


Moderate-Severe TBI as a Progressive Disorder: Patterns and Predictors of Cognitive Declines in the Chronic Stages of Injury

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Robin E. A. Green, PhD^{1,2}, Marika K. Dabek, BSc¹, Alana Changoor, MSc¹,
Julia Rybkina, MSc¹, Georges A. Monette, PhD³,
and Brenda Colella, MSc¹

Abstract

Background. Moderate-severe traumatic brain injury (TBI) has been associated with progressive cognitive decline in the chronic injury stages in a small number of studies. **Objective.** This study aimed to (i) replicate our previous findings of decline from 1 to 3+ years post-injury in a larger, non-overlapping sample and (ii) extend these findings by examining the proportion of decliners in 2 earlier time windows, and by investigating novel predictors of decline. **Methods.** N=48 patients with moderate-severe TBI underwent neuropsychological assessment at 2, 5, 12 months, and 30+ months post-injury. We employed the Reliable Change Index (RCI) to evaluate decline, stability and improvement across time and logistic regression to identify predictors of decline (demographic/cognitive reserve; injury-related). **Results.** The proportions of patients showing decline were: 12.5% (2-5 months post-injury), 17% (5-12 months post-injury), and 27% (12-30+ months post-injury). Measures of verbal retrieval were most sensitive to decline. Of the predictors, only left progressive hippocampal volume loss from 5 to 12 months post-injury significantly predicted cognitive decline from 12 to 30+ months post-injury. **Conclusions.** Identical to our previous study, 27% of patients declined from 12 to 30+ months post-injury. Additionally, we found that the further from injury, the greater the proportion of patients declining. Importantly, earlier progressive hippocampal volume loss predicted later cognitive decline. Taken together, the findings highlight the need for ongoing research and treatment that target these deleterious mechanisms affecting patients in the chronic stages of moderate-severe TBI.

Keywords

brain injuries, cognitive decline, rehabilitation, hippocampus, atrophy

Introduction

Moderate to severe traumatic brain injury (TBI) is associated with significant impairments to cognitive domains, including attention, speed of processing, memory, and executive functioning. These impairments disrupt work, school, and social activities.^{1,2} For many, these impairments are enduring, causing life-long disability, which is in turn associated with a heavy social and economic burden. On the other hand, others may experience only minimal ongoing impairments.³⁻⁶ Prognosticating how an individual will fare in the chronic stages of injury is needed to optimize treatment and clinical management; however, our ability to do so is very limited, despite extensive research into TBI recovery and predictors of outcome.^{2,7,8} The current paper

examines patterns and predictors of cognitive recovery in moderate-severe TBI and focuses on treatable causes of poor outcomes. The current study was designed to replicate and extend our prior research on long-term cognitive recovery in moderate-severe TBI.⁹

¹Toronto Rehabilitation Institute, University Health Network, Toronto, ON, Canada

²University of Toronto, Toronto, ON, Canada

³York University, Toronto, ON, Canada

Corresponding Author:

Robin E. A. Green, Toronto Rehabilitation Institute, 550 University Ave, Toronto, ON, M5G 2A2, Canada.

Email: robin.green@uhn.ca

The majority of longitudinal studies of cognitive recovery in moderate-severe TBI have found that recovery is asymptotic, with a steep early period of improvement.¹⁰⁻¹³ followed by a gradual plateauing at a level that is less than that of pre-injury functioning.¹¹ These studies typically examine patients at the group-level; however, group-based studies can mask more granular features of recovery trajectories. Indeed, across studies that have been conducted at the individual-level, a more complicated picture of recovery emerges, where for some individuals, cognition worsens in the months and years following injury.^{5,14-18} Such findings are consistent with the growing evidence that moderate-severe TBI is a progressive and neurodegenerative disorder.^{9,19,20-27}

In our 2008 study,¹⁶ we prospectively investigated long term cognitive changes from 12 to 30+ months post injury in 33 individuals with moderate and severe TBI. To evaluate clinically significant changes at the individual level, we used the Reliable Change Index (RCI).²⁸ We found that while group level changes over time were negligible, a subgroup of 27% of participants showed a significant decline (using RCI) on at least 2 subtests of a 12-test neuropsychological battery post-injury.

These findings are consistent with those from other groups.^{5,29} For example, Millis et al⁵ examined neuropsychological test performance in a cohort of complicated mild to severe TBI patients at 1 and 5 years post-injury; they found that while most individuals (63%) showed no change in functioning or improved (22%), 15% of the sample declined on 2 or more tests of their 15 test battery. Himanen et al¹⁴ examined cognitive changes in a TBI cohort tested over a period of 30 years. They found a significant decrease in a global index of cognitive function in 56% of patients, controlling for aging-related decline, with improvement in 23% and no change in 21%. More recently, Sigurdardottir et al²⁹ examined 79 patients across multiple time points on memory and executive function tests, including 1 to 10 years following moderate-severe TBI (N=48 in this subset). In the 1 to 10 year window, 11% of patients declined on memory (but not executive functioning).

As a result of considerable methodological variations across the handful of studies that have been conducted at the individual level—with differences in test batteries, times post-injury, and predictors—the proportion of patients showing declines, the relevant risk factors, and the timing of declines remains uncertain. Moreover, the question whether neurodegeneration is predictive of cognitive decline has yet to be examined (but see Farbota et al²³ who found that performance on cognitive tests at 2 months post-injury was predictive of subsequent volume loss in several associated structures).

Our first objective was to look at patterns of change across time, both by patient and by task. In objective 1a, we were interested in replicating our prior study to provide more conclusive evidence of the proportion of decliners

across the 12 to 30+ month post-injury time window. We were also interested in whether there were variations in the number of decliners as a function of time post injury. Thus, in a non-overlapping sample to that used in our previous research, we examined change in cognitive function across 3 time windows: 2 to 5 months, 5 to 12 months, and 12 to 30+ months post-injury (as in Till et al¹⁶). We developed a framework for categorizing patients as either “declined,” “stable,” or “improved,” and compared the proportion of patients falling into these categories over each period. For the purposes of this study, we operationalized the categories in a very specific and narrow sense, as opposed to global or general functional decline, for example, decline was defined as worse performance on 2 or more (of 12) tests; see Methods section for detailed explanation. We predicted that the proportion of patients demonstrating decline from 12 to 30+ months post-injury would be comparable to that observed in Till et al,¹⁶ (ie, 27%) given the similarity in methods (ie, same clinical setting, same timelines, same approach to classification of decline) used with this non-overlapping sample. Since the period of most rapid recovery occurs in the first months of injury,¹¹ and Himanen et al¹⁴ found much greater incidence of decline compared to patients in other studies when they examined out to 30 years post-injury, we predicted there would be an increasing proportion of patients declining from the early to the later windows. In objective 1b, we explored whether any cognitive domains are more vulnerable to decline than others by profiling the patterns of change—decline, stability, and improvement—for each cognitive test in the battery.

The second objective was to comprehensively examine predictors of cognitive decline. We examined variables found to be predictive in prior studies of individual recovery trajectories, including age^{5,14} and out-patient therapy hours^{16,30} along with other cognitive reserve and injury-related variables known to influence TBI cognitive outcomes.³¹⁻³³ Given evidence of neurodegeneration in the chronic stages of TBI from our own research and that of others,²⁶ we extended previous research by examining whether reductions in brain volume would predict cognitive decline. In our previous study, we found that tests of verbal retrieval showed the most decline from 12 to 30+ months post-injury.¹⁶ Therefore, we predicted that hippocampal volume loss, measured from 5 to 12 months post-injury, would be predictive of subsequent cognitive decline from 12 to 30+ months post-injury.

Methods

Participants

The current sample comprised N=48 participants with moderate to severe TBI (defined as having a Glasgow Coma Scale (GCS) score of 13 or less and/or a length of

Table 1. Demographic and Clinical Characteristics of Till et al¹⁶ Versus Current Sample.

Demographic/clinical variable	Till et al ¹⁶ sample (n = 33)	Current study sample (n = 48)
Men (%)	76	73
Women (%)	24	27
Age at injury in years	35.4 ± 14.5	42.2 ± 16.4
Years of education	12.7 ± 2.7	14.7 ± 2.8
Estimated premorbid IQ ^a	97.3 ± 15.6	109.1 ± 11.4
Cause of TBI (%)		
Motor vehicle collision	61	54
Fall	27	38
Assault	9	4
Sports injury/other	3	4
GCS score	6.48 ± 3.3	5.9 ± 3.3
Length of PTA (classification) ^b	4.76 ± 0.72	4.85 ± 0.88
Inpatient Rehab length of stay (days)	38.1 ± 18.3	43.7 ± 18.0
Socioeconomic status (%) ^c		
1. Major business/professional	6.1	21.2
2. Medium business/minor professional, technical	51.5	54.5
3. Skilled craftsperson, clerical, sales worker	15.1	30.3
4. Machine operator, semiskilled worker	27.3	15.2
5. Unskilled laborer, menial service worker	0	21.2
Total therapy time/week (h) assessment 2	5.93 ± 4.8	8.52 ± 9.7
Total therapy time/week (h) assessment 3	5.18 ± 5.4	6.06 ± 7.4
Time post-injury (days) for assessment 1	54.03 ± 17.10	65.67 ± 26.25
Time post-injury (days) for assessment 2	147.08 ± 28.58	154.92 ± 31.52
Time post-injury (days) for assessment 3	382.74 ± 32.43	392.42 ± 61.36
Time post-injury (days) for assessment 4	1077.48 ± 342.29	908.43 ± 202.46

Abbreviations: PTA, post-traumatic amnesia; TBI, traumatic brain injury.

^aEstimate based on the Wechsler Test of Adult Reading IQ³⁵

^bClassification based on severity of injury on the basis of length of amnesia ranked from 1 (mild, <5 minutes) to 5 (extremely severe, >4 weeks)³⁶

^cBased on classification from Hollingshead Four Factor Score³⁷

post-traumatic amnesia of 1 hour or more) who were part of a larger, prospective, longitudinal study of recovery (the *Toronto Rehab TBI Recovery Study*³⁴) and had been referred to the in-patient Neurorehabilitation Program at the Toronto Rehabilitation Institute. Participants in the larger study underwent neuropsychological testing at 2, 5, and 12 months post-injury. As described in Till et al,¹⁶ the participants met the following inclusion criteria: age 17 years and older, positive computed tomography or magnetic resonance imaging (MRI) findings or evidence of a moderate to severe TBI, 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 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 alcohol or substance abuse at time of testing, or failed the test of symptom validity at any of the assessments. An additional inclusion criterion of the current study was that participants

had to be enrolled in the *Toronto Rehab TBI Recovery Study* after the enrollment window was closed for the Till et al study in order to create a *non-overlapping* sample for replication. At the time of this investigation, 69 participants were eligible for inclusion. Of these, 3 were deceased, 9 could not be reached, 8 declined to participate due to lack of interest, and 1 participant recently had a neuropsychological assessment in the community. The new sample therefore comprised 48 participants corresponding to 69.6% of the 69 eligible participants. The study sample and the eligible patients who did not participate in the study (“attrition group”) did not differ on any relevant demographic or injury variables, with 1 exception: the attrition group had a higher socioeconomic status (SES) that was approaching significance ($P=.08$) as compared to the study sample group.

Injury and demographic characteristics are presented in Table 1 for the Till et al¹⁶ sample (n=33) and the current study sample (n=48). The two samples were similar overall, but the current sample was marginally older, $t(79)=-1.942$, $P=.056$, and had more years of education, $t(78)=-3.112$, $P=.003$ and a higher pre-morbid IQ, $t(59)=-2.184$, $P=.033$. In addition, there was a significant difference between

samples in the mean time post-injury for assessments 1 ($t(79)=-2.714, P=.008$), 2 ($t(79)=-2.370, P=.021$), and 4 ($t(74)=2.412, P=.021$). There was no significant difference in the mean time post-injury for assessment 3. The mean time post-injury for the assessments in both studies were approximately 2 months, 5 months, 1 year, and 2.5 years post-injury (current study) and 3 years (previous study).

Design and Procedures

The parent study employed a longitudinal design with prospective neuropsychological assessments at approximately 2, 5, 12, and 30+ months post-injury. Assessments were completed by a trained psychometrist and supervised by a Clinical Neuropsychologist. All participants received a clinical neuropsychological feedback and written report, contributing to the high retention rate of this sample in the parent study (77.8%). Prior to recruitment, each participant had already undergone 1 to 2 days of assessment that included comprehensive neuropsychological and mood testing with a trained psychometrist at 3 time points: 2 months, 5 months, and 12 months post-injury. For the current study, all participants received an additional neuropsychological assessment. While our eligibility criteria stated participants must be at least 24+ months post-injury, in our sample, the 4th assessment for all participants occurred at least 30+ months post-injury.

Objective 1a: We examined the proportion of patients showing cognitive decline, stability and improvement at 3 time windows: 2 to 5, 5 to 12, and 12 to 30+ months post-injury. As in Till et al,¹⁶ we operationalized as a “decliner” a participant that declined on 2 or more neuropsychological tests using the RCI. “Improvers” were operationally defined as those who improved on 2 or more tests using the RCI (and did not decline on 2 or more of the remaining tests that comprised our cognitive battery). In the event that patients improved on 2+ cognitive domains, but also declined on 2+ others (4-8% of our patient sample), they were categorized as a “decliner.” Those patients not categorized as an improver or a decliner were classified as “stable.” Of note—Logical Memory I and Logical Memory II were not treated as separate tests, nor were the RAVLT total learning and delayed recall scores. Thus, if patients declined on both sub-tests for either Logical Memory or RAVLT, this was counted as a single test decline, so as to avoid overestimation of decline and provide a conservative estimate.

Objective 1b: For each of the 12 tasks in the battery, we examined the proportion of patients showing decline, stability, and improvement from 12 to 30+ months post-injury because the number of decliners was greatest at this time window. Here, we included all patients in the parent study, that is, the 33 patients from Till et al,¹⁶ and the 48 patients from the current study in order to increase analytic stability.

Objective 2: To examine predictors of decline, we again examined patients from 12 to 30+ months post-injury only, and we again collapsed patients from our previous and current study to increase power and analytic stability.

Outcomes

Neuropsychological Test Battery. Please see Till et al¹⁶ for a full description of the tests in the current study, which are identical to those of Till et al.¹⁶ In brief, the twelve neuropsychological tests encompassed the domains of manual motor speed and dexterity, attention and speed of processing, verbal learning and memory, visual-spatial ability, and executive function. The test battery comprised: Block Design and Digit Span (including Digit Span Forwards and Digit Span Backwards) from the Wechsler Adult Intelligence Scale—3rd edition (WAIS-III)³⁸; and Wechsler Abbreviated Scales of Intelligence (WAS)³⁹; Symbol Digit Modalities Test (SDMT, oral only)⁴⁰; Trail Making Test (TMT)—Parts A and B^{41,42}; Logical Memory I and II subtests (LM-I/II) from the Wechsler Memory Scale—3rd edition (WMS-III)⁴³; Rey Auditory Verbal Learning Test (RAVLT, total learning and delayed recall scores)⁴⁴; Controlled Oral Word Association Test (COWAT, phonemic fluency)⁴⁵; and Grooved Pegboard (dominant hand only).^{41,42}

Hippocampal Volume Acquisition and Processing. As part of the larger study, participants underwent MRI scanning after completing an MRI screening protocol. All MRIs were acquired on a General Electric (GE) Signa Echospeed 1.5 Tesla HD scanner (SIGNA EXCITE, GE Healthcare, Milwaukee WI), using an 8 channel head coil. Sequences included sagittal T1 (TR (repetition time)/TE (echo time)=300/13 ms), slice thickness=5 mm, space 2.5 mm, matrix 256 × 128 axial gradient recalled echo TR/TE=450/20, flip angle=20°, slice thickness=3 mm no gap, matrix 256 × 192 axial fluid attenuated-inversion-recovery TR/TE=9000/45 ms, TI (inversion time)=2200 ms, slice thickness=5 mm no gap, matrix 256 × 192 axial fast spin echo proton density/T2 TR/TE 5500/3090 ms, slice thickness=3 mm no gap, matrix 256 × 192. All above mentioned sequences were obtained with a 22 cm field of view. For complete image acquisition, processing and analysis protocol, please refer to Green et al.¹⁹

The hippocampi were manually outlined using Analyze TM 8.1 Brain Imaging Resource, Mayo Clinic, MN) by an experienced tracer from coronally orientated MR images in the anterior-posterior direction. Calculations of volumes were computed automatically by multiplying the number of voxels traced in each slice, by their depth (ie, slice thickness). The hippocampi were measured according to the method described by Watson et al^{46,47} (see Maller et al,⁴⁸ for a more detailed description of this procedure).

Total percent change in hippocampal volume from 5 months to 12 months post-injury was then computed for volumes of the total left (HPCLTOT) and total right (HPCRTOT) hippocampi taking into account baseline volumes. The formula for change in total right hippocampal volume is presented below.

$$\text{HPCRTOT \% change} = \frac{\text{HPCRTOT at 12 months} - \text{HPCRTOT at 5 months}}{\frac{\text{HPCRTOT at 12 months} + \text{HPCRTOT at 5 months}}{2}} \times 100$$

Statistical Analyses

Objective 1. Following the methods of Till et al,¹⁶ we obtained test-retest reliability coefficients for the RCI calculations from Levine et al⁴⁹ for TMT (Parts A and B⁴¹); Digit Span tests,³⁸ SDMT,⁴⁰ COWAT,⁴⁵ and Grooved Pegboard.⁴¹ Reliability for RAVLT (Schmidt⁴⁴) was taken from Geffen et al⁵⁰; the WAIS-III³⁸ and WMS-III⁴³ manuals were used for the Block Design and Logical Memory subtests. Reliability coefficients ranged from 0.67 (Grooved Pegboard) to 0.82 (Block Design).

To conduct these analyses, normed scores for neuropsychological data were used to rule out potential confounds such as age, and to allow for direct comparison of groups.

The RCI allows for an understanding of change in individual subjects that is considered clinically meaningful, when sources of measurement error (including test-retest practice effects) are taken into consideration.²⁸

$RCI = (x_2 - x_1) / S_{diff}$, where x_1 represents the subject's baseline score, x_2 represents the subject's follow-up, and S_{diff} is the standard error of that difference. The S_{diff} was computed from the standard error of measurement (S_e), which is a function of the initial standard deviation of the measure and its reliability according to the following formula: $S_{diff} = \sqrt{[2(S_e)^2]}$, 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% confidence interval for the predicted score (ie, $\pm 1.64 \times S_{diff}$).

Objective 2. In preliminary testing of the models the following predictor variables were included: demographic/cognitive reserve variables including, sex, age, years of education, SES,³⁷ and estimated pre-morbid IQ on the Wechsler Test of Adult Reading^{35,51}; severity of injury variables including, GCS,⁵² and length of post-traumatic amnesia (LPTA⁵³); percent-change in left and right hippocampal volumes from 5 to 12 months post-injury (ie, hippocampal atrophy),¹⁹ mean therapy hours at 5 and 12 months post-injury; and self-reported symptoms of depression from the Beck Depression Inventory,⁵⁴ and anxiety from the Beck Anxiety Inventory.⁵⁵ Only progressive hippocampal atrophy (left and right) 5 to 12 months post-injury was found to be

significantly correlated with decliner status, and LPTA showed a trend.

Logistic regression analyses were conducted for Objective 2 in which we regressed decliner status (ie, decline vs no-decline) from 12 to 30+ months post-injury against progressive hippocampal atrophy (left and right) 5 to 12 months post-injury. The model controlled for LPTA because of the possibility of it being a confounding variable in the relationship between decliner status and atrophy. In addition, we regressed on left and right hippocampal atrophy from 5 to 12 months post-injury (controlling for LPTA) and we regressed on left hippocampal atrophy from 5 to 12 months post-injury (controlling for LPTA and *right* hippocampal atrophy from 5 to 12 months post-injury (and ipso facto vice versa).

IBM SPSS statistical package (Version 25, 2019, were used for all *t*-test comparisons and R⁵⁶ was used for the Objective 2 logistic regression analyses.

Results

Objective 1. Pattern of Cognitive Decline Across Time by Patient and by Neurocognitive Task

Figure 1 presents the incidence at each time window of those who declined, improved or remained stable. Grey lines represent movement of participants to different categories across time. At each time window, the majority of patients either remain stable or improve. Nonetheless, overall, 58.3% patients were classified as having declined in at least 1 time window. The proportion of patients classified as a decliner during 1 window-only was 29.2%. The proportion of patients classified as a decliner at 2 time windows was 12.5% (N=5), with 4 of these 5 patients showing decline from 2 to 5 months and from 12 to 30+ months post-injury rather than at contiguous time windows. Only 1 patient showed decline at all 3 time windows.

Figure 1 can also be used to directly compare the findings of the replication sample to that of the original sample studied by Till et al.¹⁶ The proportion of decliners in the replication sample between 5 and 12 months post-injury was 27.1%, which is nearly identical to that of the Till et al¹⁶ sample, which was 27.3% over the same time period. The figure also indicates a greater proportion of patients showing declines the further post-injury, which was consistent with our hypothesis. From 2 to 5 months post-injury, 12.5% show decline; from 5 to 12 months, 17% showed decline.

We collapsed the data for patients classified as decliners from both the Till et al¹⁶ sample and the current sample to look at the pattern of decline across neuropsychological tests. The results are illustrated in Figure 2. Delayed recall on the RAVLT test (RAVLT-dr) and on Logical memory (LMII), and verbal retrieval (COWAT) had the greatest

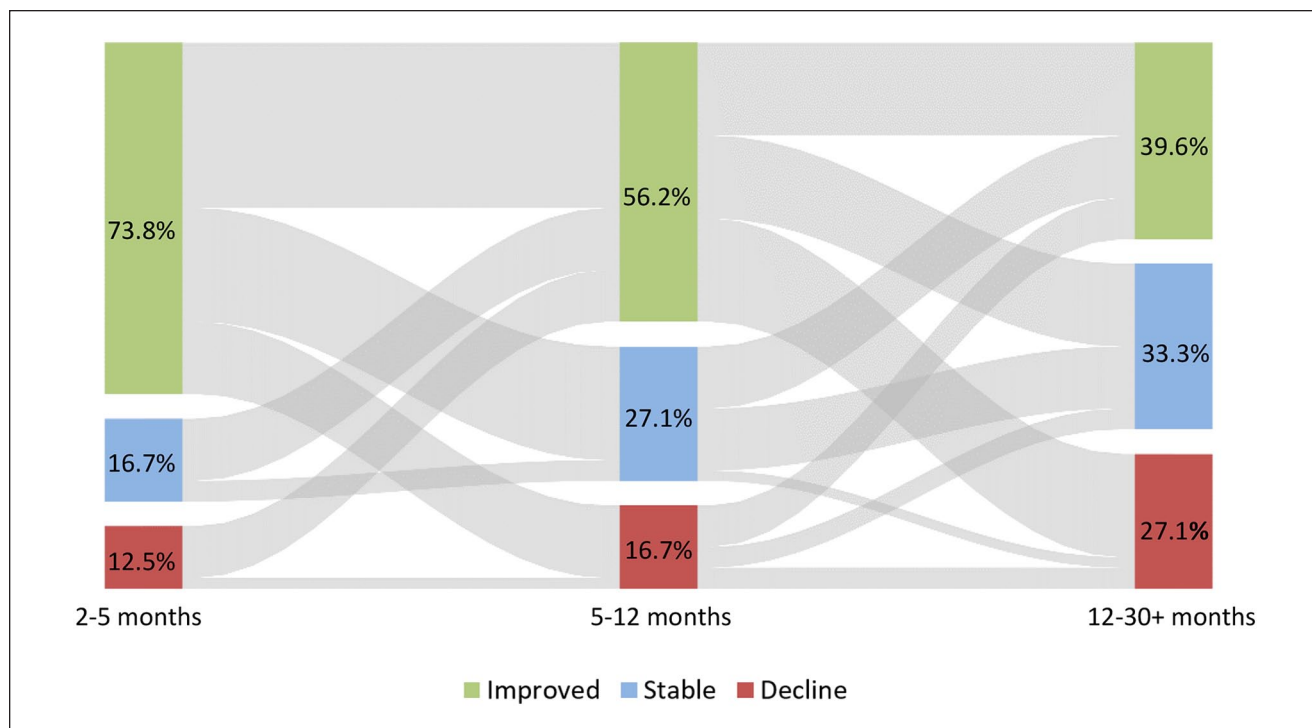


Figure 1. Clinically significant decline, improvement and stability (arranged bottom to top, respectively) using RCI from 2 to 5, 5 to 12, and 12 to 30+ months post-injury time windows.

Abbreviation: RCI, Reliable Change Index.

As described in the Methods, a “declined” classification in red color was assigned to those with decline on the RCI index on ≥ 2 cognitive tests; “improved” classification in green color was assigned to those with improvement on ≥ 2 cognitive tests (and declines on < 2 cognitive tests). All others were classified as “stable,” in blue color. Grey lines represent movement of participants to categories across time points. There are $n = 48$ patients at each time window.

number of decliners, with greater than a third of decliners declining on these measures.

Objective 2. Predictors of Cognitive Decline

In our regression models only left hippocampal atrophy from 5 to 12 months (controlling for LPTA) was predictive of decliner status from 12 to 30+ months post-injury (regardless of controlling for right hippocampal atrophy from 5 to 12 months) $z = -2.371$, $P = .018$ (see Tables 2 and 3).

Discussion

The first aim of the current study was to provide a more granular understanding of cognitive recovery and decline from 2 months to 30+ months post-injury, both at the level of the patient and the task. In measuring performance at 12 and 30+ months post-injury, we found that 27.1% of our sample declined, which replicated our previous study (Till et al¹⁶) that had found a decline rate of 27.3% across nearly the identical timeliness. Given the consistent methodology across the 2 studies, the findings underscore that more than a quarter of patients are at risk of cognitive decline in the

first year after moderate-severe TBI. Looking across all 3 time windows of the study, there was an increasing proportion of decliners the more remote patients were from injury (ie, from 12.5% in the first window to 27.1% in the third). To our knowledge, no previous study has examined decline across more than 1 time window within the same cohort. Although the majority of the patients are remaining stable or improving, the findings nonetheless point towards a cognitive picture that worsens as patients move further from injury. Generating hypotheses for future research, we looked at the specific tests on which patients showed the largest number of declines. We found that over a third showed declines on measures of verbal retrieval (ie, RAVLT-dr; Logical Memory-II; COWAT). This finding also guided the second objective of the study, which was to examine “atrophy” (ie, progressive volume loss) of brain structures as a predictor of cognitive decline. In our previous research, we have examined atrophy of the whole brain, grey and white matter structures, and found ubiquitous declines.³³ We therefore assessed whether progressive volume losses in the hippocampi might explain the progressive cognitive declines observed here, and we found that, indeed, left hippocampal volume loss was a predictor of decliner

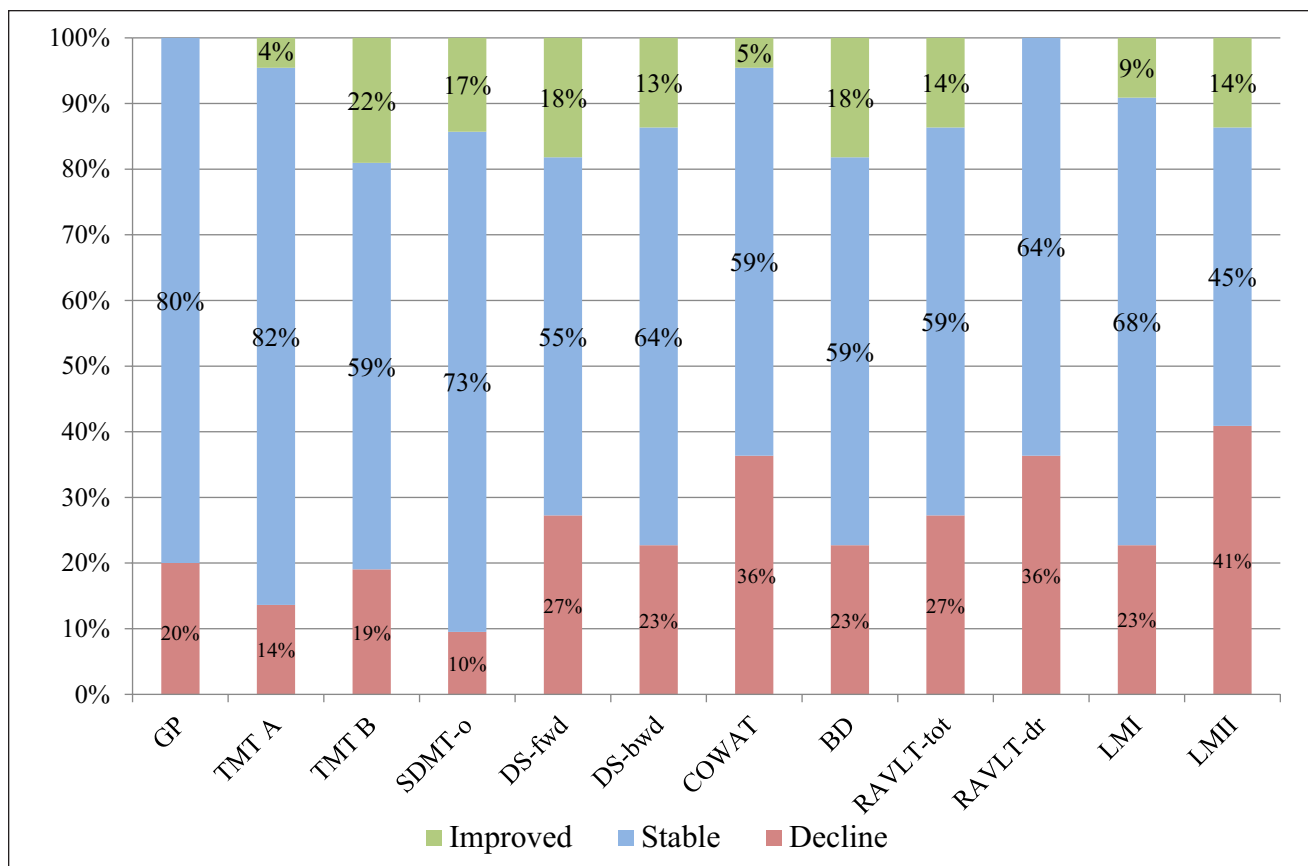


Figure 2. Decline, stability, and improvement (arranged bottom to top, respectively) by neuropsychological task. Abbreviations: SDMT, symbol digit modalities test; DS Fwd, digit span forward; DS bwd, digit span backward; VF, verbal fluency; RAVLT, rey auditory verbal learning test; LM, logical memory. Data are presented for all patients classified as *decliners* from 12 to 30+ months post-injury collapsed across the Till et al¹⁶ sample and the current study sample (n = 22).

Table 2. Logistic Regression Results for Cognitive Reserve Variables, Therapy Hours, and LPTA as Predictors of Decliner Status 12 to 24 months Post-Injury.

Age at injury	0.025 (0.019)
Years of education	0.116 (0.121)
Estimated pre-morbid IQ (WTAR)	-0.008 (0.021)
Total therapy hours (at 5 months post-injury)	-0.079 (0.058)
LPTA	-0.502 (0.385)

Standard errors are reported in parentheses. Abbreviations: WTAR, Wechsler Test of Adult Reading; LPTA, length of post-traumatic amnesia.

status. The current results highlight the need to continue research and clinical care well into the chronic stages of injury, and to better understand what is contributing to declining function.

Our current findings are compatible with previous research. When comparing our current findings with our own past findings (Till et al¹⁶), we very closely replicated: with 27.1% (current) versus 27.3% (previous). Patients in

Table 3. Logistic Regression Results HPCLTOT and HPCRTOT Decline From 5 to 12 Months Post-Injury as Predictors of Decliner Status 12 to 24 Months Post-Injury Controlling for Age and Estimated Pre-Morbid IQ.

Left HPC % change 5 to 12 month post-injury	-0.480* (0.203)
Right HPC % change 5 to 12 month post-injury	0.311 (0.197)
Age at injury	0.005 (0.025)
Estimated pre-morbid IQ (WTAR)	-0.013 (0.022)

Standard errors are reported in parentheses. Significance code: *0.05. Estimated Pre-morbid IQ is based on the WTAR score collected at 5 months post-injury. Abbreviations: HPC, hippocampus; WTAR, Wechsler Test of Adult Reading.

both studies were drawn from the same large, urban setting in Canada’s largest TBI rehabilitation setting. Thus, the findings offer some degree of confidence in the rate of cognitive decline during this window, at least in Canadian samples. With regard to the increasing number of patients declining the further post-injury, no study has previously compared time windows. However, taking all prior studies

together, our findings converge somewhat with the literature. For example, Himanen et al¹⁴ studied patients more than 30 years post-injury and found the greatest rate of decline (ie, 56%) of all studies; Ruff et al,¹⁵ studied decline in verbal memory earliest post-injury and found the least amount of decline of 20%. However a more recent study examining patients up to 10 years post-TBI found significant declines only in memory, when examining several cognitive domains, and only in 11% of patients.²⁹

The overall pattern observed in the current study raises the question whether it reflects the product of multiple beneficial and deleterious mechanisms that operate concurrently after moderate-severe TBI, but with slightly differing timelines. Specifically, while TBI results in a period of spontaneous cognitive recovery, moderate-severe TBI also appears to set in motion acute and long-term processes that are harmful to the brain, including necrosis, apoptosis, diaschisis, protracted neuroinflammation, damage to microtubular transport, and possibly overuse.^{57,58} The pattern of increasing declines across time may reflect spontaneous recovery reaching coming to an end, as more deleterious and neurodegenerative processes are commencing or continuing. In the absence of spontaneous recovery, the deleterious processes may now play a more predominant role in clinical presentation. Consistent with this pattern, in a group longitudinal study examining recovery of executive function, we observed evidence of early recovery (on a measure of intra-individual variability) followed by later decline.¹⁷

When we explored the tests that were most sensitive to decline (focusing only on decline from 12 to 30+ months post-injury, and collapsing the data from the current study with those from Till et al¹⁶) the 3 tests showing the maximum number of decliners were tests of verbal retrieval, delayed recall and verbal fluency. Those tasks with the least number of patients showing decline were tests of attention and speed of processing, namely Symbol Digit, and Trails A and Trails B, 2 of which are also considered measures of executive function (ie, Symbol Digit and Trails B). Our findings add to a growing evidence base that long-term TBI outcomes are not uniform across different cognitive domains, and that verbal retrieval may be particularly susceptible to persisting impairment and perhaps decline.¹¹ For example, a longitudinal study by Marsh (2018)⁵⁹ that found that by 5 years post-injury, while 80% of patients were unimpaired on measures of general intelligence, simple attention and visual perception, 60% demonstrated impairments specific to verbal memory, and 28% demonstrated impairment in verbal fluency. Sigurdardottir et al²⁹ found *declines* in memory, but not other cognitive domains in their recent long-term follow up study. As well, a meta-analysis that looked at over at over 70 studies of episodic memory changes following moderate to severe TBI implicated *verbal* memory as being more sensitive to ongoing injury effects.⁶⁰

Our second objective was to examine predictors of decline. Here, we again collapsed the current sample with those from Till et al¹⁶ in order to increase power and analytic stability, and we focused on decliner status from 12 to 30+ months post-injury where we had observed the largest number of decliners. In our first model we examined cognitive reserve variables (age, years of education, estimated premorbid IQ), total therapy hours at 5 months post-injury, and LPTA as a measure of injury severity. None of these variables was predictive of decliner status from 12 to 30+ months post-injury. Notably, therapy hours at 5 months—for which the decliner group had significantly less therapy hours than the non-decliner group in our previous study—was not a significant predictor of cognitive decline.

Given the growing evidence of degeneration in the chronic stages of moderate-severe TBI,^{9,19,22,24-27} we were interested in the possibility that the cognitive declines we observed may be attributable to neural degeneration. Therefore, we examined whether progressive atrophy of the hippocampi—due to the predominance of verbal retrieval measures on which patients showed decline—might be predictive. We found left hippocampal volume loss was a significant predictor of decline. More specifically, when each of the hippocampi were examined while controlling for influences of the contralateral hippocampus, only atrophy of the left hippocampus was significant. This is the first study to our knowledge examining neural, and in particular neurodegenerative predictors of cognitive decline at the individual subject level.

The above findings support the idea that moderate-severe TBI must be considered not only a chronic disorder, but also a progressive one.¹⁹ They also underscore that multiple mechanisms underlie behavioral change during the first years of injury, those that are beneficial to recovery (eg, functional reorganization, restitution, unmasking, resolution of diaschisis⁶¹⁻⁶⁴ and those that may be deleterious (eg, delayed apoptosis and neuroinflammation)^{57,58}—as both recovery and decline are observed within and between patients at each time point. Additional neurobiological mechanisms may also be at play long-term, such as chronic neuroinflammation, axonal injury, and tauopathy.^{19,65-68} TBI disrupts the glymphatic system, leading to impaired waste clearance and toxic substance buildup.⁶⁹ Excitotoxicity and blood-brain barrier dysfunction further contribute to neural damage.⁷⁰ Negative neuroplasticity may result in maladaptive changes, negatively impacting cognitive function.^{71,72} These interrelated mechanisms highlight the complex nature of TBI-related cognitive decline, emphasizing the need for further research to develop a greater understanding of these mechanisms, and how they may influence one another, in order to better predict outcomes and mitigate decline.

The current study shows that hippocampal volume loss predicted subsequent cognitive decline. Further research is needed to understand how to protect the brain from such declines. The current results highlight the need for ongoing

clinical management of patients into the chronic stages of injury, and to deliver clinical strategies that promote brain health, such as intensive physical and cognitive exercise, and mindfulness meditation.⁷³⁻⁷⁶

A limitation of the current study, one that would affect the generalizability and reliability of the findings, is the relatively small sample size, particularly given the heterogeneity of the moderate-severe TBI population. Mitigating against this concern, however, is the consistency in prevalence of decliners across the Till et al,¹⁶ and the current study. Another concern regarding the generalizability of the findings is the difference between the Canadian healthcare system for brain injury and that of other contexts. Within the Canadian healthcare system, the large majority of patients are receiving some form of rehabilitation therapy at 5 months post-injury. One might argue, therefore, that our findings underestimate the extent of decline occurring in contexts where patients receive less rehab at 5 months post-injury. However, we did not find evidence of a relationship between therapy hours at 5 months post-injury and decline at 12 to 24 months post-injury. This finding suggests that early therapy might not be protective of later decline, though, our findings are quite limited in the ability to answer this question in that the content of therapy varied considerably across patients. Lastly, absence of a healthy control group is another limitation of our study. In the absence of controls, alternative explanations for the declines include: (1) new onset of a neurological disorder (eg, Alzheimer's disease); (2) aging-related declines; (3) normal test-retest variability in performance.⁴⁹ Onset of new neurological disorder was an exclusion criterion, although undiagnosed dementia in a participant cannot be conclusively ruled out. With regard to aging-related decline, the magnitude of decline observed across the 7-month time window (ie, 5-12 months post-injury) and approximately 18 month time window (ie, 12-30 months post-injury) is not compatible with our understanding of the typical rate of cognitive decline in adults of this age-range.⁷⁷ With regard to the third alternative explanation, the use of RCI is intended to mitigate against measurement-related test-retest variability. However, it is important to note that recent studies have shown transient declines in healthy adult cognitive performance. Therefore, it is possible that the prevalence of decline observed in these studies is an overestimate.

Conclusions

The current results, replicating past results, suggest that cognitive decline in the chronic stages of injury (ie, 12-30+ months post-injury) affects at least a quarter of patients, and with an increasing proportion of patients showing decline across time windows (ie, 2-5 months, 5-12 months, and 12-30+ months post-injury)—though for the most part, it is not the same patients declining at each window. Tests of verbal retrieval appeared to be most sensitive to decline,

and our findings suggest that hippocampal volume loss—within the left hippocampus in particular—may explain this decline. No other predictors of decline, offered clear prognostic value in our sample. Further research is needed to better understand who is at risk of decline, and critically, to determine how to prevent decline.


Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors report no conflicts of interest and assert that all procedures contributing to this work comply with the ethical standards of the University Health Network Research Ethics Board on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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ORCID iDs

Robin E. A. Green  <https://orcid.org/0000-0001-9451-3963>

Julia Rybkina  <https://orcid.org/0000-0001-5996-3512>

Georges A. Monette  <https://orcid.org/0000-0003-0076-5532>

References

1. Benedictus M, Spikman JM, van der Naalt J. Cognitive and behavioral impairment in traumatic brain injury related to outcome and return to work. *Arch Phys Med Rehabil*. 2010;91(9):1436-1441. doi:10.1016/j.apmr.2010.06.019
2. Colantonio A, Ratcliff G, Chase S, Kelsey S, Escobar L, Vernich L. Long term outcomes after moderate to severe traumatic brain injury. *Disabil Rehabil*. 2004;26(5):253-261.
3. Forslund MV, Perrin PB, Sigurdardottir S, et al. Health-related quality of life trajectories across 10 years after moderate to severe traumatic brain injury in Norway. *J Clin Med*. 2021;10(1):157.
4. Stenberg M, Godbolt AK, Nygren De Boussard C, Levi R, Stålnacke B-M. Cognitive impairment after severe traumatic brain injury, clinical course and impact on outcome: a Swedish-icelandic study. *Behav Neurol*. 2015;2015:680308. doi:10.1155/2015/680308
5. Millis SR, Rosenthal M, Novack TA, et al. Long-term neuropsychological outcome after traumatic brain injury. *J Head Trauma Rehabil*. 2001;16(4):343-355.
6. Vincent AS, Roebuck-Spencer TM, Cernich A. Cognitive changes and dementia risk after traumatic brain injury: implications for aging military personnel. *Alzheimers Dement*. 2014;10(3):S174-S187. doi:10.1016/j.jalz.2014.04.006
7. Fleminger S, Ponsford J. Long term outcome after traumatic brain injury. *BMJ*. 2005;331(7530):1419-1420. doi:10.1136/bmj.331.7530.1419

8. Zador Z, Sperrin M, King AT. Predictors of outcome in traumatic brain injury: new insight using receiver operating curve indices and Bayesian network analysis. *PLoS One*. 2016;11(7):e0158762. doi:10.1371/journal.pone.0158762
9. Ng K, Mikulis DJ, Glazer J, et al. Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch Phys Med Rehabil*. 2008;89(12):S35-S44. doi:10.1016/j.apmr.2008.07.006
10. Basso A. Spontaneous recovery and language rehabilitation. In: Seron X, Deloche G, eds. *Cognitive Approaches in Neuropsychological Rehabilitation*. Lawrence Erlbaum; 1989:17-37.
11. Christensen BK, Colella B, Inness E, et al. Recovery of cognitive function after traumatic brain injury: a multilevel modeling analysis of Canadian outcomes. *Arch Phys Med Rehabil*. 2008;89(12):S3-S15.
12. Fame A, Buxbaum LJ, Ferraro M, Frassinetti F, Whyte J, Veramonti T. Patterns of spontaneous recovery of neglect and associated disorders in acute brain damaged patients. *J Neurosurg Psychiatry* 2004;75:1401-1410.
13. Heinemann AW, Hamilton B, Linacre JM, Wright BD, Granger C. Functional status and therapeutic intensity during inpatient rehabilitation. *Am J Phys Med Rehabil*. 1995;74(4):315-326.
14. Himanen L, Portin R, Isoniemi H, Helenius H, Kurki T, Tenovuo O. Longitudinal cognitive changes in traumatic brain injury: a 30-year follow-up study. *Neurology*. 2006;66(2):187-192.
15. Ruff RM, Young D, Gautille T, et al. Verbal learning deficits following severe head injury: heterogeneity in recovery over 1 year. *J Neurosurg*. 1991;75(5S):S50-S58.
16. Till C, Colella B, Verwegen J, Green RE. Postrecovery cognitive decline in adults with traumatic brain injury. *Arch Phys Med Rehabil*. 2008;89(12):S25-S34.
17. Vasquez BP, Tomaszczyk JC, Sharma B, Colella B, Green REA. Longitudinal recovery of executive control functions after moderate-severe traumatic brain injury: examining trajectories of variability and ex-Gaussian parameters. *Neurorehabil Neural Repair*. 2018;32(3):191-199. doi:10.1177/1545968318760727
18. Changoor A, Colella B, Monette G, Green R. Moderate-Severe TBI as a progressive disorder: cognitive declines in the chronic stages of injury (5035). *Neurology*. 2020; 94(15):5035.
19. Green RE, Colella B, Maller JJ, Bayley M, Glazer J, Mikulis DJ. Scale and pattern of atrophy in the chronic stages of moderate-severe TBI. *Front Hum Neurosci*. 2014;8:67. doi:10.3389/fnhum.2014.00067
20. Terpstra AR, Girard TA, Colella B, Green REA. Higher anxiety symptoms predict progressive hippocampal atrophy in the chronic stages of moderate to severe traumatic brain injury. *Neurorehabil Neural Repair*. 2017;31:1063-1071.
21. Bendlin BB, Ries ML, Lazar M, et al. Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *NeuroImage*. 2008;42(2):503-514. doi:10.1016/j.neuroimage.2008.04.254
22. Bigler ED. Traumatic brain injury, neuroimaging, and neurodegeneration. *Front Hum Neurosci*. 2013;7:395. doi:10.3389/fnhum.2013.00395
23. Farbota KD, Bendlin BB, Alexander AL, Rowley HA, Dempsey RJ, Johnson SC. Longitudinal diffusion tensor imaging and neuropsychological correlates in traumatic brain injury patients. *Front Hum Neurosci*. 2012;6:160. doi:10.3389/fnhum.2012.00160
24. Sidaros A, Skimminge A, Liptrot MG, et al. Long-term global and regional brain volume changes following severe traumatic brain injury: a longitudinal study with clinical correlates. *NeuroImage*. 2009;44(1):1-8. doi:10.1016/j.neuroimage.2008.08.030
25. Trivedi MA, Ward MA, Hess TM, et al. Longitudinal changes in global brain volume between 79 and 409 days after traumatic brain injury: relationship with duration of coma. *J Neurotrauma*. 2007;24(5):766-771.
26. Belchev Z, Gilboa A, Binns M, et al. Progressive neurodegeneration across chronic stages of severe traumatic brain injury. *J Head Trauma Rehabil*. 2022;37:E144-E156. doi:10.1097/htr.0000000000000696
27. Cole JH, Jolly A, de Simoni S, et al. Spatial patterns of progressive brain volume loss after moderate-severe traumatic brain injury. *Brain*. 2018;141:822-836. doi:10.1093/brain/awx354
28. Jacobson T. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. 1991;59(1):12-9.
29. Sigurdardottir S, Andelic N, Røe C, Schanke AK. Trajectory of 10-year neurocognitive functioning after moderate-severe traumatic brain injury: early associations and clinical application. *J Int Neuropsychol Soc*. 2020;26(7):654-667. doi:10.1017/s1355617720000193
30. Boman L. Cognitive training in home environment. *Brain Injury*. 2004;18(10):985-995.
31. Stromberg KA, Agyemang AA, Graham KM, et al. Using decision tree methodology to predict employment after moderate to severe traumatic brain injury. *J Head Trauma Rehabil*. 2019;34(3):E64-E74. doi:10.1097/htr.0000000000000438
32. Walker WC, Stromberg KA, Marwitz JH, et al. Predicting long-term global outcome after traumatic brain injury: development of a practical prognostic tool using the traumatic brain injury model systems national database. *J Neurotrauma*. 2018;35(14):1587-1595. doi:10.1089/neu.2017.5359
33. West SL. Substance use among persons with traumatic brain injury: a review. *NeuroRehabilitation*. 2011;29(1):1-8. doi:10.3233/nre-2011-0671
34. Green RE, Colella B, Christensen B, et al. Examining moderators of cognitive recovery trajectories after moderate to severe traumatic brain injury. *Arch Phys Med Rehabil*. 2008;89(12):S16-S24.
35. Wechsler D. *Wechsler Test of Adult Reading (WTAR)*. The Psychological Corporation; 2001.
36. Hannay HJ HD, Loring DW, Fischer JS, Lezak MD. Neuropathology for neuropsychologists. In: Lezak MD HD, Loring DW, eds. *Neuropsychol Assessment* Oxford University Press; 2004:160.
37. Hollingshead A, Redlich F. *Social Class and Mental Illness: A Community Study*. John Wiley; 1958.
38. Wechsler D. *Wechsler Adult Intelligence Scale - 3rd Edition (WAIS-III)*. The Psychological Corporation; 1997.
39. Wechsler D. *Wechsler Abbreviated Scale of Intelligence (WASI)*. The Psychological Corporation; 1999.

40. Smith A. *The symbol digit modalities test (SDMT) manual*. Western Publication Services; 1982.
41. Heaton RK, Grant I, Matthews CG. *Comprehensive norms for an expanded Halstead-Reitan Battery*. Psychological Assessment Resources; 1992.
42. Lezak MD. *Neuropsychological Assessment*. 3rd ed. Oxford University Press; 1995.
43. Wechsler D. *Wechsler Memory Scale®—Third Edition (WMS®—III)*. Psychological Corporation; 1997.
44. Schmidt M. *Rey Auditory and Verbal Learning Test: A Handbook*. Western Psychological Services; 1996.
45. Benton AL, Hamsher K. *Multilingual Aphasia Examination*. Neurology. University of Iowa Hospitals and Clinics; 1983.
46. Watson C, Andermann F, Gloor P, et al. Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. *Neurology*. 1992;42(9):1743-1743.
47. Watson C, Jack CR, Cendes F. Volumetric magnetic resonance imaging: clinical applications and contributions to the understanding of temporal lobe epilepsy. *Arch Neurol*. 1997;54(12):1521-1531.
48. Maller JJ, Daskalakis ZJ, Fitzgerald PB. Hippocampal volumetrics in depression: the importance of the posterior tail. *Hippocampus*. 2007;17(11):1023-1027.
49. Levine AJ, Miller EN, Becker JT, Selnes OA, Cohen BA. Normative data for determining significance of test-retest differences on eight common neuropsychological instruments. *Clin Neuropsychol*. 2004;18(3):373-384. doi:10.1080/1385404049052420
50. Geffen GM, Butterworth P, Geffen LB. Test-retest reliability of a new form of the auditory verbal learning test (AVLT). *Arch Clin Neuropsychol*. 1994;9(4):303-316.
51. Green RE, Melo B, Christensen B, Ngo LA, Monette G, Bradbury C. Measuring premorbid IQ in traumatic brain injury: an examination of the validity of the Wechsler Test of Adult Reading (WTAR). *J Clin Exp Neuropsychol*. 2008;30(2):163-172.
52. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2(7872):81-84.
53. Russell WR, Smith A. Post-traumatic amnesia in closed head injury. *Arch Neurol*. 1961;5:4-17. doi:10.1001/archneur.1961.00450130006002
54. Beck AT. *Beck Depression Inventory*. Springer; 1987.
55. Beck AT, Steer RA. *Beck Anxiety Inventory*. Springer; 1993.
56. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2022.
57. Akamatsu Y, Hanafy KA. Cell death and recovery in traumatic brain injury. *Neurotherapeutics*. 2020;17(2):446-456. doi:10.1007/s13311-020-00840-7
58. Schimmel SJ, Acosta S, Lozano D. Neuroinflammation in traumatic brain injury: a chronic response to an acute injury. *Brain Circ*. 2017;3(3):135-142. doi:10.4103/bc.bc_18_17
59. Marsh NV. Cognitive functioning following traumatic brain injury: the first 5 years. *NeuroRehabil*. 2018;43:377-386.
60. Vakil E, Greenstein Y, Weiss I, Shtein S. The effects of moderate-to-severe traumatic brain injury on episodic memory: a meta-analysis. *Neuropsychol Rev*. 2019;29(3):270-287. doi:10.1007/s11065-019-09413-8
61. Katušić A. Early brain injury and plasticity: reorganization and functional recovery. *Translat Neurosci*. 2011;2(1):33-42. doi:10.2478/s13380-011-0006-5
62. Nudo RJ. Recovery after brain injury: mechanisms and principles. *Front Hum Neurosci*. 2013;7:887. doi:10.3389/fnhum.2013.00887
63. Su YS, Veeravagu A, Grant G. Neuroplasticity after traumatic brain injury. In Laskowitz D, Grant G, eds. *Translational Research in Traumatic Brain Injury*. CRC Press/Taylor and Francis Group; 2016. <https://www.ncbi.nlm.nih.gov/books/NBK326735/>
64. Feeney DM. Pharmacologic modulation of recovery after brain injury: a reconsideration of diaschisis. *J Neurol Rehabil*. 1991;5(1-2):113-128. doi:10.1177/136140969100500111
65. Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain*. 2013;136(1):28-42.
66. Smith C, Gentleman SM, Leclercq PD, et al. The neuroinflammatory response in humans after traumatic brain injury. *Neuropathol Appl Neurobiol*. 2013;39(6):654-666.
67. Gorgoraptis N, Li LM, Whittington A, et al. In vivo detection of cerebral tau pathology in long-term survivors of traumatic brain injury. *Sci Transl Med*. 2019;11(508):eaaw1993.
68. Johnson VE, Stewart W, Smith DH. Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans. *Brain Pathol*. 2012;22(2):142-149.
69. Ferrara M, Bertozzi G, Volonnino G, et al. Glymphatic system a window on TBI pathophysiology: a systematic review. *Int J Mol Sci*. 2022;23(16):9138.
70. Baracaldo-Santamaría D, Ariza-Salamanca DF, Corrales-Hernández MG, Pachón-Londoño MJ, Hernandez-Duarte I, Calderon-Ospina C-A. Revisiting excitotoxicity in traumatic brain injury: from bench to bedside. *Pharmaceutics*. 2022;14(1):152.
71. Evans JJ, Bateman A, Turner G, Green R. Research digest. *Neuropsychol Rehabil*. 2008;18(3):372-384. doi:10.1080/09602010801909153
72. Miller LS, Colella B, Mikulis D, Maller J, Green RE. Environmental enrichment may protect against hippocampal atrophy in the chronic stages of traumatic brain injury. *Front Hum Neurosci*. 2013;7:506. doi:10.3389/fnhum.2013.00506
73. Archer T, Svensson K, Alricsson M. Physical exercise ameliorates deficits induced by traumatic brain injury. *Acta Neurol Scand*. 2012;125(5):293-302. doi:10.1111/j.1600-0404.2011.01638.x
74. Bédard M, Felteau M, Mazmanian D, et al. Pilot evaluation of a mindfulness-based intervention to improve quality of life among individuals who sustained traumatic brain injuries. *Disabil Rehabil*. 2003;25(13):722-731. doi:10.1080/0963828031000090489
75. Alwis DS, Rajan R. Environmental enrichment and the sensory brain: the role of enrichment in remediating brain injury. *Front Syst Neurosci*. 2014;8:156. doi:10.3389/fnsys.2014.00156
76. Frasca D, Tomaszczyk J, McFadyen B, Green R. Traumatic brain injury and post-acute decline: what role does environmental enrichment play? A scoping review. *Front Hum Neurosci*. 2013;7:31. doi:10.3389/fnhum.2013.00031
77. Salthouse TA. When does age-related cognitive decline begin? *Neurobiol Aging*. 2009;30(4):507-514.