBI from a well characterized sample with low attrition.

Interventions: Not applicable.

Main Outcome Measures: Recovery of functioning was ascertained through repeat neuropsychological assessments over the first 5 years postinjury. Cognitive decline from a baseline of 12 months postinjury to a follow-up evaluation conducted on average \pm SD 2.1 \pm 0.99 years later. Change was calculated using the reliable change index (RCI) for 12 neuropsychological tests commonly used in the assessment of TBI.

Results: At the group level, negligible changes in cognitive function were observed over time. However, application of the RCI using 90% confidence intervals showed statistically significant cognitive decline on at least 2 neuropsychological measures in 27.3% of study participants. Decline was most commonly observed on a test of verbal fluency and the delayed recall portion of a test of verbal list learning (Rey Auditory Verbal Learning Test), although substantial variability existed across patients. Decline was significantly correlated with hours of therapy received at 5 months postinjury ($P<.02$).

Conclusions: Consistent with a small number of previous studies, cognitive deterioration may follow an initial period of recovery. Overall, the pattern of decline across tests varied across individuals. Possible mechanisms of decline are discussed. Further research is needed to understand the stability of this finding and its functional implications.

Key Words: Brain injuries; Cognition; Follow-up studies; Neuropsychological tests; Recovery of function; Rehabilitation.

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RECOVERY FROM TRAUMATIC brain injury has been a topic of wide interest for many decades.¹⁻⁷ An understanding of recovery has implications not only for prognosis but also

for our understanding of recovery mechanisms, and by extension for the development of treatments to improve outcome from TBI. In most longitudinal studies examining recovery, grouped means have been compared across time.^{1,8} This conventional method of analysis is limited in its ability to describe the variability in the types of behavioral impairments and rates of recovery shown by individuals with TBI. For example, even in a group of moderately and severely impaired patients with TBI, some individuals will show no initial impairment on some neuropsychological tests, and consequently no recovery on those tests.⁹ Change scores of the group means would therefore underestimate recovery on these tests.

More recent studies have used statistical analyses that allow for an examination of the individual growth trajectory.¹⁰⁻¹⁴ These studies have consistently exposed substantial variability from patient to patient in the degree of cognitive change across time. In addition, these studies have shown that patients may also vary in the degree to which they maintain recovery, once achieved. This latter type of variability across patients, and the predictors of this variability, have been little studied to date. Indeed, a survey of the literature revealed that only a handful of studies has explicitly examined the possibility of "post-recovery cognitive decline,"^{11,15-17} a term we use to refer to cognitive deterioration that follows an initial period of recovery. These studies have found, importantly, that the incidence of decline is nontrivial. For example, Millis et al¹¹ examined changes in neuropsychological test performance from 1 to 5 years postinjury in 96 individuals enrolled in the TBI Model Systems Project. The average severity of injury of the sample was moderate, and change was indexed by a significant increase or decrease on 2 or more tests of a 15-test battery as determined by the RCI.¹⁸ The RCI allows for the measurement of clinically significant change and helps to control for the unreliability of the measurement tools in repeated measures designs. Millis¹¹ found that 63% of individuals showed no change in functioning, 22% improved, and 15% declined. The group also found that older age and difficulties in verbal learning capacity at 1

List of Abbreviations

ALC	alcohol
CI	confidence interval
COWAT	Controlled Oral Word Association Test
GCS	Glasgow Coma Scale
LOS	length of stay
MVC	motor vehicle collision
PAI	Personality Assessment Inventory
PTA	posttraumatic amnesia
RAVLT	Rey Auditory Verbal Learning Test
RCI	reliable change index
SDMT	Symbol Digit Modalities Test
TBI	traumatic brain injury
TMT	Trail Making Test
WAIS-III	Wechsler Adult Intelligence Scale-3rd Edition
WMS-III	Wechsler Memory Scale-3rd Edition

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year were significant risk factors for long-term decline. One limitation of this study, as the authors noted, was an attrition rate of greater than 90%. Sample bias could have therefore confounded the estimate of decline in this study, with those faring best disproportionately represented in the sample. In addition, the conclusion that verbal learning capacity was a predictor of later decline is weakened by the lack of independence between the predictor and decline variable.

Himanen et al.¹⁵ studied changes in the cognitive performance levels of 61 patients with TBI who were tested twice over an almost 30-year interval. This study measured the evolution of cognitive impairment across 8 neuropsychological tests. Results revealed a significant increase in the overall index of cognitive impairment at approximately 30 years post-TBI relative to the baseline level, which was, on average, 2.5 years postinjury. However, not all patients contributed to this change: while 56% of participants showed decline, 23% showed improvement, and 21% remained at the same level as in the original examination. Again, older age was a risk factor for decline, as was male sex. However, this study too had a high attrition rate (>70%) as the authors pointed out, as well as a biased follow-up sample, consisting of patients who were "... referred to the neurology clinic or neuropsychologist because of a recent nontrivial injury or disability,"^{15(p187)} which would have inflated the true incidence of decline after TBI. Of note, this study controlled for age-related decline over the lengthy follow-up interval by comparing performances of their subjects at each time point to normative data. However, there is mounting evidence that the apolipoprotein E allele 4 increases the likelihood of premature dementia after TBI,¹⁹⁻²¹ which has important implications related to the underlying mechanisms of postrecovery cognitive decline in the aging brain. Therefore, the preponderance of decline in their study may partially reflect the deleterious interactions between aging and TBI.

Studies have also reported evidence of postrecovery cognitive decline occurring over shorter follow-up intervals. In 1 study of 40 adults by Ruff et al.,¹⁶ approximately 33% of the sample declined, 50% remained stable, and 17% showed ongoing recovery within the first year post-TBI on a measure of learning and memory. Low education and worsening of depressive symptoms were risk factors for decline. In another study of 21 brain-injured adults¹⁷ who were at least 6 months postinjury at the time of their first assessment, significant deterioration on a timed test of spatial recognition accuracy was observed in the mean group data over an average follow-up interval of 9 months. The incidence of decline across individuals in this TBI group was not examined.

Overall, studies to date have found evidence that postrecovery cognitive decline occurs in patients with TBI^{11,15,17}; however, these studies have contained significant methodologic limitations, including very high attrition rates. Further research is warranted, therefore, to confirm the phenomenon of postrecovery cognitive decline, and to add to our understanding of the incidence and correlates of decline. Identifying predictor variables that account for outcome variance is needed clinically for long-term prognostication, which in turn is important for planning and the possibility of prophylactic intervention. Moreover, an understanding of factors associated with decline can shed light on the mechanisms of decline, and ultimately facilitate the development of efficacious interventions.

In the current study, we examined postrecovery cognitive decline in a prospectively studied group of 33 patients with moderate and severe TBI using 12 of the 15 tests administered in the study by Millis et al.¹¹ Using the RCI,¹⁸ we predicted

that decline would be greater than that reported by Millis¹¹ because of a selection bias that may have underestimated the incidence of decline in that study. In addition, we examined characteristics that may distinguish the individuals who show decline versus those who do not show decline. Based on previous research, we predicted that increased age and depression would be associated with decline. We also explored novel predictors, including ALC and substance use, and low participation in outpatient rehabilitation services, as risk factors for decline.

METHODS

Participants

The study sample comprised 33 patients with moderate to severe TBI. All participants were part of a larger, longitudinal study on cognitive and motor recovery that was undertaken in the inpatient neurorehabilitation program at the Toronto Rehabilitation Institute.

This study was approved by the Research Ethics Board of the Toronto Rehabilitation Institute.

Participants in the larger study underwent neuropsychological testing at 2, 5, and 12 months postinjury and met the following inclusion criteria: age 17 years and older, positive computed tomography or magnetic resonance imaging findings or evidence of a moderate to severe TBI as determined by a GCS²² score of 13 or less and/or PTA of 1 hour or more, proficiency in English as judged by the treating speech language pathologist and/or psychometrist, and functional use of 1 or both upper extremities. Individuals were excluded from the larger study if they had sustained their TBI secondary to another neurologic event (eg, a fall caused by a stroke), had a history of psychotic disorder, had another neurologic disorder or systemic disorder known to affect cognitive functioning or recovery (eg, Lupus, Korsakoff encephalopathy, sleep apnea), were known to be actively engaged in ALC or substance abuse at time of testing, or failed the test of symptom validity (Test of Memory Malinger²³) at any of the assessments.

Patients were eligible for the current study if they were at least 2 years postinjury, but were subsequently excluded if they had sustained another brain injury since the original injury. At the time of this investigation, 48 patients in the larger study were at least 2 years postinjury and eligible for recruitment. Of these, 2 had sustained a subsequent brain injury and 1 was deceased, leaving 45 eligible participants. Four could not be reached, and a further 8 declined to participate because of lack of interest (n=6) and distance (n=2). The sample therefore was composed of 33 patients corresponding to 69% of the original 48 potentially eligible participants.

Table 1 shows the demographic and injury characteristics of the study sample as well as those patients who were not recruited. The study sample was a typical group of moderately to severely impaired patients with TBI, with a high ratio of men to women subjects, an average estimated premorbid Intelligence Quotient (based on the North American Adult Reading Test-Verbal IQ²⁴ or Wechsler Test of Adult Reading estimate²⁵), an average "medium" level socioeconomic class based on the Hollingshead Four Factor Score,²⁶ and most injuries sustained by MVCs. The study sample and the eligible patients who did not participate in the study did not differ significantly on any of the demographic or injury-related parameters. Therefore, the sample was without evidence of bias caused by selective attrition.

Table 1: Demographic and Clinical Characteristics of the Study Sample and of Those From the Larger Sample Who Were Not Recruited

Variable	Study Sample (n=33)	Subjects Not Recruited* (n=15)
Men, no. (%)	25 (75.8%)	14 (93.3%)
Injury age (y)	35.36±14.52	41.20±19.35
Years of education	12.70±2.72	11.80±3.36
GCS score	6.48±3.34	7.50±3.89
Etiology, no. (%)		
MVC	20 (60.6%)	6 (40%)
Fall	9 (27.3%)	6 (40%)
Assault	3 (9.1%)	3 (20%)
Sports injury	1 (3.0%)	0 (0%)
LOS in rehabilitation hospital (d)	38.09±18.31	45.93±18.31
Total therapy received a week (h) at 4.5-month assessment	5.93±4.79	4.31±4.55
Socioeconomic status [†]	38.47±10.67	37.29±13.28
Premorbid IQ score [‡]	97.33±15.58	96.50±20.07
Litigation cases, no. (%)	5 (13.9%)	2 (13.3%)
Days postinjury at assessment 1	54.03±17.10	55.08±14.32
Days postinjury at assessment 2	147.08±28.58	148.71±30.10
Days postinjury at assessment 3	382.74±32.43	369.09±15.86

NOTE. Values are mean ± SD unless otherwise noted.

*Includes patients lost to follow-up as well as those who were subsequently excluded because of another brain injury or death.

[†]Based on classification from Hollingshead Four Factor Score.²⁶

[‡]Estimate based on the North American Adult Reading Test-Verbal IQ²⁴ or Wechsler Test of Adult Reading.²⁵

Materials

Neuropsychological and clinical psychologic test battery.

Twelve neuropsychological tests were used to assess performance on a broad range of cognitive abilities, including attention, speed of processing, verbal learning and memory, executive function, visual-spatial ability, and manual motor dexterity. The test battery was composed of the Block Design and Digit Span subtests (Digit Span Forwards and Digit Span Backwards) from the WAIS-III²⁷/Wechsler Abbreviated Scale of Intelligence,²⁸ SDMT (oral only),²⁹ TMT (Parts A and B),³⁰ Logical Memory I and II subtests from the WMS-III,³¹ RAVLT³² (total learning and delayed recall scores), COWAT (phonemic fluency),³³ and Grooved Pegboard (dominant hand only).³⁴ As a repeated-measures design was employed in the current study, alternate forms were used where available to minimize practice effects. The tests selected do not have known, appreciable floor or ceiling effects for this sample.

For comparison purposes, tests were selected from the battery used in our larger study of recovery to overlap with those used in the long-term outcome study of Millis et al,¹¹ with the exception of tests that show (1) large practice effects (ie, the Wisconsin Card Sorting Test),^{35,36} and (2) limited variance with patients with TBI based on our clinical experience (ie, Tokens Test³³). Depression and anxiety-related symptoms were assessed using total scores from the Beck Depression Inventory³⁷ and the Beck Anxiety Inventory,³⁸ respectively.

Test-retest correlations for the RCI calculations were obtained from Levine et al³⁹ for TMT (Parts A and B),³⁰ Digit Span tests,²⁷ SDMT,²⁹ COWAT,³³ and grooved pegboard.³⁴ Reliability for RAVLT³² was taken from Geffen et al⁴⁰; the WAIS-III²⁷ and WMS-III³¹ manuals were used for the Block Design and Logical Memory subtests. Reliability coefficients ranged from .67 (Grooved Pegboard) to .82 (Block Design).

Design and Procedures

The study was a within-subjects, longitudinal design employing both group and individual test-retest comparisons.

The battery of tests administered was divided into 4 blocks of tests, with a fixed order of tests within each block designed to minimize interference between tests. Order of the blocks was counterbalanced across participants at each assessment.

The baseline, comparison data used in the present study were obtained from the 12-month assessment. We specifically chose to examine cognitive change from 12 months to long-term follow-up based on the literature that most cognitive functions begin to show a plateau in their recovery by 1 year postinjury⁶ whereas a baseline taken at an earlier time point (ie, 4.5-month assessment) might not have reflected full recovery across all cognitive domains and individuals. Comparison of mean performance levels between the 4.5-month and 12-month assessments showed marginally higher performance at the 12-month assessment on 10 of 12 tests; however, differences were not significant.

The long-term follow-up neuropsychological testing was completed between 2 and 5 years postinjury (mean time postinjury, 37.2±11.9mo). Neuropsychological testing was generally completed within 1 day. After each assessment, all patients were provided with oral and written feedback of results by a psychologist.

Analyses

All analyses were performed with the SPSS statistical package.^a Raw score neuropsychological data for each test were standardized to rule out effects of aging on performance decrements and to place all scores on a common metric in order to enable direct comparisons of groups. Normed scores were used for all analyses.

Data considerations. Baseline data for 3 individuals were taken from the 5-month assessment rather than the 12-month assessment because these individuals did not return for the 12-month assessment. Use of the 5-month data here was considered to be conservative for the following reasons: (1) all 3 patients did not return for the 12-month assessment because they had returned to work by 1 year (and were still at their respective jobs at long-term follow-up); therefore, from a functional point of view, they showed good recovery; (2) use of this earlier baseline is conservative with respect to our hypotheses (ie, decline is more likely to be underestimated in our sample because the 5 baseline level is biased toward being lower than the 1-year baseline, and thus leaving less room for decline); (3) the addition of these 3 cases decreased the standard error of difference score used in the RCI calculation on 4 of 12 neuropsychological measures (suggesting that their 5-month scores were similar to the mean 12-month assessment levels); and (4) scores on the 12 subtests at 5 months postinjury were higher for the 3 cases relative to the mean 12-month scores of the remaining sample.

Within-subjects group comparisons. Two-tailed, paired sample *t* tests with a *P* value of .05 were used to compare the cognitive performances between baseline and follow-up on each neuropsychological measure. If variables were not normally distributed as determined by the Shapiro-Wilk statistic, then the Wilcoxon *P* nonparametric test was used. Given the exploratory nature of this analysis and small sample size, the Sidak adjustment⁴¹ was employed, which takes into consideration the correlations between the outcome variables. Using an α of .05, 12 comparisons, and an overall correlation of .29 between measures, the corrected α for significance is .009.

Individual analyses. To measure individual change in cognitive performance over time, RCI described by Jacobson and Truax¹⁸ was used. The RCI is defined by the following:

$$RCI = (x_2 - x_1) / S_{diff}$$

where x_1 represents the subject's baseline score, x_2 represents the subject's follow-up, and S_{diff} is the SE of that difference. Although alternate versions of the RCI have been developed to control for the contribution of practice effects,⁴² the current study employed the original RCI method given that practice effects were minimized in 2 ways: (1) alternate forms of tests were used and (2) participants were exposed to the tests twice before the 1-year postinjury assessment, which has been shown to decrease the magnitude of practice effects.⁴³ The S_{diff} can be computed from the SE of measurement (S_e), which is a function of the initial SD of the measure and its reliability according to the following formula:

$$S_{diff} = \sqrt{2(S_e)^2}, \text{ where } S_e = s \sqrt{1 - r_{xx}}$$

Reliable change is established when the difference between the follow-up and baseline scores exceeds the 90% CI for the predicted score (ie, $\pm 1.64 \times S_{diff}$).

Participants were classified as decliners or nondecliners if they showed significant decline on 2 or more neuropsychological tests based on the RCI. This dichotomous classification was chosen as the dependent variable in order to examine changes in performance across the entire battery, rather than focusing on changes on individual tests, for which there was considerable heterogeneity.

Characteristics of decliners versus nondecliners. Injury-related and patient characteristics were compared between those assigned to the decliner versus nondecliner groups using the Student *t* test for continuous (and normally distributed data) or Pearson chi-square test for categorical data (eg, injury etiology, clinical elevation on the ALC scale of the PAI,⁴⁴ and insurance status). The 2 groups were compared on (1) age at injury, (2) years of education, (3) sex, (4) premorbid IQ, (5) severity of injury as estimated using acute care LOS (found to be more predictive of outcome than PTA classification scores in a related study), (6) GCS, (7) initial level of impairment on a verbal learning measure (RAVLT; assessed at 2mo postin-

jury), (8) total hours of therapy received (at approximately 5mo postinjury when 27 of 33 individuals were continuing to receive therapy either at our institute or as an outpatient through insurance), (9) litigation at time of 12-month baseline assessment, (10) socioeconomic status,²⁶ (11) length of test-retest interval, (12) insurance status, (13) depressive and anxiety-related symptoms at baseline and follow-up, and (14) preinjury ALC and substance abuse or dependence (assessed using the ALC and Drug clinical scales on the PAI).⁴⁴

RESULTS

Group Data

Descriptive statistics for the standardized neuropsychological measures for the TBI sample are displayed in table 2. Means at the 12-month baseline and follow-up assessments fell within the normative range across all tests. The only statistically significant change across time, after adjusting for multiple comparisons, was an improvement on the TMT Part A ($t_{30}=3.50$, $P=.001$). The magnitude of change was one half an SD, and showed a medium effect size. Cohen d ⁴⁵ effect size differences for all other comparisons across time were small.

Individual analyses. Although mean performance fell within the normative range across all cognitive domains at both baseline and follow-up, this finding conceals the heterogeneity in recovery outcomes across patients, and underscores the limitations of examining only group data for this population. Examination of individual scores across the sample revealed clinically significant deficits (ie, mild impairment or greater) across all measures at both baseline and follow-up, particularly on timed and unstructured tests (eg, SDMT, grooved pegboard, TMT [Parts A and B], and RAVLT).

Change findings based on RCI: proportion of subjects showing decline. Frequencies of change on specific neuropsychological measures as determined via the RCI method are presented in table 3. Any score that fell within the 90% CI was considered to be unchanged. Test scores were considered to have changed (either in the direction of improvement or decline) if they fell outside this CI.

In order to determine whether a subgroup of individuals contributed to these significant declines, patients were classi-

Table 2: Comparison of Neuropsychological Test Performance in z-Score Units for Patients With TBI Between 12-Month Baseline and Follow-Up Evaluation

Test	N*	12-Month	Follow-Up	Difference Score	Statistic			RCI 90% CI†
					t test	P	d	
Grooved pegboard	27	-0.96±1.32	-0.72±1.13	0.24±0.93	-1.10	.28	-0.18	±1.26
TMT Part A	31	-0.42±1.16	0.15±1.11	0.57±0.90	-3.50	.001	-0.49	±1.15
TMT Part B	30	-0.23±1.36	-0.01±1.65	0.22±1.13	-1.06	.30	-0.16	±1.44
SDMT (oral)	30	-0.65±1.33	-0.25±1.28	0.40±0.89	-2.47	.02	-0.30	±0.91
Digit Span Forwards	32	-0.13±1.41	0.15±1.63	0.28±1.55	-2.17†	.03	-0.20	±1.57
Digit Span Backwards	32	0.08±1.40	0.22±1.48	0.14±1.05	-1.98†	.05	-0.10	±1.06
COWAT	30	-0.43±1.02	-0.63±0.80	-0.20±0.66	1.69	.10	0.20	±0.73
Block Design	31	0.28±1.22	0.38±1.14	0.10±0.67	-1.73	.48	-0.08	±0.66
RAVLT (learning score)	30	-0.67±1.43	-0.44±1.22	0.23±0.95	-1.32	.20	-0.17	±1.05
RAVLT (delayed recall)	29	-0.75±1.55	-0.83±1.46	-0.08±1.02	0.35	.73	0.05	±1.13
Logical Memory I	32	-0.20±1.02	0.10±0.79	0.30±0.85	-1.38	.17	-0.29	±0.95
Logical Memory II	32	0.07±1.09	0.18±1.04	0.11±0.89	-1.59	.12	-0.10	±1.01

NOTE. Values are mean ± SD unless otherwise noted. Reliable change index intervals and associated effect sizes shown. Cohen effect size is designated by d.

*Some participants did not complete all tests because of time constraints and/or fatigue.

†Based on the Wilcoxon signed-rank test.

‡Difference scores that fell outside this 90% CI represented statistically reliable change in our sample.

Table 3: Proportion of TBI Sample (N=33) Showing Significant Cognitive Change Using the RCI Method

Test	% Declined	% Improved	% Stable
Grooved pegboard	7.4	7.4	85.2
TMT Part A	0	19.3	80.7
TMT Part B	6.7	10.0	83.3
Digit Span Forwards	9.4	25.0	65.6
Digit Span Backwards	9.4	25.0	65.6
SDMT (oral)	0	13.3	86.7
COWAT	23.3	10.0	66.7
Logical Memory I	9.4	18.8	71.9
Logical Memory II	9.4	12.5	78.1
RAVLT (learning)	6.7	30.0	63.3
RAVLT (delayed recall)	20.7	17.2	62.1
Block Design	16.1	22.6	61.3

fied according to the number of negative performance change scores they revealed on the test battery. Based on the criterion developed by Millis et al.,¹¹ an individual was classified as a decliner if performance fell below the 90% RCI CI on at least 2 neuropsychological tests. Using this criterion, 9 (27.3%) of 33 individuals showed significant declines in overall performance compared with 24 individuals (72.7%) who did not show significant decline.

The manifestation of cognitive declines varied in breadth and severity. Table 4 displays the significant changes in performance (ie, exceeding the RCI 90% CI range for each test) for the 9 individuals classified as decliners. Inspection of these results shows that declines were most prominent on the COWAT (with 5 of 9 patients showing significant decline on this test) followed by memory tests (with 4 of 9 declining on the RAVLT: delayed recall and 3 of 9 declining on Logical Memory II). Of the 9 decliners, 3 showed significant declines on more than 2 tests. Table 4 also shows the variability across individuals in the magnitude of their respective changes in performance. In 2 cases, declines greater than 2 SDs were observed on the Logical Memory subtests. In 7 of the 8 cases, the number of significant declines was greater than the number of improvements demonstrated across tests.

Patterns across tests. Inspection of individual change scores across cognitive tests revealed a considerable degree of heterogeneity. Changes in both directions were observed for all tests, except for TMT Part A and SDMT, for which significant improvements but not declines were observed. The tests on which significant improvement was most frequently observed, occurring in at least 20% of the sample, included Digit Span (Forwards and Backwards), RAVLT learning score, and Block Design. The tests on which declines were most prominent, affecting at least 20% of the sample, included COWAT and RAVLT (long delay recall).

Characteristics of decliners versus nondecliners. Table 5 summarizes the demographic, environmental, and injury-related characteristics of the individuals who were classified as showing decline versus those who were classified as remaining stable or improving. Inspection of the descriptive statistics showed only 1 significant difference between the groups: amount of therapy received at 5 months postinjury was significantly higher in the group of nondecliners versus the decliners ($t_{31} = -2.98, P = .006$). To rule out the possibility that this relationship was attributable to injury severity or degree of cognitive impairment, we examined the correlations between these variables and hours of therapy. Results showed that the number of hours of therapy received at 5 months postinjury was not significantly correlated with GCS score ($r = -0.19, P = 0.35$) or acute care LOS ($r = -0.09, P = 0.64$) nor with severity of persisting impairments at 5 months, assessed by correlating hours of therapy with verbal learning and memory (RAVLT; $r = -0.02, P = 0.92$), mental processing speed (SDMT; $r = 0.16, P = .39$), and grooved pegboard ($r = -0.01, P = .96$). Therefore, it is unlikely that the relationship between therapy hours at 5 months postinjury and long-term decline can be explained by severity of impairments or injury.

Other factors that may contribute to the amount of therapy received include access to postacute rehabilitation services among patients. The extent of postacute rehabilitation may differ among individuals with and without access to third-party insurance funding (eg, through car insurance for patients after MVC), especially with respect to access to home support rehabilitation services. Results showed that proportionately more nondecliners (18 of 24) received third-party insurance

Table 4: Significant Improvements and Declines on Each Neuropsychological Test in the Battery for the 9 Patients Labeled as Decliners

Test	Subject Number								
	205	211	221	223	305	316	320	322	331
Grooved pegboard	=	=	NA	=	=	↓	=	=	NA
TMT-Part A	=	=	↑	=	=	=	=	=	=
TMT-Part B	=	=	↑	=	=	=	↑↑	NA	↓
Digit Span Forwards	↑	↓	↓	=	↑	=	(↑)	=	=
Digit Span Backwards	(↑)	=	=	(↓)	=	=	=	=	(↑)
SDMT (oral)	NA	=	=	↑	=	=	=	↑	=
COWAT	↓	(↓)	↓	=	(↓)	=	(↓)	=	=
Logical Memory I	=	=	↓↓	=	=	=	↑	↓	=
Logical Memory II	↓↓	=	↓	=	=	=	↑	↓	(↑)
RAVLT (learning)	↓	=	=	=	↑	↓	=	=	=
RAVLT (delayed recall)	↓	=	=	=	=	↓	↓	=	↓
Block Design	=	=	=	↓	↓	=	(↑)	=	(↑)
No. declines	4	2	4	2	2	3	2	2	2
No. improvements	2	0	2	1	2	0	5	1	3

NOTE. Magnitude of change in performance (in standard deviation (SD) units) is shown using the following criteria: (↓/↑) refers to an increase/decrease between .50 to .99 SD; ↓/↑ refers to an increase/decrease between 1.00 to 1.99 SD; ↓↓/↑↑ refers to an increase/decrease between ≥2.00 SD; = refers to no change or change that is less than 0.5 SD. Abbreviation: NA, not applicable.

Table 5: Characteristics of the Subset of Individuals Showing Cognitive Decline Versus Those Who Were Classified as Remaining Stable or Improving

Characteristic	Decline Group (n=9)	No Decline Group (n=24)
Men, no. (%)	7 (77.8%)	18 (75.0%)
Injury age (y)	41.33±17.66	33.13±12.87
Years of education	13.45±2.69	12.31±2.71
GCS score	8.14±3.43	5.95±3.21
Etiology, no. (%)		
MVC	3 (33.3%)	17 (70.8%)
Fall	6 (66.7%)	3 (12.5%)
Assault	0 (0%)	3 (12.5%)
Sports injury	0 (0%)	1 (4.2%)
Total therapy hours a week at 5-month assessment	2.11±2.71*	7.07±4.68
Receiving private insurance, no. (%) [‡]	4 (44.4%) [†]	18 (75.0%)
Socioeconomic status score	41.56±8.22	37.26±11.47
Premorbid IQ score [§]	101.11±13.40	98.30±14.28
Litigation cases, no. (%)		
Medical legal	2 (20.0%)	2 (8.7%)
Criminal charge	1 (10.0%)	4 (17.4%)
ALC/ substance use, no. (%)		
Elevated ALC scale	3 (33%) [†]	2 (8.3%)
Elevated Drug scale	0 (0%)	4 (16.6%)
Months between baseline and follow-up	27.33±12.61	24.89±12.01
Emotional functioning total score		
BDI at baseline	5.67±4.42	10.75±9.67
BDI at follow-up	6.33±8.35	10.77±8.83
BAI at baseline	4.44±4.42	5.91±6.40
BAI at follow-up	5.22±6.67	7.73±8.82
Level of impairment on RAVLT learning at 1.5 months postinjury	-2.10 ±2.20	-1.63±1.87

NOTE. Values are mean ± SD unless otherwise noted. Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory.

* $P < .01$; [†] $P \leq .10$.

[‡]All cases with private insurance were patients after MVC who had car insurance.

[§]Based on the North American Adult Reading Test Verbal Intelligence/Wechsler Test of Adult Reading estimate.

^{||}Proportion of individuals with a T score of 60 or higher on the PAI.

funding than decliners (4 of 9), and this difference approached significance ($\chi^2=2.75$, $P=.10$). Because having insurance coverage may explain in part why the nondecliners group received significantly more hours of therapy after discharge, we examined in the overall sample the difference in hours of therapy between individuals who received third-party insurance funding versus those who do not. This comparison confirmed our expectation: individuals who were insured ($n=22$) received more hours of therapy after discharge (mean ± SD, 6.69±4.4h) than those who were not insured ($n=11$; mean ± SD, 3.32±5.21h), and this difference approached significance ($t_{31}=1.96$, $P=.06$). Of note, all of the patients who received third-party insurance were patients after MVC.

Regarding preinjury ALC use/dependence, a trend approaching significance was observed with a higher proportion of individuals in the decliner group reporting elevated scores on the ALC scale (T score ≥ 60) than those in the nondecliner group (33% vs 8.3%, $\chi^2=2.78$, $P=.09$). No statistically sig-

nificant differences between the decliner and nondecliner group were revealed on any of the other demographic and injury-related variables examined.

DISCUSSION

In some settings, there is a tacit assumption that cognitive gains made over the early recovery period are maintained into the long-term or may even increase. However, using the RCI, we showed that 27% of our sample (9 of 33) manifested cognitive decline on at least 2 subtests (of a 12 subtest neuropsychological battery) between a 12-month baseline evaluation and a follow-up evaluation conducted 1 to 4 years later. Although most individuals in the current study remained stable or showed ongoing improvement, the proportion and magnitude of decline observed in some individuals, as well as those of a small number of prior studies in humans^{11,16,17,46,47} and animals,^{48,49} is nontrivial.

With regard to the pattern of findings across cognitive domains, the common thread in our study was verbal retrieval. The tests for which the largest number of patients showed decline were COWAT and RAVLT delayed recall. Interestingly, there was minimal overlap in the cognitive tests that showed the most predominant decline in our study and the study by Millis et al.¹¹ This discrepancy may reflect variability between the TBI samples and methodologic differences including the timing of assessments (earlier testing before recovery is complete might result in underestimation of decline, particularly for slower recovering functions). In addition, the Millis¹¹ study did not control for the effects of age-related decline even though the effects of aging may be more deleterious in a compromised brain, as shown in a number of animal studies.⁵⁰⁻⁵³

In the present study, we also conducted preliminary explorations of the correlates of decline, although the small size of our cohort limits the power of these analyses. Results showed that individuals who received more hours of rehabilitation at 5 months postinjury were less likely to show cognitive decline. Importantly, increased rehabilitation was not confounded by severity of injury or initial severity of cognitive impairment, because there was no association between these factors and the amount of therapy provided. One explanation for the observed relationship between rehabilitation and lower likelihood of decline is that engagement in rehabilitation may support the maintenance of cognitive functioning, as observed in the environmental enrichment studies of cognitively vulnerable populations, such as the elderly,⁵⁴⁻⁵⁸ high-risk children,⁵⁹ and brain-injured animals exposed to complex environments.⁶⁰ However, important factors that may contribute to an individual's post-acute care services, such as a funding source to access private rehabilitation resources even within a system with access to universal care,⁶¹ should also be considered when interpreting these results.

Another factor that is worthy of further research is a history of ALC abuse or dependence. One third of the individuals classified as showing decline reported problems with ALC use compared with less than 10% of individuals who did not show decline. Although the association showed only a trend towards significance, the small sample size limited the power to detect true associations that may have existed. Past studies have shown that a history of ALC abuse might predispose the brain to an exaggerated response to a TBI.⁶² Whether a history of ALC abuse predisposes the brain to atrophy after a period of recovery has yet to be demonstrated, but given the brain's sensitivity to ALC, at least in very high volumes (eg, Korsakoff syndrome⁶³), and the high prevalence of preinjury ALC abuse in adults who sustain brain injuries,⁶⁴ a possible link between

substance abuse and decline would seem to warrant further investigation.

Previous studies have also observed older age,^{11,15} exacerbation of depressive symptoms,¹⁶ and lower levels of education⁶⁵ to be risk factors for decline or worse outcome. These factors were not significant in the current study, even though the individuals in the decline group were slightly older and reported a marginal increase in depressive symptomatology over time relative to individuals in the nondecliner group. We also examined whether initial level of verbal learning on the RAVLT assessed during the acute recovery period was predictive of later decline. Our results did not replicate a significant association between this measure and outcome as shown by Millis et al,¹¹ but not Chu et al.¹² However, the current study used an early measure of verbal learning (assessed at 2 months postinjury) rather than the actual baseline from which decline was assessed, as done by Millis.¹¹ This obviates the confound of statistical dependence between predictor and outcome. Other studies that have used early neuropsychological testing to predict long-term functional outcomes (that are independent of the predictor) in TBI samples have also shown mixed results, with some studies supporting the prognostic value of early neuropsychological testing (see examples^{9,66}) and others showing limited support.⁶⁷ Across these studies, much variability also exists regarding the specific tests that are indeed predictive of outcome.

Mechanisms of Postrecovery Cognitive Decline

Findings to date have shown broad discrepancies with regard to the proportion of patients showing decline, the tests on which decline is observed, and the predictors of decline. These differences raise questions regarding the underlying mechanisms of decline. A number of explanations are possible.

The first explanation that must be considered is whether the observation of postrecovery cognitive decline is a measurement artifact rather than a bona fide clinical phenomenon. Spurious decline may be attributable to poor reliability of the test measure or regression to the mean. Mitigating these explanations is (1) the use of the RCI, a conservative method of identifying statistically significant decline that takes into account the reliability of the measure, and (2) the observation of decline even when baseline performances were not above average (and thus less vulnerable to regression to the mean). Multiple baselines and follow-up testing would be a powerful means of distinguishing between an explanation of measurement artifact versus true cognitive deterioration. This approach would also help obviate spurious findings caused by intraindividual variability, which is a hallmark of TBI.^{68,69} In addition, biologic evidence of brain deterioration over time, such as accelerated brain atrophy in the decliners, would lend further support to our findings as reflecting a bona fide clinical phenomenon. We are currently exploring this association.

Assuming that postrecovery decline is a bona fide clinical phenomenon, there are at least 3 broad neuropsychological explanations possible. One possibility is that brain vulnerability in a particular area (eg, prefrontal cortex) or a type of tissue (eg, white matter) results in a decline in those patients with damage in that area. Such an explanation is consistent with findings of progression of atrophy in white matter after TBI caused by the deposition of amyloid⁷⁰ or neuroinflammatory processes affecting white matter after TBI.^{71,72} If certain brain regions are vulnerable to decline, particularly in older rather than younger brains as shown in a number of animal studies,⁵⁰⁻⁵³ then we would predict decline to be most pronounced in the cognitive domains served by those areas.

A second possible explanation is that the severity of brain injury (regardless of location or tissue type) would predict decline. In the stroke recovery literature⁷³ as well as in the model by Robertson and Murre⁷⁴ of recovery and rehabilitation after brain injury, the argument has been put forward that large lesions show reduced recovery potential than medium-sized and small-sized lesions. Cortical areas distant from the injury have been shown to undergo major neuroanatomic reorganization⁷⁴⁻⁷⁹ over time. Loss of projections to distant areas functionally related to the injured areas, combined with increased disuse over time of functionally severed areas,⁸⁰ could provide an underlying mechanism for a delayed and gradual decline after TBI recovery.

Last, subject and/or environmental variables may predict decline. Low education, older age, and cognitive inactivity have been associated with a faster rate of cognitive decline in the Alzheimer disease literature,^{57,58} and some of these variables have also been associated with rate of recovery after TBI.^{12,65,81,82} These subject and environmental variables may mediate cognitive recovery and decline regardless of the location or severity of injury sustained, or they might interact with this putative mechanism.

All of these possibilities are highly speculative at this point, but generate testable hypotheses. Further research is needed to discriminate between explanations.

Study Limitations

Several limitations should be considered when interpreting the results. First, the lack of multiple long-term assessments raises questions regarding the validity and reliability of the observation of decline. However, we have argued that the use of RCI mitigates against an explanation of measurement error. Second, we examined cognitive decline from 12 months postinjury. However, Ruff et al¹⁶ observed decline within the first year of injury. Thus, the present study may have underestimated overall decline in some individuals by examining decline only from the later time point. We chose the later time point in order to maximize the likelihood of finding changes over time. Use of the 12-month baseline was more likely to ensure a higher, if not a full, level of recovery.⁶ Also, use of the 12-month baseline allowed us to make direct comparisons with the study conducted by Millis et al,¹¹ which used the same baseline. Nevertheless, it should be acknowledged that decline may have occurred earlier in some individuals or for some cognitive functions, as shown to be the case by Ruff et al.¹⁶

Another limitation of our study was the small sample size. With only 9 individuals identified as showing significant decline in the long term, we were unable to draw strong conclusions about correlates of postrecovery cognitive decline. However, our low attrition and rigorous inclusion and exclusion criteria offset some concerns associated with small samples in longitudinal studies of heterogeneous populations (eg, sample bias).

Clinical Implications

Understanding whether postrecovery cognitive decline is a bona fide phenomenon, and if so, who is at risk and under what conditions, is vitally important information for patients with TBI and for clinicians and researchers. Clinicians require such information in order to improve long-term prognostication and to counsel patients and their families appropriately about functional implications of cognitive decline in order to facilitate future planning. Indeed, clinical counseling on long-term outcome was identified as a key area for future TBI research in a consensus conference sponsored by the National Institutes of

Health.⁸³ The information could also be used by clinicians to advise on potential approaches to minimizing long-term decline. Researchers, too, could use this information to develop interventions to avert or minimize decline.

Implications of postrecovery cognitive decline may also affect resource allocation. At present, the first months postinjury correspond to the period of most intensive therapeutic intervention for patients with TBI. All patients in this study received inpatient therapy within the first 4 months of injury. After discharge, therapies typically diminished in frequency, particularly over the latter part of the first year and especially among individuals who did not have funding to access community resources and ongoing rehabilitation. It is possible that the removal of these therapeutic supports—even among cases that show good recovery—may result in poorer outcomes. Our findings suggest that ongoing rehabilitation (at least in the early subacute stages) may be related to maintenance of gains. Research regarding the relationship between ongoing rehabilitation (or the provision of occasional therapeutic booster sessions) and the prevention of decline is clearly needed.

CONCLUSIONS

The results of this study suggest that postrecovery decline does occur in a considerable proportion of individuals with moderate to severe TBI and may affect an array of cognitive functions. These findings are important clinically because they demonstrate that a normalized early recovery does not necessarily predict maintenance of recovery, let alone continued recovery. Our findings also provide some clues about the risk factors that may contribute to late decline. The strongest correlate of decline in the current study was the extent of therapy received at 5 months postinjury. Patients who received more rehabilitation in the early months postinjury, irrespective of injury severity and level of neuropsychological impairment, were less likely to show decline in the long term. This relationship may be mediated by other factors, such as mechanism of injury, age at injury, and ALC use. Further research with larger sample sizes and similarly well defined samples with low attrition is needed to elucidate risk factors.

Credible information about the incidence of postrecovery decline in individuals with TBI is critical in order to evaluate the scope of the problem, which in turn can be used to affect policy decisions and resource allocation. Population-based estimates are still needed to supplement the estimates from our and other studies, to understand the functional implications of postrecovery cognitive decline, and to examine further the risk factors associated with decline. Finally, further research is needed to shed light on underlying pathologic processes in order to develop effective treatments and prognostication capabilities.

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