ORIGINAL ARTICLE

Recovery of Cognitive Function After Traumatic Brain Injury: A Multilevel Modeling Analysis of Canadian Outcomes

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Objective: To ascertain patterns of cognitive recovery during the first year after traumatic brain injury (TBI). Specifically, differential recovery across cognitive domains was investigated.

Design: Prospective, longitudinal, naturalistic, 1-year follow-up study.

Setting: Large, urban inpatient neurorehabilitation program.

Participants: Patients (N=75) with moderate to severe TBI.

Interventions: Not applicable.

Main Outcome Measures: Patients with TBI were followed over the course of 1 year, during which participants' neuropsychological status was repeatedly evaluated at 3 time points (2, 5, and 12 months postinjury).

Results: Multilevel modeling results were consistent with previous research, demonstrating that recovery in the first year postinjury is asymptotic in nature, with more accelerated recovery occurring during the first 5 to 6 months. Importantly, results also suggest that recovery is not uniform across cognitive domains. From 2 to 5 months postinjury, steeper recovery curves were revealed for indices of memory, speeded executive function, verbal abstraction, and manual dexterity relative to untimed tests of executive function and word knowledge. Recovery trajectories did not significantly vary as a function of cognitive domain over the course of the last 5 to 12 months.

Conclusions: These results are the first to explore trajectories of recovery directly as a function of multiple cognitive domains. They are expected to have implications for rehabilitative efforts as well as our understanding of the architecture of natural recovery after TBI.

Key Words: Brain injuries; Cognition; Longitudinal studies; Neuropsychology; Rehabilitation.

AFTER MODERATE TO SEVERE TBI, patients experience deficits across a range of cognitive functions. Commonly, impairments occur in attention and speed of processing, psychomotor skills, learning and memory, verbal and visuospatial skills, fluid intellectual functioning, and a range of executive functions[1,2] While it is well accepted that some degree of recovery occurs across all of these cognitive domains,[3,4] relatively little is known about the intradomain consistency and temporal characteristics of this recovery.[1,5] For example, do memory functions recover at the same rate as psychomotor speed? Does recovery occur during discrete windows of time or is it relatively continuous? Few studies have examined a broad range of domains within the same study, necessitating cross-study comparisons to assess differences in recovery between domains. Moreover, the bulk of previous studies have used only 2 time points, making the detection of nonlinear recovery patterns impossible. In addition, most previous studies have used functional outcome measures such as the FIM[6-12] or GOS,[8,12-14] which are insufficiently sensitive to capture impairments persisting beyond the very early recovery period.[12,15,16]

Information about consistency versus variation across cognitive domains and time promises to be especially useful to practitioners. Presumably, knowledge of these variables could help to tailor therapies such that the right patients could receive the right therapy at the right time, thereby enhancing recovery and overall quality of life. The current study, therefore, sought to investigate these questions in the context of a prospective study in which patients with moderate to severe TBI were repeatedly assessed over a period of 12 months using a comprehensive neuropsychological battery. In addition, data were analyzed within a multilevel statistical framework to enhance information regarding individual change trajectories (ie, 3-point recovery curves).

Functional Recovery After TBI: Global Outcomes

Review of the extant TBI cognitive recovery literature clearly indicates that recovery does indeed occur after TBI and that recovery curves are likely to be differentially sensitive to both recovery domain and time. The bulk of these studies, however, have employed global measures of functional out-

List of Abbreviations

ANOVA	analysis of variance
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
IQ	intelligence quotient
PIQ	performance intelligence quotient
PTA	posttraumatic amnesia
RAVLT	Rey Auditory Verbal Learning Test
TBI	traumatic brain injury
VIQ	verbal intelligence quotient
WAIS-III	Wechsler Adult Intelligence Scale–3rd edition

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come including: vocational status,[17-29] GOS,[8,12-14,30-34] the Disability Rating Scale,[6,7,17,23,35-40] the Community Integration Questionnaire,[17,21,41-46] and the FIM.[6-12] Although these studies converge in demonstrating that recovery is detectable, asymptotic (when more than 3 points are measured), and commonplace after TBI, they remain equivocal about the pace of change over time and the point at which a plateau in recovery is achieved. Expressly, some studies observe continued recovery as late as 2 years postinjury,[6,7,47] while others note no further recovery after 1 year,[11] while still others indicate full recovery as early as 6 months postinjury.[48,49] The discrepancies between findings may be attributable to the disparity across studies with regard to both study design and outcome measures.[50] In addition, the use of global assessment tools, which are limited in their sensitivity to detect subtle and specific deficits in individual domains of functioning, must also be considered a threat to the validity of these findings,[51,52] and also likely accounts for some of the differences across studies.

Cognitive Recovery After TBI: Domain-Specific Outcomes

In addition to research targeting global outcomes, a number of studies have also employed more specific measures to examine the recovery of discrete cognitive functions after TBI.[4,51,53-68] Results from these studies suggest that a wide range of cognitive impairments is apparent immediately after moderate to severe TBI.[4,53,57,59,60] Importantly, however, there exists preliminary evidence that recovery takes place at a differential rate across cognitive domains.[5,53,59,61] For example, learning and memory, complex attention and speed of processing, and complex language functions (eg, inferential semantics) appear to recover more slowly and/or less than other functions.[53,55,59,68,69] Conversely, some findings imply that visual perceptual abilities and verbal intelligence recover relatively more quickly.[52,63,67] It should be noted, however, that the latter finding is confounded by the use of the Wechsler Adult Intelligence Scales, for which verbal and nonverbal intelligence vary in their composition of timed versus untimed tests. Nevertheless, these studies collectively serve to suggest that cognitive domains recover in a separable manner over time.

Recovery as a Function of Time Postinjury

Past studies have also queried the temporal characteristics of cognitive recovery after TBI. For example, whether the greatest degree of improvement occurs in the early, middle, or late phases of recovery has important implications for the timing of service delivery. In a retrospective study of 876 persons with TBI, Mazaux et al[70] reported that early (rather than later) intervention improved outcome. Moreover, the argument that recovery benefits from the proper timing of intervention is also indirectly supported by related research showing that exercise increased neuroplasticity, but only during discrete time windows.[71] Similarly, investigators have suggested that different neurobiologic mechanisms may be active at different stages of recovery.[72-74] For example, Kolb[74] identified 2 neuroplastic responses after TBI, each with different time courses: an early-onset, “injury-induced” neuroplastic mechanism, which decreases dendritic spine density, and a later-onset, “experience-dependent” mechanism, which increases neuronal spine density and is longer-lasting.

Conversely, there is also evidence that the brain can maladaptively rewire as a function of intervention timing.[75,76] Taub and Morris[77] demonstrated that forced use of an impaired limb (eg, paretic arm or leg) during the early stages of recovery can result in poorer recovery. In contrast, DeBow et al[78] found that the use of constraint induced movement therapy immediately postinjury results in poorer outcomes in animals. As well, Humm et al[79] demonstrated that intensive, very early behavioral stimulation can hinder spontaneous neurophysical and neurochemical repair of the brain after injury. Overall, these findings suggest that the time course of recovery is an important consideration when attempting to deliver therapy at the right time, so as to improve outcome and avert harm.

Methodologic and Statistical Limitations of Past Research

Although several important findings have emerged in the literature reviewed here on post-TBI cognitive recovery, many central questions remain unanswered. Chief among these questions relates to the general temporal characteristics of cognitive recovery and whether performances in certain cognitive domains recover at differential rates. Contributing to the murky nature of this literature is the lack of comparability, from both design and measurement perspectives, across studies. For example, participant samples have varied significantly across demographic and injury characteristics. Discrepant test batteries have been delivered across disparate testing schedules, spanning from as little as 3 months to as long as 5 years between assessments. Variable sample sizes have resulted in unequal power to detect change across studies. Most previous studies have employed 2 assessments, allowing for the modeling of linear effects only; this is problematic in the face of existing evidence suggesting recovery is best characterized as curvilinear (namely asymptotic). Collectively, these limitations serve to recommend large-scale, prospective studies that employ comprehensive cognitive testing at more than 2 occasions. The primary advantage of such a study is the ability to ascertain the timing and nature of recovery across cognitive domains within a single sample, thereby overcoming problems inherent in cross-study comparisons.

Additionally, past studies have been hampered by their use of customary statistical models of change. That is, the behavioral and clinical sciences have traditionally analyzed change over time as a characteristic of groups at the expense of considering change as a characteristic of persons.[80] Methods typically applied to longitudinal data for the purpose of studying mean group differences in change over time include mixed-model ANOVA, multivariate/repeated measures ANOVA, and analysis of covariance. These means-as-outcome approaches regrettably sacrifice the heterogeneity of individual change as a meaningful parameter. One could imagine, for example, the unlikely scenario in which change for half of a sample of subjects, whose performance was above the mean at time 1, was exemplified by a decline, such that their time 2 performance was now equivalent to the scores of the lower half of the sample at time 1. Imagine that, in parallel, the lower scoring half of the sample experienced a similarly robust increase, such that their time 2 performance was now at a level similar to that at which the top half of the sample performed at time 1. In this illustrative example, one can visualize that mean group performance scores would not change over time, yet at the individual level very robust and important change has occurred. A second problem with traditional analytic techniques is that they are optimally designed to describe linear change. This is especially problematic for characterizing recovery from TBI given consistent indications that it is in fact nonlinear and strongly asymptotic.[66] An extension of ANOVA models that allows for analysis of curvilinear functions is polynomial trend analysis. However, design restrictions associated with these techniques still limit their overall flexibility. In particular, it is generally necessary that all participants have data at all time points and that participants with missing data be excluded from the analysis. In longitudinal TBI studies, in which missed appointments and dropout rates are high, the exclusion of patients with missing data would result in much smaller and potentially biased samples. Second, these techniques allow the incorporation of discrete, but not continuous, predictors of change.[81]

Multilevel Modeling: A Solution to Limitations of Previous Recovery Research

In recent decades, a statistical approach has been developed that overcomes the obstacles described here: multilevel modeling (also known as mixed-effects modeling, hierarchical linear modeling, covariance component modeling, or random-coefficient modeling). This analytic technique was developed to evaluate complex patterns of variability, with a focus on nested sources of variability. A prototypical example of a nested data structure is children nested within families. Multilevel modeling can also be readily applied to longitudinal analyses because repeated observations across time can be conceptualized as nested within a single participant. This approach has several advantages. First, change can be modeled at the individual level by parameters (namely intercepts and slopes plus random error) from individual growth curves (ie, a curve composed of time point data graphed for each individual subject). Employing intercepts and slopes as outcomes circumvents the difficulties inherent in modeling change at the group level only. In addition, however, multilevel modeling provides other notable general advantages, including improved estimation of individual effects, modeling cross-level effects, and partitioning of variance-covariance components. Detailed discussion of these topics is beyond the scope of this article; however, the interested reader is directed to one of the many excellent texts on the subject.[81,82] Such general advantages confer several specific rewards in the case of longitudinal design—namely, greater flexibility in terms of data requirements for variable number and spacing of time points across subjects. Because observations are viewed as nested within persons rather than as the same fixed set for all persons, the number and timing of observations can vary randomly across participants. Moreover, all effects and their interactions are tested simultaneously, thereby allowing for the ascertainment of moderator effects from any given level of the model (eg, individual, group, community). This is generally attractive to the longitudinal researcher because growth trajectories can be conditionalized on third variables emanating from any level of the model. For example, it is feasible to test how individual change varies as a function of level 2 variables (eg, sex, experimental treatment), level 3 variables (eg, community, country of origin), and so on.

Previous Studies of Recovery From Brain Injury Using Multilevel Methods

A handful of studies have used multilevel modeling for examining the nature of recovery after TBI. Spikman et al[66] studied 60 patients with a closed head injury over the course of 1 year postinjury with repeated assessments of attention (ie, Stroop Color-Word Test, Paced Auditory Serial Addition Task, Reaction Time Discrimination Task, Reaction Time Dual Task, Wisconsin Card Sort Perseverative Error Score, and Trail-Making Test). Results indicated that, across most tasks, performance improved for both patient and control groups. (Exceptions to this rule were noted on the perseverative error score and reaction time distraction task, on which control participants failed to show performance change over time.) Overall, patients demonstrated greater recovery than control subjects, which was nonlinear in nature and occurred more quickly than controls within the first 6 months postinjury. In addition, advanced age negatively impacted recovery, and more severely injured patients showed greater improvement than less severely injured patients (although this was at least partially attributable to the lower starting point, allowing more room for improvement).

Similarly, Wong et al[67] used multilevel modeling to establish whether PIQ recovers at a different rate than VIQ in a sample of 319 patients with TBI. Results indicated that PIQ recovered at a rate that was almost 4 times slower than VIQ. Moreover, recovery for both domains was asymptotic. Recovery in both domains was moderated by length of coma (with greater impact observed on PIQ versus VIQ), while sex and age of subjects did not add significantly to recovery prediction. More recently, Chu et al[54] performed a comparable analysis on patterns of recovery within the verbal memory domain (ie, on the RAVLT). They found considerable variability in initial performance at 1-year postinjury with only modest improvements over the subsequent course of 5 years (ie, an average growth rate of .13 words, of a total possible 80 words a year). Between-subject variation was also large; it was estimated that 84.9% of variation in outcome was between persons while the remaining 15.1% was within persons. Like the results of Spikman et al,[66] results from this study demonstrated that both age and length of PTA significantly moderated verbal memory recovery at 1 year postinjury. Sex and performance during acute rehabilitation were not significant predictors of verbal memory performance at the 1-year point.

Collectively, the studies reviewed here converge to reveal that recovery from TBI is largely asymptotic over the first year postinjury and significantly moderated by age and injury severity. They also demonstrate the value of multilevel modeling for investigating these phenomena. An important drawback, however, is that each study investigates a relatively narrow domain of cognitive recovery (ie, attention, IQ, or memory). Yet, data from several of these experiments imply that recovery across domains is uneven. Therefore, the main purpose of the current study was to use multilevel methods to examine differential recovery curves as a function of cognitive domain within the first year postinjury of a TBI.

METHODS

The study protocol was approved by the Research Ethics Board at the Toronto Rehabilitation Institute, where the study was conducted. The procedures of the study were in accordance with the standards of the Research Ethics Board.

Participants

The 75 patients with TBI in this study were recruited to a larger study investigating the natural history of cognitive and motor recovery in the inpatient, Neurorehabilitation Program of the Toronto Rehabilitation Institute, a large, urban, Canadian rehabilitation hospital. Inclusion criteria for the study were as follows: (1) acute care diagnosis of TBI, (2) PTA of 1 hour or more and/or GCS score of 12 or less either at their emergency admission or the scene of accident and/or positive computed tomography or magnetic resonance imaging findings, (3) age between 18 and 80 years, (4) able to follow simple commands in English based on the speech language pathologist intake assessment, and (5) competency to provide informed consent for study or availability of legal decision-maker. Exclusion criteria included (1) orthopedic injuries affecting both upper extremities and/or both lower extremities (relevant to the larger study, which was investigating motor recovery as well); (2) diseases primarily or frequently affecting the central nervous system, including dementia of Alzheimer type, Parkinson disease, multiple sclerosis, Huntington disease, lupus, and stroke, ascertained via medical records and/or screening of family members for patients over 60 years regarding any definite or possible prior diagnosis of dementia; (3) history of psychotic disorder; (4) failure to emerge from PTA by 6 weeks postinjury, as measured by the Galveston Orientation Amnesia Test; (5)TBI secondary to other brain injury (eg, a fall caused by stroke); and (6) failure on a test of symptom validity (Test of Memory Malingering)[83] at any of the assessments.

The present sample was predominantly composed of young to middle-aged (mean age ± SD, 37.37±15.49y) men (80%) with a high school education (mean level of education ± SD, 12.71±2.78y). Most participants were injured as a result of a motor vehicle collision (55.7%), followed by falls (32.9%), assaults (8.69%), and sports injuries (2.9%). On average, participants had experienced a moderate to severe brain injury (mean lowest/GCS score ± SD, 6.97±3.59), which resulted in an approximately 40-day acute care hospitalization (mean acute care length of stay ± SD, 38.03±17.17d). Premorbidly, most participants were employed as minor professionals or technical workers (35.7%), followed by machine operators or semiskilled workers (31.4%), skilled craftsmen or clerical staff (20%), professionals (10%), and unskilled laborers (1.4%). The average ± SD estimated premorbid IQ (indexed via the North American Adult Reading Test[84] or Wechsler Test of Adult Reading[85]) for the sample was 100.43±12.51.

Materials

Cognitive tests were selected to measure the following cognitive domains: premorbid IQ,[85] language skills,[86,87] visuospatial skills,[86,87] verbal and visuospatial attention/concentration,[88] speed of processing,[1,89,90] learning and memory,[1,88] executive functioning,[1,86,87] and general intellectual function.[86,87] Table 1 lists the cognitive tests used in the current study. All tests have demonstrated adequate validity and reliability for brain-injured populations.[1,91] In some cases, comprehensive assessment within a domain (eg, executive function) could not be achieved with standardized, clinical tests; in such cases, experimental tests were used (eg, Sustained Attention to Response Test,[92] Modified Hayling Sentence Completion Task—computerized administration). Tests were selected to have minimal timed, manual motor demands; where unavoidable (eg, choice reaction time and Trail-Making Test part B), subtraction tests (eg, simple reaction time; Trail-Making Test part A) were used to control for motor contributions, and alternate forms were employed to minimize practice effects. The battery required approximately 4.5 hours to administer to severely brain-injured patients.

Table 1: Neuropsychological Tests Administered and Corresponding Cognitive Domains

Cognitive Domain	Neuropsychological Test	Reference
All Memory	WMS-III Logical Memory I	Wechsler, 1997*[88]
	WMS-III Logical Memory II	Wechsler, 1997*[88]
	RAVLT–Long Delay	Lezak, 1995‡[1]
	RAVLT–Short Delay	Lezak, 1995‡[1]
	RAVLT–Total	Lezak, 1995‡[1]
	Rey Visual Design Learning Test–Total	Lezak, 1995‡[1]
Attention Span	WMS-III Digit Span Forward	Wechsler, 1997*[88]
	WMS-III Visual Span Forward	Wechsler, 1997*[88]
Executive General	Stroop Color-Word Test–Interference	Lezak, 1995‡[1]
	WAIS-III Matrix Reasoning	Wechsler, 1997†[87]
Executive Timed	Symbol Digit Modalities Test (oral)	Smith, 1982[89]
	Verbal Fluency	Lezak, 1995‡[1]
Executive Working Memory	WMS-III Digit Span Backward	Wechsler, 1997*[88]
	WMS-III Visual Span Backward	Wechsler, 1997*[88]
Language	WAIS-III Vocabulary	Wechsler, 1997†[87]
Manual Motor	Grip Strength	Lezak, 1995‡[1]
Logical Memory	WMS-III Logical Memory I	Wechsler, 1997*[88]
	WMS-III Logical Memory II	Wechsler, 1997*[88]
Memory–RAVLT	RAVLT–Long Delay	Lezak, 1995‡[1]
	RAVLT–Short Delay	Lezak, 1995‡[1]
	RAVLT–Total	Lezak, 1995‡[1]
Visual Memory	Rey Visual Design Learning Test–Total	Lezak, 1995‡[1]
Motor Speed	Grooved Pegboard	Lezak, 1995‡[1]
	Trail Making Test part A	Lezak, 1995‡[1]
Speed of Processing Motor	Symbol Digit Modalities Test (written)	Smith, 1982[89]
	Trail-Making Test part B	Lezak, 1995‡[1]
Speed of Processing Simple	Stroop Color-Word Test–Color Naming	Lezak, 1995‡[1]
	Stroop Color-Word Test–Word Naming	Lezak, 1995‡[1]
Verbal Abstraction	WAIS-III Similarities	Wechsler, 1997†[87]
Visuospatial	WAIS-III Block Design	Wechsler, 1997†[87]
	WAIS-III Matrix Reasoning	Wechsler, 1997†[87]

Abbreviation: WMS-III, Wechsler Memory Scale–3rd Edition.
*Refers to reference: Wechsler D. Wechsler Memory Scale–3rd Edition (WMS–III). San Antonio: Psychological Corp; 1997.
†Refers to reference: Wechsler D. Wechsler Adult Intelligence Scale–3rd Edition (WAIS-III). San Antonio: Psychological Corp; 1997.
‡Refers to reference: Lezak MD. Neuropsychological Assessment–3rd edition. New York: Oxford Univ Pr; 1995.

Procedure

The current study employed a prospective, repeated-measures design. Patients were tested at 2, 5, and 12 months postinjury. The cognitive battery was divided into 5 blocks of tests, with a fixed order of tests within each block designed to minimize interference between tests (eg, verbal memory test contained nonverbal tests between learning and delayed recall phases). Test blocks were matched as much as possible for the number of timed tests and effortful tests. Each block contained a maximum of 1 memory test. Block order was counterbalanced, but each participant received the same block order across testing sessions. Cognitive tests with known practice effects contained 2 or more alternate forms. In some cases, the same form was administered a second time (ie, where only an original plus 1 alternate form was available); however, this occurred only between the 2-month and 12-month assessments, and thus a gap of approximately 10 months separated the 2 occasions of testing. Order of alternate forms was counterbalanced across subjects. The 2-month testing window ranged from 1.5 to 2.5 months postinjury and took place during the inpatient stay. Neuropsychological assessment was administered over a maximum 72-hour period, with individual testing sessions ranging from 0.5 hour to 3 hours, as tolerated by the patient. The 5-month window ranged from 3.5 to 5.5 months postinjury, and all testing took place over a 2-day period. The 12-month window ranged from 11 to 13 months postinjury, and again, all testing took place during the same 2-day period.

Data Analysis

Data transformation and reduction. A limitation of many previous studies on cognitive recovery after TBI is the use of raw test scores in statistical analyses. This approach confounds the well documented general effects of aging on cognitive performance with the potential moderating effects of aging on recovery from TBI. Although this article does not address the effect of moderators (eg, age, depressive symptomatology) on recovery after TBI (but see Green et al[93]), it is nevertheless critical to parcel out these general effects of aging on performance in order to produce accurate recovery trajectories. As a result, for the purpose of this study, all raw test scores obtained from standardized neuropsychological measures were transformed into normative units using published normative data for the particular test.

In order to increase reliability[94] of neuropsychological tests, all cognitive test scores were transformed to a common metric and combined into larger domain aggregates. Tests were selected for each domain on the basis of clinical knowledge of the tests and on the strength of zero-order correlations between tests. To combine the tests, each test with normative data was converted to a *z* score using external standardization. (Percentile norms were converted to *z* scores by using the normative score corresponding to the percentile.) Thus, the *z* scores for domains based on tests with external standards are obtained by combining external information on individual tests with empirical information on their correlations. The resulting *z* scores for those domains that are based only on externally standardized components are believed to be close to the values they would have had if the domains had been externally standardized directly. This approach allows valid comparisons of recovery trajectories between domains. Tests not externally standardized were internally standardized using the SD of the tests administered after 5 months postinjury. Aggregate score domains based on these tests were standardized in a similar way, but these domains are not compared with each other. They are used only to study the within-domain recovery trajectories. The *z* scores for the tests in a common aggregate were then added and the sum restandardized using an estimated SD derived from the empirical correlations between the tests.

Multilevel modeling. The longitudinal multilevel model used in the analysis of the first 3 waves of data has the following form:

$$Y_{it} = \beta_{0i} + \beta_{1i}T_{it} + \beta_{1i}(T_{it} - 5)_{+} + \varepsilon_{it}$$

where Y_{it} is an outcome of a test administered to the *i*th subject on the *t*th occasion at time T_{it} measured in months postinjury. The expression (T_{it}–5) is equal to 0 if T_{it} is less than 5 and to T_{it}–5 otherwise. Consequently, the expression

$$\beta_{0i} + \beta_{1i}T_{it} + \beta_{1i}(T_{it} - 5)_{+}$$

represents a linear spline in *T* with a knot at 5 months: β_{0i} is the expected level of *Y* for the *i*th subject at month 0, β_{1i} is the expected rate of recovery a month before the fifth month, and β_{1i} is the change in the expected recovery rate at the fifth month. Thus, ($\beta_{1i}+\beta_{1i}$) is the expected recovery rate after the fifth month. The error term, ε_{it}, represents random variability in test results from one occasion to the other for a given subjects. Its expected magnitude is related to the test-retest reliability of a particular test.

Longitudinal multilevel models allow the intercept β_{0i} and the slopes β_{1i} and β_{1i} to vary randomly from subject to subject. As discussed, domains whose components are externally standardized can be treated as if they are externally standardized themselves, thus allowing comparisons between domains. Various aspects of the trajectories of different domains can be compared, including initial impairment, the rate of recovery, and impairment at 1 year postinjury. In addition, pertinent baseline differences between participants were statistically controlled for by modeling these variables as covariates. Covariates were chosen based on 2 criteria: (1) they demonstrated a significant, unique (ie, jointly significant partial correlations) association with the outcome variable of interest (ie, cognitive domain) and (2) were rationally deemed to be time-invariant. Consequently, covariates diverge as a function of the cognitive domain being tested. Broadly speaking, covariates constellations were composed of a selection of the following 3 variables: age, estimated premorbid IQ, and length of acute rehabilitation hospitalization. This procedure was an attempt to minimize baseline differences rather than assess the impact of these variables on recovery curves (for data regarding the impact of moderator variables on recovery curves, see Green[93]). For purposes of statistical inference, multiple domains form a multivariate multilevel response vector whose analysis using likelihood-based methods is much more complex than that of a univariate response variable. A relatively simple and robust method for between-domain comparisons is based on an analysis that uses bootstrapping. The subject-to-subject variability of interdomain comparisons was estimated by using 4000 bootstrap resamples of the subjects. The *P* values for these comparisons are then adjusted for multiple comparisons using the Bonferroni-Holms method. This approach allows valid comparisons between domains that generalize to the population from which the study subjects are deemed to have been drawn.

RESULTS

Figure 1 plots the recovery trajectories in standard scores as a function of cognitive domain. Visual inspection indicates an asymptotic function for most domains, with most recovery taking place in the initial 5 months postinjury. Table 2 presents individual parameter coefficients, accompanying estimates of

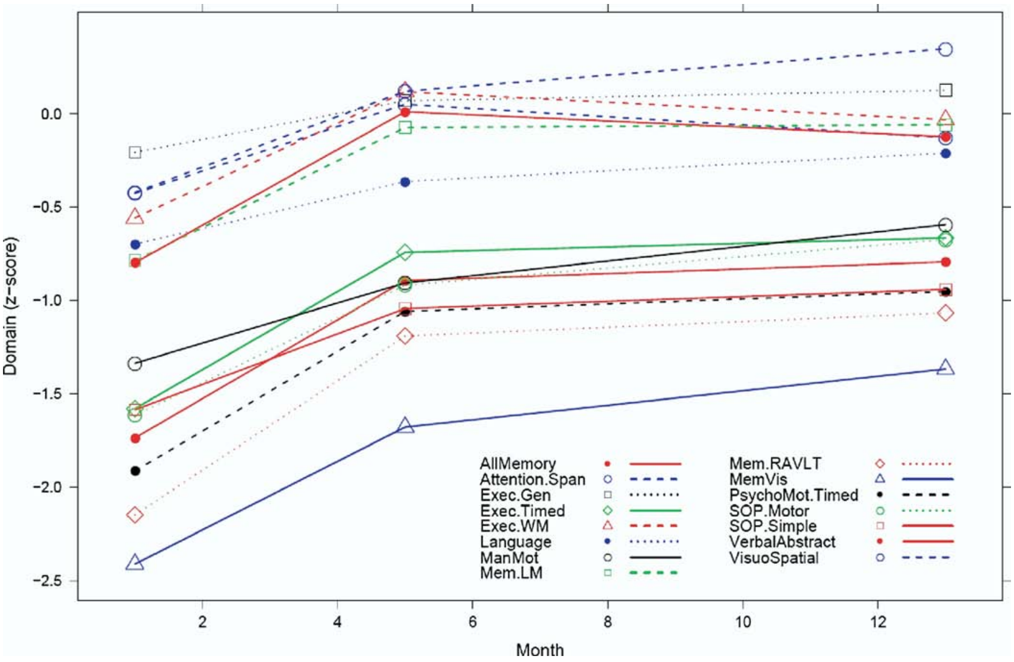

Fig 1. Average recovery curves for all participants with TBI plotted as a function of cognitive domain. Neuropsychological assessment occurred at 2, 5, and 12 months postinjury. Domain scores are represented as standard scores and calculated using external normative data (see Methods). Normative average corresponds to a standard score of 0. Abbreviations: AllMemory, All Memory domain; Attention.Span, Attention Span domain; Exec.Gen, Executive General domain; Exec.Timed, Executive Timed domain; Exec.WM, Executive Working Memory domain; Language, Language domain; ManMot, Manual Motor domain; Mem.LM, Logical Memory domain; Mem.RAVLT, Memory RAVLT domain; Mem.Vis, Visual Memory domain; PsychoMot.Timed, Motor Speed domain; SOP.Motor, Speed of Processing Motor domain; SOP.Simple, Speed of Processing Simple domain; VerbalAbstract, Verbal Abstraction domain; VisuoSpatial, Visuospatial domain.

parameter variability (ie, SE or SD), and significance testing for each parameter of interest included in the multilevel model. Initial status corresponds to the intercept parameter, while change coefficients denote slope parameters. The slope parameter denoting change between months 5 and 12 is calculated relative to the initial slope (ie, change between months 2 and 5). In this vein, the second slope parameter gives an indication of change in slope during the second epoch compared with the first epoch. Stated differently, the second slope gives an estimate of alteration in the trajectory at the 5-month point or the size of the elbow connecting the 2 linear functions at the 5-month point. These results clearly demonstrate that slopes across the first epoch significantly depart from 0—that is, significant quantitative improvement occurred across all domains from month 2 to month 5. Moreover, slopes denoting change during the second epoch are uniformly negative, indicating that, across all domains, change was attenuated relative to the first epoch. Consistent with previous research, this suggests that cognitive recovery in the first year after TBI conforms to an asymptotic function. In most cases this attenuation was statistically significant; however, notable exceptions are the results for the Executive General (relative change=−0.06; SE=0.03; t=–1.80; P=.07) and Language (relative change=–0.07; SE=0.05; t=–1.34; P=.18) domains. Each of these domains demonstrates nonsignificant relative change in the second epoch compared with the first. Closer inspection (see fig 1) shows that slopes from both epochs across both domains are relatively shallow and nearly flat, supporting the observation that change in these 2 domains is relatively meager against other cognitive functions.

In the context of slowed cognitive recovery over the second epoch, does recovery cease in some domains? To test this question, linear effects (ie, Does the slope of this trajectory significantly depart from 0?) were tested for the second recovery epoch. Recall that slopes for the first testing epoch were uniformly nonzero (see table 2). In contrast, however, the vast majority of slopes (those from 12 of a total of 15 domains) from the second recovery epoch were statistically indistinguishable from 0 (t range, 0.11–1.65). Exceptions to this rule included small yet significantly accelerating slopes associated with the Manual Motor (slope=0.03; SE=0.19; t=2.04; P=.044) and Visuospatial domains (slope=0.02; SE=0.013; t=2.23; P=.028). Similarly, a positive slope, significant at trend levels, was revealed over this epoch for the Visual Memory (slope=0.04; SE=0.022; t=1.74; P=.085) domain. The evidence suggests, therefore, that while recovery comes to a halt for most domains during the second half of the first year postinjury, small improvements continue to happen over this time for skills in the aforementioned 3 domains.

The second objective of the current study was to ascertain whether cognitive recovery across domains was uniform or differential. To obtain estimates of differential recovery curves, slope parameters were statistically compared across domains in a pairwise fashion. Table 3 summarizes the main findings from this analysis. Presented in table 3 are the pairwise differences between the slopes from 2 domains with their accompanying estimate of variability (SE). Also included are significance testing parameters including a Wald statistic, regular P value, and Bonferroni-Holm corrected P value. In order to economize the presentation of intradomain differences, only those comparisons rendering a sufficiently large difference between slopes are presented. In this regard, it was arbitrarily decided to include slope differences above 0.45. In all cases, slope differences from the 2-month to 5-month epoch reaching this criterion involved comparisons to the Executive General and Language domains (with these 2 domains uniformly rendering the smaller slope in each comparison). Relative to these 2 domains, the domains of All Memory, Executive Timed, Memory RAVLT, Motor Speed, and Verbal Abstraction produced slope differences greater than 0.45. In addition, each of these comparisons produced Wald statistics that were significant (all *P* values $<.03$) using conventional probability statistics. However, only 3 comparisons survived correction for multiple comparisons using the Bonferroni-Holm procedure. These included Executive Timed versus Executive General, Motor Speed versus Executive General, and Verbal Abstraction versus Executive General domains. No other pairwise comparisons between recovery slopes by domain were statistically significant.

Intradomain slopes from the 5-month to 12-month epoch were similarly contrasted. Again, using a difference score criterion of 0.45, 6 comparisons were notable (see table 3). In general, these 6 comparisons reflect the opposing impact of 2 accelerating linear functions (ie, functions denoting the trajectories for the Manual Motor and Visual Memory domains) and 3 decelerating linear functions (ie, functions denoting the trajectories for the Attention Span, Executive Working Memory, and Verbal Abstraction domains). However, the magnitude of intradomain slope differences from the 5-month to 12-month epoch are generally lower than those obtained from the 2-month to 5-month epoch. These lower magnitude slope differences are in the context of comparable SEs resulting in higher probability of Type I error. Indeed, none of the domain comparisons from the second epoch survived α correction with the Bonferroni-Holm procedure. Therefore, these differences cannot be considered reliable, and the slopes from the 5-month to 12-month epoch should be considered equivalent.

DISCUSSION

The broad objectives of the current study were 2-fold: first, to characterize cognitive recovery trajectories (ie, examining more than 2 time points) across multiple domains of cognitive function within a single prospective study during the first year postinjury, and second, to ascertain whether this recovery pattern differed as a function of cognitive domain. Not surprisingly, and consistent with previous literature, the present results show that, as a group, patients undergoing rehabilitation for a TBI demonstrate cognitive recovery across all domains. The pattern of recovery across all domains was highly consistent; that is, most recovery curves were shown to be asymptotic in nature with much more accelerated recovery during the first 5 months than the last 7 months of the first year postinjury. The asymptotic nature of the curves is borne out by 2 statistical results. The first is consistent with previous literature—that is, more improvement occurs during the early periods of recovery. Multilevel modeling showed that, relative to the slope over the 2-month to 5-month epoch, slopes from the 5-month to 12-month epoch were attenuated (see table 2). To our knowledge, this is the first study to illustrate this finding across a broad range of cognitive domains using these techniques. Thus, the current results provide support for the standard approach to rehabilitative therapy provision, which entails the delivery of intensive treatment during the first months postinjury to all domains of (impaired) cognitive functioning.

The second result adds specificity to our knowledge of the patterns of recovery and also suggests that some adaptation to the standard approach to treatment delivery may augment outcomes. When slopes from the 2-month to 5-month epoch were tested for their departure from 0, all were significantly greater than 0 (*t* range, 2.25–6.68) (see table 2). Similarly, slopes from the 5-month to 12-month epoch were tested for their departure from 0. Here, only 2 slopes (those for the Manual Motor and Visuospatial domains) were significant (both in a positive direction), with a third slope (for the Visual Memory domain) significant at trend levels (also in a positive direction). These findings of ongoing recovery suggest a wider therapeutic window for selected domains. Ongoing therapies focusing on restoration/remediation of functioning (as opposed to more compensatory approaches like the use of external aids) might serve to augment recovery. From a clinical perspective, these areas may be of particular relevance to certain types of careers and activities (ie, those with an emphasis on manual and visuospatial capacities, such as art, skilled labor, or architecture). Therefore, patients whose productivity is especially related to these functions might be identified early postinjury as potential candidates for longer, targeted therapies. Of course, further research is needed before the null hypothesis is accepted for other domains with regard to the absence of ongoing recovery. Moreover, subgroups or moderator analyses should be undertaken to ascertain whether persons within these groups vary in their ongoing recovery as a function of specific factors, like age or years of education.

A related, and important, question is whether cognitive improvement over the first year postinjury represents complete recovery. In the current study, we examined not only recovery slopes but also recovery levels. The average level of function after the first year postinjury remained below that of the normative average (see fig 1). In contrast, the mean estimated premorbid IQ from this sample was almost exactly average from a normative standpoint. This suggests that, across several domains, the sample failed to return to premorbid levels of functioning. It should be noted, however, that because the focus of the current study was that of recovery (ie, change over time), group averages at discrete time points were not statistically tested against the normative average. Graphic inspection of the 12-month data (see fig 1) suggests that 2 distinct domain groups exist with respect to persisting impairment. The domains of Attention Span, Executive General, Executive Working Memory, Language, Logical Memory, Verbal Abstraction, and Visuospatial domains were particularly close to the normative average and much less likely to be significantly below normative than the remaining 8 domains. (Note that significant ongoing recovery of visuospatial functioning was observed in the latter part of the first year postinjury, and the measure of premorbid function employed was language-based. Therefore, the finding that visuospatial domains were near premorbid IQ levels should be interpreted with caution). In contrast, performance across All Memory, Executive Timed, Manual Motor, Memory–RAVLT, Visual Memory, Motor Speed, Speed of Processing Motor, and Speed of Processing Simple domains fell well below that of those listed above. Performance at 2 months postinjury mirrored these findings. The pattern raises several important scientific and clinical questions. For example, do those domains that are initially more impaired suffer disproportionately from the effects of TBI? Given that those domains with a relatively low initial intercept are the same domains that remain low at 12 months postinjury, is it possible that lower domains catch up to the higher domains after a year postinjury? Do those functions that fare better carry a cognitive reserve that confers buffering and recuperative benefits after TBI, or are the functions that fare better simply subserved by brain matter that differs by location or morphology in such a way that greater protection is provided against initial injury?

As noted, the domains tested in this study inherently divide themselves into 2 groups based on the overall magnitude of patients' initial deficit (ie, intercept values). This also raises the

Table 2: Results From Multilevel Modeling of Recovery Curves Over the Course of 1 Year Post-TBI as a Function of Cognitive Domain

Domain	Effect	Parameter	Coefficient	SE (fixed)/SD (random)	*t*	*P*
All Memory	Fixed	Initial status	–1.95	0.172	–11.32	.000
		Change 2–5mo	0.21	0.038	5.61	.000
		Relative change 5–12mo	–0.19	0.049	–4.06	.000
		Age	–0.08	0.130	–0.63	.527
		Premorbid IQ	0.61	0.131	4.62	.000
	Random	Initial status		1.012		
		Level 1 error		0.604		
Attention Span	Fixed	Initial status	–0.54	0.132	–4.10	.000
		Change 2–5mo	0.11	0.030	3.86	.000
		Relative change 5–12mo	–0.14	0.040	–3.53	.000
		Premorbid IQ	0.27	0.094	2.92	.004
	Random	Initial status		0.716		
		Level 1 error		0.499		
Executive General	Fixed	Initial status	–0.28	0.103	–2.68	.008
		Change 2–5mo	0.07	0.026	2.61	.010
		Relative change 5–12mo	–0.06	0.034	–1.80	.073
		Premorbid IQ	0.31	0.062	5.05	.000
	Random	Initial status		0.431		
		Level 1 error		0.432		
Executive Timed	Fixed	Initial status	–1.79	0.142	–12.51	.000
		Change 2–5mo	0.21	0.033	6.31	.000
		Relative change 5–12mo	–0.20	0.427	–4.66	.000
		Acute length of stay	–0.40	0.096	–4.16	.000
		Premorbid IQ	0.30	0.978	3.10	.000
	Random	Initial status		0.692		
		Level 1 error		0.490		
Executive Working Memory	Fixed	Initial status	–0.73	0.134	–5.39	.000
		Change 2–5mo	0.17	0.033	5.06	.000
		Relative change 5–12mo	–0.19	0.043	–4.33	.000
		Premorbid IQ	0.29	0.089	3.33	.001
	Random	Initial status		0.650		
		Level 1 error		0.539		
Language	Fixed	Initial status	–0.78	0.143	–5.48	.000
		Change 2–5mo	0.08	0.037	2.25	.027
		Relative change 5–12mo	–0.07	0.048	–1.34	.183
		Premorbid IQ	0.74	0.923	8.04	.000
	Random	Initial status		0.551		
		Level 1 error		0.551		
Manual Motor	Fixed	Initial status	–1.44	0.188	–7.69	.000
		Change 2–5mo	0.11	0.046	2.35	.021
		Relative change 5–12mo	–0.07	0.589	–1.17	.246
		Acute length of stay	–0.33	0.119	–2.82	.007
	Random	Initial status		0.758		
		Level 1 error		0.641		
Logical Memory	Fixed	Initial status	–0.96	0.148	–6.51	.000
		Change 2–5mo	0.18	0.034	5.25	.000
		Relative change 5–12mo	–0.18	0.044	–4.02	.000
		Premorbid IQ	0.60	0.107	5.62	.000
	Random	Initial status		0.817		
		Level 1 error		0.539		
Memory–RAVLT	Fixed	Initial status	–2.38	0.232	–10.29	.000
		Change 2–5mo	0.24	0.054	4.42	.000
		Relative change 5–12mo	–0.23	0.070	–3.18	.002
		Premorbid IQ	0.57	0.164	3.51	.001
	Random	Initial status		1.235		
		Level 1 error		0.864		
Visual Memory	Fixed	Initial status	–2.59	0.248	–10.47	.000
		Change 2–5mo	0.18	0.051	3.61	.001
		Relative change 5–12mo	–0.14	0.066	–2.20	.030
		Age	–0.03	0.196	–0.13	.894
		Premorbid IQ	0.69	0.199	3.48	.001
	Random	Initial status		1.156		
		Level 1 error		0.783		

Table 2 (Cont'd): Results From Multilevel Modeling of Recovery Curves Over the Course of 1 Year Post-TBI as a Function of Cognitive Domain

Domain	Effect	Parameter	Coefficient	SE (fixed)/SD (random)	*t*	*P*
Motor Speed	Fixed	Initial status	–2.12	0.172	–12.40	.000
		Change 2–5mo	0.21	0.039	5.47	.000
		Relative change 5–12mo	–0.20	0.050	–4.01	.000
		Acute length of stay	–0.31	0.118	–2.59	.012
	Random	Initial status		0.767		
		Level 1 error		0.525		
Speed of Processing Motor	Fixed	Initial status	–1.79	0.195	–9.18	.000
		Change 2–5mo	0.17	0.044	3.95	.000
		Relative change 5–12mo	–0.14	0.056	–2.55	.013
		Acute length of stay	–0.36	0.131	–2.79	.007
		Premorbid IQ	0.14	0.132	1.16	.274
	Random	Initial status		0.930		
		Level 1 error		0.627		
Speed of Processing Simple	Fixed	Initial status	–1.72	0.103	–16.68	.000
		Change 2–5mo	0.14	0.020	6.68	.000
		Relative change 5–12mo	–0.12	0.026	–4.66	.000
		Premorbid IQ	0.37	0.084	4.47	.000
	Random	Initial status		0.657		
		Level 1 error		0.318		
Verbal Abstraction	Fixed	Initial status	–1.00	0.139	–7.21	.000
		Change 2–5mo	0.20	0.036	5.60	.000
		Relative change 5–12mo	0.22	0.047	–4.65	.000
		Premorbid IQ	0.48	0.084	5.77	.000
	Random	Initial status		0.558		
		Level 1 error		0.567		
Visuospatial	Fixed	Initial status	–0.56	0.141	–3.94	.000
		Change 2–5mo	0.13	0.029	4.71	.000
		Relative change 5–12mo	–0.11	0.037	–2.87	.005
		Premorbid IQ	0.37	0.112	3.33	.001
	Random	Initial status		0.893		
		Level 1 error		0.461		

possibility that slopes for the domains with less severely impaired initial scores may follow an artificially shallow trajectory secondary to ceiling effects. This possibility was tested by directly comparing the average slope obtained across the Attention Span, Executive General, Executive Working Memory, Language, Logical Memory, Verbal Abstraction, and Visuospatial domains to the average slope obtained across the All Memory, Executive Timed, Manual Motor, Memory–RAVLT, Visual Memory, Motor Speed, Speed of Processing Motor, and Speed of Processing Simple domains. Average slopes between these groups of domains were not significantly different one from another (slope difference=–0.183; Wald statistic=–2.09;

Table 3: Pairwise Comparisons of Slope Parameters as a Function of Cognitive Domain

	Domains	Slope Difference	SE	Wald Statistic	*P*	B-H *P*
Months 2–5	All Memory vs Executive General	0.57	0.192	2.94	.003	.338
	All Memory vs Language	0.50	0.224	2.23	.025	1.0
	Executive Timed vs Executive General	0.55	0.144	3.86	.000	0.011
	Executive Timed vs Language	0.49	0.197	2.49	.013	1.0
	Memory RAVLT vs Executive General	0.68	0.255	2.65	.008	0.804
	Memory RAVLT vs Language	0.61	0.276	2.21	.027	1.0
	Motor Speed vs Executive General	0.59	0.137	4.73	.000	0.001
	Motor Speed vs Language	0.53	0.211	2.52	.011	1.0
	Verbal Abstraction vs Executive General	0.54	0.116	4.70	.000	0.000
	Verbal Abstraction vs Language	0.47	0.202	2.37	.018	1.0
Months 5–12	Attention Span vs Manual Motor	0.49	0.152	3.23	.001	0.129
	Attention Span vs Visual Memory	0.49	0.216	2.29	.022	1.0
	Executive Working Memory vs Manual Motor	0.46	0.198	2.36	.018	1.0
	Executive Working Memory vs Visual Memory	0.47	0.206	2.28	.023	1.0
	Manual Motor vs Verbal Abstraction	0.45	0.199	2.26	.024	1.0
	Visual Memory vs Verbal Abstraction	0.45	0.183	2.47	.013	1.0

Abbreviation: BH, Bonferroni-Holm procedure.

$P > .05$). Therefore, differing slopes secondary to ceiling effects are not likely to account fully for the observed effects.

Domains showing persisting deficits in this study were memory and speed of processing. These results are consistent with those of a recent meta-analysis[95] examining very long-term outcome from moderate and severe TBI, which shows that memory and speed of processing impairments are the 2 most persisting deficits into the longer term. These findings, therefore, have several important clinical implications. We have recommended that for those domains in which ongoing recovery takes place over a longer period, the time window of remediate intervention should be commensurately widened. The findings of persisting impairments in memory and speed of processing, it might be argued, suggest the importance of ongoing therapy, but arguably more compensatory in nature. (Ideally, one would ascertain, individual by individual, when cognitive recovery was reaching an asymptote, and then commence a more compensatory therapeutic approach to treatment.) The aim here would be to help offset the implications of persisting impairments for return to productive activities. Indeed, a number of studies have shown a relationship between memory and return to productive activities, including work and school.[96] The relationship between speed of processing and return to productivity is less clear (see Ruttan et al[95] for review), perhaps because adaptations to slower speed of processing (eg, staying later at work) are easier to implement than adaptations needed to remember, for example, all the details of an important conversation with a colleague.

Results also demonstrate that recovery differs as a function of domain. This is particularly true when one considers intradomain differences between slopes over the 2-month to 5-month period. Although several domains show significant and disproportionate improvement when analyzed using conventional α criteria, only 3 domains survive correction for multiple comparisons: Verbal Abstraction, Motor Speed, and Executive Timed. All of these domains are significantly different from only a single other domain: Executive General. The tests with the faster recovering domains include the WAIS-III Similarities, Grooved Pegboard Test, Trail-Making Test part A, Symbol Digit Modalities Test, and Verbal Fluency. In contrast, tests with the slower recovering domain include the Stroop Color-Word Test (interference score) and WAIS-III Matrix Reasoning. A simple or unifying explanation of why these functions and not others demonstrate differential rates of recovery is elusive. However, it is reasonable to observe that the tests in the accelerated recovery category significantly depend on visuomotor function (with the exceptions of WAIS-III Similarities). This notion is partially convergent with previous research in that some studies have demonstrated more rapid recovery for visual perceptual abilities.[52,63] In contrast, measures of selective attention/cognitive control and nonverbal problem solving demonstrated a more sluggish recovery curve. This result too is somewhat consistent with previous research in that both of these faculties rely on fluid and nimble processing, perhaps akin to previous studies showing slowed recovery for complex attention, speed of processing, and nonverbal problem-solving.[53,55,59,67,68]

Of the previous studies specifically using multilevel modeling to characterize cognitive recovery after TBI, Wong et al[67] is the most relevant for the present results because it is the only study to compare recovery rates directly across specific cognitive domains—namely PIQ and VIQ. These authors observed that PIQ recovered at a rate that was 4 times slower than that of VIQ. These results are somewhat consistent with data from the current study—for example, one of the significantly faster recovery domains was Verbal Abstraction, which is made up solely of WAIS-III Similarities, a test that is also part of the VIQ index. Inconsistently, however, performance on the Symbol Digit Modalities Test, which loads on the PIQ index, also recovered disproportionately quickly. These results suggest, potentially, that while the aggregated indices of PIQ and VIQ demonstrate differential rates of improvement when considered at this global level, important differences may still exist at the individual subtest level. For example, it is plausible that Similarities is one of the main drivers of the VIQ acceleration finding of Wong et al,[67] while Digit Symbol contributed negligibly, or in an opposing fashion, to the same finding.

Study Limitations

Limitations of the current study include its relatively modest sample size. As a consequence, power to detect statistical differences and the ability to produce stable parameter estimates may have been compromised. This possibility is bolstered by the fact that several domains with similarly large recovery slopes did not survive correction for multiple comparisons. This raises the possibility that, with increased participants, recovery slopes from several more domains would be revealed as differentially impacted. Taken together, these observations serve to caution the reader against interpreting the current data as perfectly valid in the absence of replication from independent samples. In addition, a potential confound of the current analyses is variability across domains of inherent measurement error. Unreliability serves to bias the measurement of change such that unreliable measures frequently underestimate the magnitude of change when raw scores are converted to standard scores. Consider a given expected change in a raw score measure. If the measure has high reliability, then its variance will come mainly from interperson variability. If it has low reliability, the interperson variability will be inflated by measurement error. Because the standard score in each case is obtained by dividing the raw score by its SD, the expected difference for the raw score with low reliability will transform into a smaller difference in standard scores. Therefore, in order to estimate the effect of reliability on slope parameters in the current analysis, test-retest reliability coefficients were computed for each domain. Next, reliabilities were correlated with slope parameters from the 2-month to 5-month recovery epoch. Reliabilities were only modestly and nonsignificantly correlated with slopes from this section of the recovery curve ($r = .124$; $P = .752$), undermining the likelihood that the variability in magnitude of slopes could be entirely accounted for by differences in domain reliabilities.

CONCLUSIONS

These results hold the potential to inform clinical practice. The accelerated recovery for all domains during the early portions of the first year postinjury confirms that this period may be highly receptive to concentrated rehabilitation effort, as is currently the practice. Those areas of cognitive function that show continued recovery from 5 to12 months postinjury should receive continued attention because they suggest the possibility of a wider therapeutic window in which restorative treatments may be effective. Finally, for those functions that show marked persisting impairments at 1 year postinjury, we suggest that more aggressive compensatory treatments may be warranted in order to offset the impact on reintegration to the community, particularly in light of findings that show a relationship between impairments in these areas and return to productivity.

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