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Table of Contents

COMMENTARY

- S1 **Traumatic Brain Injury: Recovery, Prediction, and the Clinician**
Ian H. Robertson, PhD

ORIGINAL ARTICLES

- S3 **Recovery of Cognitive Function After Traumatic Brain Injury: A Multilevel Modeling Analysis of Canadian Outcomes**
Bruce K. Christensen, PhD, CPsych, Brenda Colella, MA, Elizabeth Inness, MSc, Deborah Hebert, MSc (Kin), Georges Monette, PhD, Mark Bayley, MD, FRCP(C), Robin E. Green, PhD, CPsych
- S16 **Examining Moderators of Cognitive Recovery Trajectories After Moderate to Severe Traumatic Brain Injury**
Robin E. Green, PhD, CPsych, Brenda Colella, MA, Bruce Christensen, PhD, CPsych, Kadeen Johns, BA, Diana Frasca, MSc, Mark Bayley, MD, FRCPC, Georges Monette, PhD
- S25 **Postrecovery Cognitive Decline in Adults With Traumatic Brain Injury**
Christine Till, PhD, Brenda Colella, MA, Joel Verwegen, Robin E. Green, PhD, CPsych
- S35 **Magnetic Resonance Imaging Evidence of Progression of Subacute Brain Atrophy in Moderate to Severe Traumatic Brain Injury**
Kevin Ng, MBBS, FRANZCR, David J. Mikulis, MD, Joanna Glazer, MSc, Noor Kabani, PhD, Christine Till, PhD, Gahl Greenberg, MD, Andrew Thompson, MBBS, FRANZCR, Dorothy Lazinski, MD, Ronit Agid, MD, Brenda Colella, MA, Robin E. Green, PhD, CPsych
- S45 **Use of Diffusion Tensor Imaging to Examine Subacute White Matter Injury Progression in Moderate to Severe Traumatic Brain Injury**
Gahl Greenberg, MD, David J. Mikulis, MD, Kevin Ng, MBBS, FRANZCR, Danielle DeSouza, BSc, Robin E. Green, PhD, CPsych
- S51 **Prediction of Return to Productivity After Severe Traumatic Brain Injury: Investigations of Optimal Neuropsychological Tests and Timing of Assessment**
Robin E. Green, PhD, CPsych, Brenda Colella, MA, Deborah A. Hebert, MSc (Kin), Mark Bayley, MD, FRCPC, Han Sol Kang, BSc, Christine Till, PhD, CPsych, Georges Monette, PhD
- S61 **The Efficacy of Cognitive Behavior Therapy in the Treatment of Emotional Distress After Acquired Brain Injury**
Cheryl L. Bradbury, PsyD, CPsych, Bruce K. Christensen, PhD, CPsych, Mark A. Lau, PhD, RPsych, Lesley A. Ruttan, PhD, CPsych, April L. Arundine, BA, MSc (Cand), Robin E. Green, PhD, CPsych
- S69 **Long-term Cognitive Outcome in Moderate to Severe Traumatic Brain Injury: A Meta-Analysis Examining Timed and Untimed Tests at 1 and 4.5 or More Years After Injury**
Lesley Ruttan, PhD, CPsych, Krystle Martin, MA, Anita Liu, HBS, Brenda Colella, MA, Robin E. Green, PhD, CPsych
- S77 **Traumatic Brain Injury in Patients With Traumatic Spinal Cord Injury: Clinical and Economic Consequences**
Cheryl L. Bradbury, PsyD, CPsych, Walter P. Wodchis, PhD, David J. Mikulis, MD, Ephrem G. Pano, BSc, MSc (Cand), Sander L. Hitzig, MA, Colleen F. McGillivray, MD, Fahad N. Ahmad, BSc, B. Catherine Craven, MD, Robin E. Green, PhD, CPsych

Table of Contents (*continued*)

S85 Use of Diffusion-Tensor Imaging in Traumatic Spinal Cord Injury to Identify Concomitant Traumatic Brain Injury

Corie W. Wei, MD, Januthy Tharmakulasingam, BSc, Adrian Crawley, PhD, David M. Kideckel, MSc, David J. Mikulis, MD, Cheryl L. Bradbury, PsyD, CPsych, Robin E. Green, PhD, CPsych

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COMMENTARY

Traumatic Brain Injury: Recovery, Prediction, and the Clinician

Ian H. Robertson, PhD

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Traumatic Brain Injury produces long term disabling effects in a young population of normal life expectancy, yet very little is known about its medium to long-term outcome with the underlying pathologies often invisible to standard brain imaging methods. This collection of papers offers a major advance in defining the course of recovery following TBI, and demonstrating the utility of new brain imaging techniques such as diffusion-tensor imaging to predict outcome and detect hitherto concealed pathologies. These pathologies partly explain the profound behavioral deficits that have been widely demonstrated in TBI but often disputed in courts and elsewhere because of the lack of correlates in underlying brain structure. This edition also offers the first clear evidence of progressive postinsult long-term brain atrophy in some cases of TBI, as well as highlighting important neuropsychological and behavioral predictive variables for recovery, and including the possibility of effective behavioral treatments to mitigate some of these profoundly disabling deficits. This collection of papers is outstanding in a number of ways - in giving the clinician a sense of what can be said to the worried family and what cannot, and in offering researchers important insights from imaging and neuropsychology into the possible mechanisms for the postacute recovery process. But they are important in a third, even more important way - in yielding some real pointers as to how the course of recovery may be influenced.

Key Words: Atrophy; Brain injuries; Magnetic resonance imaging; Neuropsychology; Prognosis; Rehabilitation.

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WHAT DOES ONE SAY to the family of a young person who has been in an accident and is just regaining consciousness? The joy and relief of survival are very quickly followed by questions about the future—about how soon a return to normal life will happen, about what sort of treatment or rehabilitation will be needed, and so on. The possibility of long-term disability—that the person may never regain completely the old roles, abilities, and attributes—may only occur to a minority of families at this stage. The possibility of further decline after the acute recovery phase is an even rarer thought in the minds of both families and professionals.

This collection of articles is outstanding in a number of ways—in giving the clinician a sense of what can be said to the worried family and what cannot, and in offering researchers important insights from imaging and neuropsychology into the

possible mechanisms for the postacute recovery process. But they are important in a third, even more important way: in yielding some real pointers as to how the course of recovery may be influenced.

TBI is an invisible disability in many parts of the world. It is common for people to be discharged after treatment of their orthopedic and other injuries into a bewildering world, which looks and feels very different now that the walking and talking person has profoundly changed. The development of imaging and other methods for diagnosing these often invisible problems may be one of the most important ways of increasing the visibility of the disability.

Wei et al¹ show how DTI can distinguish between spinal cord-injured persons with and without a TBI, the former showing white matter changes in the genu and splenium of the corpus callosum, among other areas. Given that standard MRI often fails to reveal pathologies in people who have had TBI and who are showing significant neuropsychological deficits, the possible use of DTI to increase the capacity for diagnosis, and hence the visibility, of TBI is exciting. Bradbury et al² highlight how important the TBI diagnosis is in the overall pathology and functional status of people who have had spinal cord injury.

Greenberg et al³ report a study of the highest importance to TBI research, in which progressive deterioration in crucial frontal and temporal white matter was observed over a 5-month 2.5-year postacute period. The complementary study by Ng et al⁴ shows that in 10 out of 14 people over a comparable 2-year postacute period, quantitative MRI-measured atrophy in the hippocampi was observed, as well as an increased cerebrospinal fluid volume. Taken together with the neuropsychological study by Till et al⁵ showing that roughly a quarter of persons showed a decline in cognitive function from 1 to 2.5 years postinjury, this collection of studies give a very important—if not daunting—picture on which clinicians will partly base their predictions when talking to people and families affected by TBI.

The study by Green et al⁶ of return to productivity—achieved by roughly 30% of a sample of moderate to severe TBI 1 year postinjury—is of great interest also. The superior methodology of this study compared with previous ones, eliminating motor slowness in measuring cognitive speed, for instance, yields some important and clinically very useful findings. Memory (and only Logical Memory—a memory test with a strong executive function loading) and executive function emerge as significant predictors of this most crucial of outcomes: return to productivity. Timed tests have no particular predictive value, confirming that the role of speed of processing in mediating the deficits of TBI is highly dubious compared

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List of Abbreviations

DTI	diffusion tensor imaging
MRI	magnetic resonance imaging
TBI	traumatic brain injury

with the executive functions so easily disrupted by white matter damage. Assessments at 2 months postinjury did not significantly predict return to productivity, but the 5-month assessment did, quite strongly. In another article examining prediction of outcome, Green et al⁷ demonstrated that using mixed-effects modeling and multiple assessment points, we can look at how (and not just whether) certain moderators may influence the pattern of cognitive recovery (eg, an impact on early vs late recovery). Such a “recuperative” impact of moderators has implications for the mechanisms of impairment and recovery (speaking to cognitive reserve capacity, for example) and on how we might want to deliver therapies. These are studies packed full of clinically applicable information that will help clinicians talk to the family in practical, robust ways.

Till et al⁵ found that those declining neuropsychologically between 12 and 24 years had a significantly smaller amount of therapy at 4.5 months postinjury, and this relationship was not mediated by the severity of the injury. While alcohol and insurance issues may explain this relationship, it is also possible that there is a causal link between the therapy and the decline, although this can only be a hypothesis at this stage. But what of the postacute apoptotic brain changes in white and grey matter, which should be such a source of concern to clinicians and families? Are any of these changes experience-dependent? Are they at least partly modifiable by behavioral or pharmacologic interventions (or indeed a combination of the 2)?

This series of studies points to a new level of sophistication in rehabilitation of TBI. They point to a future in which the nature and timing of rehabilitation are grounded in excellent science, state-of-the-art imaging, and a strong evidence base of effectiveness.⁸ The opening article by Christensen et al⁹ provides the context for the above articles, describing the sound methodologies and powerful statistical approaches of this larger program of research. The study by Bradbury et al¹⁰ of cognitive behavior therapy for TBI is an excellent exemplar of the possibility of behavior change, and the challenge now is first to develop more such methods and second to integrate them into a theoretic understanding of the nature of the brain impairment and its psychologic downstream effects.

Or perhaps one should also consider the possibility of psychologic impairments, which have downstream brain effects. The effects of stress on hippocampal function in nonbrain-damaged people is an example of this,¹¹ and it may be that the shockingly changed world that the brain-injured person faces results in psychologic stressors that exacerbate the brain impairments caused by the original injury. It is not surprising, then, that the meta-analysis by Ruttan et al¹² confirmed chronic neuropsychological impairments at both 1 year and 4.5+ years postinjury.

This series of articles is of the highest importance and is likely to have far-reaching consequences for the lives of people with TBI and their families throughout the world.

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ORIGINAL ARTICLE

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

Bruce K. Christensen, PhD, CPsych, Brenda Colella, MA, Elizabeth Inness, MSc, Deborah Hebert, MSc (Kin), Georges Monette, PhD, Mark Bayley, MD, FRCP(C), Robin E. Green, PhD, CPsych

ABSTRACT. Christensen B, Colella B, Inness E, Hebert D, Monette G, Bayley M, Green RE. Recovery of cognitive function after traumatic brain injury: a multilevel modeling analysis of Canadian outcomes. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S3-15.

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.

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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 FIM⁶⁻¹² 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-

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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

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 al⁷⁰ 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, Kolb⁷⁴ 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 Morris⁷⁷ 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 al⁷⁸ found

that the use of constraint induced movement therapy immediately postinjury results in poorer outcomes in animals. As well, Humm et al⁷⁹ 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 anal-

ysis. 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 al⁶⁶ 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 al⁶⁷ 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 al⁵⁴ 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 \pm SD, 37.37 \pm 15.49y) men (80%) with a high school education (mean level of education \pm SD, 12.71 \pm 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 \pm SD, 6.97 \pm 3.59), which resulted in an approximately 40-day acute care hospitalization (mean acute care length of stay \pm SD, 38.03 \pm 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 \pm SD estimated premorbid IQ (indexed

via the North American Adult Reading Test⁸⁴ or Wechsler Test of Adult Reading⁸⁵) for the sample was 100.43 \pm 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 functioning.^{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}
	Symbol Digit Modalities Test (written)	Smith, 1982 ⁸⁹
Speed of Processing Motor	Trail-Making Test part B	Lezak, 1995 ^{†1}
	Stroop Color-Word Test—Color Naming	Lezak, 1995 ^{†1}
Speed of Processing Simple	Stroop Color-Word Test—Word Naming	Lezak, 1995 ^{†1}
	WAIS-III Similarities	Wechsler, 1997 ^{†87}
Verbal Abstraction	WAIS-III Block Design	Wechsler, 1997 ^{†87}
Visuospatial	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 al⁹³), 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 reliability⁹⁴ 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 Green⁹³). 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

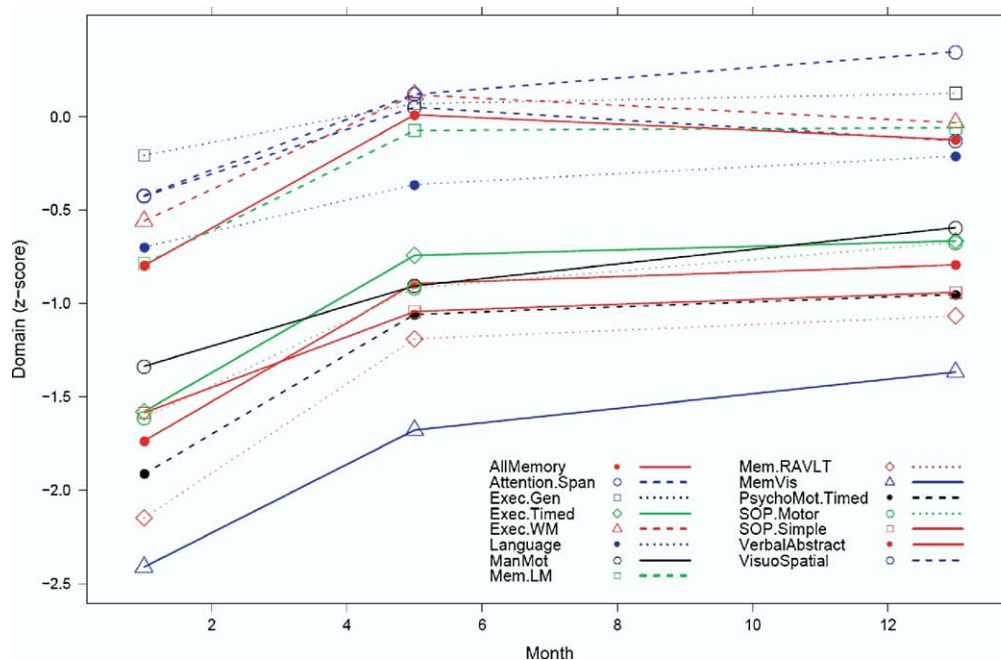


Fig 1. Average recovery curves for all participants with TBI plotted as a function of cognitive domain. Neuropsychological assessment occurred at 2, 5, and 12 months postinjury. Domain scores are represented as standard scores and calculated using external normative data (see Methods). Normative average 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 crite-

tion 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		
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		
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
	Random	Premorbid IQ	0.14	0.132	1.16	.274
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		
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		
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 Visuo-

spatial 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
Months 5-12	Verbal Abstraction vs Language	0.47	0.202	2.37	.018	1.0
	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-analysis⁹⁵ 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 al⁹⁵ 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 al⁶⁷ 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 to 12 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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Examining Moderators of Cognitive Recovery Trajectories After Moderate to Severe Traumatic Brain Injury

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ABSTRACT. Green RE, Colella B, Christensen B, Johns K, Frasca D, Bayley M, Monette G. Examining moderators of cognitive recovery trajectories after moderate to severe traumatic brain injury. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S16-24.

Objectives: To examine the influence of cognitive reserve-related moderator variables on recovery trajectories during the first year after traumatic brain injury (TBI). Using mixed effects models, we measured (1) the level of cognitive function at 2 and 12 months postinjury and (2) the trajectories of cognitive recovery during the first 12 months postinjury.

Design: Repeated-measures design with neuropsychological testing at 2, 5, and 12 months postinjury.

Setting: Large, urban inpatient neurorehabilitation program.

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

Interventions: Not applicable.

Main Outcome Measures: Primary outcomes: neuropsychological composite scores including simple speed of processing, complex speed of processing, memory, untimed executive functions, and attention span. Primary predictors: age, estimated premorbid intelligence quotient (IQ), and years of education.

Results: Only age significantly moderated trajectories. Decreasing age significantly enhanced recovery of speed of processing, both simple (2–12mo postinjury, $P < .001$) and complex (2–12mo postinjury, $P < .05$; 5–12mo postinjury, $P < .005$). Decreasing age and increasing estimated premorbid IQ were associated with higher performance at 2 and 12mo postinjury for simple speed of processing (premorbid IQ, 2 and 12mo), complex speed of processing (age, 2 and 12mo), untimed executive functions (premorbid IQ, 2 and 12mo), and memory (premorbid IQ, 2 and 12mo).

Conclusions: Recovery of speed of processing (both simple and complex) was favorably moderated by younger age. Older age is associated with more neuronal loss and less integrity of white matter, and speed of processing is associated with white matter networks. The recuperative effects of younger age may therefore be attributable to greater reserve capacity (as indexed by white matter integrity). Lower age and higher estimated premorbid IQ were associated with higher functioning on a variety of cognitive outcomes. This may reflect the buffering effects of reserve capacity or premorbid differences in age and

IQ-related cognitive functioning. Implications for rehabilitation and recovery mechanisms are discussed.

Key Words: Brain injuries; Prognosis; Rehabilitation.

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AFTER TRAUMATIC brain injury, a pressing question of patients and families is whether a patient will recover their preinjury level of cognitive functioning, and if so, by when. However, the heterogeneity of brain injuries and the people that sustain them represents a challenge for outcome prediction, as does a growing but incomplete understanding of the mechanisms underlying recovery. Consequently, the ability of clinicians to predict cognitive outcomes is modest, despite much research in this area.¹⁻²¹

The bulk of research to date examines the predictive validity of injury severity and demographic variables.¹⁻¹⁰ Injury severity studies have generally shown that duration of PTA and length of coma predict longer-term cognitive outcome,^{1,4,5,7,10-15} and that the GCS predicts initial level of function, but demonstrates limited correlation with outcome at 1 year.^{1,4-6,13} Other measures, too, have been observed to correlate with neuropsychological outcome, such as the Head-Abbreviated Injury Scale.^{3,21} Demographic variables shown to correlate with poorer cognitive outcome after TBI include advancing age,^{8,10,16,21} low education level,^{9,12,16} sex (male),¹² and minority status.¹²

Table 1 presents a summary of studies examining demographic and injury-related predictors of neuropsychological outcome. As illustrated in the table, while a predictor may account for significant outcome variance in some studies, other studies using the same predictor variables may show weak or no association with cognitive outcomes. This is likely explained by differences across studies in outcome measures, timing of assessments, and sample characteristics. However, methodologic limitations, too, may account for inconsistencies across studies. As noted by Chu et al,¹⁰ many studies employ short-term follow-up assessments, very small sample sizes, and weaknesses in statistical analysis. With regard to the last, most longitudinal studies of cognitive recovery have not allowed for the heterogeneity in recovery outcomes to be examined because they have used multivariate analysis of variance. Chu

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List of Abbreviations

GCS	Glasgow Coma Scale
IQ	intelligence quotient
LOS	length of stay
NAART	North American Adult Reading Test
PTA	posttraumatic amnesia
RAVLT	Rey Auditory Verbal Learning Test
TBI	traumatic brain injury
TMT-A	Trail-Making Test part A
TMT-B	Trail-Making Test part B
WTAR	Wechsler Test of Adult Reading

Table 1: Summary of Literature for Demographic and Injury-Related Predictors of Cognitive Outcome

Variables	Main Findings							
	Positive Findings				Negative/Weak Findings			
	Study	Design		Cognitive Tests*	Study	Design		Cognitive Tests
Pro/Ret		Size	Pro/Ret			Size		
Demographic	Kesler et al ¹⁷	Pro	S	Battery	Chu et al ^{10†}	Ret		RAVLT
	Niemeier et al ¹²	Ret	L	WCST	Lannoo et al ⁵	Pro	L	Battery
	Novack et al ¹³	Pro	L	Battery	Millis et al ⁸	Ret	M	Battery
	Ruff et al ⁹	Ret	S	Battery			L	
	Sherer et al ¹⁶	Pro	M	Battery				
Age	Chu et al ^{10†}	Ret	L	RAVLT	Chu et al ^{10†}	Ret	L	RAVLT
	Millis et al ⁸	Ret	L	Battery	Lannoo et al ⁵	Pro	M	Battery
	Novack et al ¹³	Pro	L	Battery	Lezak et al ^{18†}	Pro	S	RAVLT; DS
	Sherer et al ¹⁶	Pro	M	Battery	Ruff et al ⁹	Ret	S	Battery
	Zwaagstra et al ^{21†}	Ret	S	SOP				
Premorbid IQ					Kesler et al ¹⁷	Pro	S	Battery
Injury-Related	Positive Findings				Negative/Weak Findings			
	Study	Pro/Ret	Size	Cognitive Tests*	Study	Pro/Ret	Size	Cognitive Tests
Duration of PTA	Chu et al ^{10†}	Ret	L	RAVLT	Chu et al ^{10†}	Ret	L	RAVLT
	Hellawell et al ^{4†}	Pro	M	Battery	Formisano et al ¹⁹	Pro	S	Battery
	Lannoo et al ⁵	Pro	M	Batter	Millis et al ⁸	Ret	L	Battery
	Levin et al ¹¹	N/A	N/A	Memory	Novack et al ¹³	Pro	L	Battery
	Mandelberg ²⁰	Pro	L	WAIS-VIQ/PIQ				
Length of coma	Dikmen et al ¹	Pro	M	Battery	Ruff et al ⁹	Ret	S	Battery
	Lannoo et al ⁵	Pro	M	Battery	Formisano et al ¹⁹	Pro	S	Battery
	Levin et al ⁷	Pro	S	Battery	Lannoo et al ⁵	Pro	M	Battery
	Lezak et al ^{18†}	Pro	S	RAVLT; DS				
	Niemeier et al ¹²	Ret	L	WCST				
	Ross et al ¹⁴	Pro	L	Battery				
	Wong et al ¹⁵	Ret	L	WAIS R-PIQ/VIQ				
GCS	Dikmen et al ¹	Pro	M	Battery	Lannoo et al ⁵	Pro	M	Battery
	Levin et al ⁶	Pro	L	Battery	Novack et al ¹³	Pro	L	Battery
					Ruff et al ⁹	Ret	S	Battery
Acute Care LOS					Novack et al ¹³	Pro	L	Battery
					Formisano et al ¹⁹	Pro	S	Battery
Time since injury								

NOTE. Summary information is provided for preinjury demographic and injury-related predictors, experimental design, and outcome measures of studies. Only predictive (as opposed to concurrent) studies have been included. Tests with 3 or more assessments are noted. Abbreviations: DS, digit span; L, large sample size (N>100); M, medium sample size (N=51-100); PIQ, performance IQ; Pro, prospective study; Ret, retrospective study; S, small sample size (N=0-50); SOP, speed of processing; VIQ, verbal IQ; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WCST, Wisconsin Cart Sorting Test; WMS-R, Wechsler Memory Scale-Revised.

*Where more than 3 cognitive tests were measured in a study, we have used the word "Battery."

†Denotes that 3 or more time points of assessments were used.

et al¹⁰ highlighted the value of using mixed-effects models, which can accommodate this intraindividual heterogeneity and have the additional advantage of accommodating missing data, which is a common feature of longitudinal TBI studies.²²

One of the most important benefits of mixed effects models for studying recovery from TBI is that they allow for an examination of the impact of predictor variables on recovery trajectories. Most previous studies have examined the influence of variables on level of function, either at the acute or subacute stages. Such studies can shed light on the protective or buffering effects of a moderator—that is, whether a predictor variable (eg, higher years of education) results in a milder impact of the brain injury on level of cognitive performance. However, an understanding of whether and how a moderator might augment recovery can only be achieved by an examination of recovery trajectories. Determining whether a moderator can enhance or diminish recovery, and whether such putative effects would manifest during the early or chronic stages of recovery, could be informative for prognostication and for decisions regarding distribution of clinical resources. For ex-

ample, patients at risk for a slow early recovery for a given cognitive function could be alerted to this, and targeted intervention to offset the slow early recovery might theoretically enhance overall recovery of that function.

Understanding the impact of moderators on recovery trajectories might also allow for a greater understanding of the mechanisms of recovery. For example, some variables examined as predictors of TBI outcome are associated directly or indirectly with the notion of reserve capacity (eg, premorbid IQ, years of education, age). The concept of reserve capacity can be used as a heuristic for discussing brain injury. This construct derives from the observation that the degree of brain pathology during disease (or after brain injury) is not directly proportionate to the clinical manifestations of that pathology.^{17,23,24} Reserve capacity has been described as being both actively accrued, through exogenous influences such as education and lifestyle, and passively existing because of endogenous factors that determine premorbid brain size, innate intelligence, or numbers of neurons. Implementation of reserve capacity has been characterized as both the compensatory

recruitment of alternative pathways (or altered, existing networks) to perform a function and as the consumption of a finite reserve, which, once depleted, gives way to the clinical manifestations of illness.^{17,25}

If reserve capacity serves solely to buffer the effects of injury, then we might expect an impact of reserve capacity variables on initial level of cognitive performance after brain injury,¹⁹ but not on recovery trajectories. On the other hand, if reserve capacity confers resources that support restitution of function or functional reorganization of the brain during recovery,²⁶⁻²⁸ then we would arguably expect an impact of those variables on the trajectories of recovery. A better understanding of the nature of reserve capacity could be gained by identifying which cognitive trajectories were moderated by which predictor variables. For example, if recovery of speed of processing (associated with functional connectivity and mediated by white matter tracts^{29,30}) were moderated by years of education and/or age, one might argue that in the healthy brain, reserve capacity could accrue with years of education (through increased complexity/connectivity of white matter tracts) or diminish through age-related white matter loss.³¹

Only a handful of cognitive recovery studies in TBI have examined recovery trajectories, and of these, few have used mixed-effects models.^{10,15,21,32} Still fewer have examined directly the influence of reserve capacity-related variables on recovery. Chu et al¹⁰ examined the impact of age on memory recovery from 1 to 5 years postinjury, using the total learning score of the RAVLT.³³ Their study retrospectively examined 794 patients from a larger group of patients from a multisite study of TBI recovery (the TBI Model System program patients); they also examined length of PTA and early postinjury memory performance as moderators of recovery. They found that age and length of PTA significantly predicted level of memory performance at 1 year postinjury, but none of the variables influenced the trajectory of recovery from 1 to 5 years postinjury (see table 1). One limitation of the Chu¹⁰ study was that, looking over a long period, Chu¹⁰ used a quadratic term to capture possible curvature in the recovery trajectory. However, because TBI recovery trajectories are likely to rise to an asymptotic level, an asymptotic model may have been more appropriate in this case (for discussion, see Wong et al¹⁵). Zwaagstra et al²¹ used mixed-effects modeling to examine 24 severely brain-injured patients with TBI on a small group of tests of speed of processing. Testing patients from 3 months to 4 years postinjury, they found that age (and duration of coma) moderated recovery on simple and complex tests of speed of processing.

In the current study, we examined predictors of cognitive recovery in a prospective study with low attrition using mixed effects modeling. We examined recovery over the first year postinjury using a linear spline model (ie, a model that allows a possible change in rate of recovery around 5 months postinjury) to capture the asymptotic nature of recovery. (Because we were not studying recovery over a long period, a true asymptotic model was not an option). We examined demographic predictors that are associated with cognitive reserve: age (indirectly related through loss of neurons/white matter integrity),³¹ years of education, and estimated premorbid intellectual function. The cognitive outcome variables examined were composite scores representing a series of cognitive domains known to be disrupted after TBI: simple and complex speed of processing, memory, executive function, and attention span.³³ Composite scores were used because of the increased reliability attained by aggregating related tests. We were particularly interested in examining speed of processing because it is arguably the most ubiquitous cognitive deficit in TBI,^{29,34-41} and

its recovery the most protracted.^{21,30,42} We examined the moderating influences of these variables on level of cognitive function at 2 months and 12 months postinjury, and on recovery trajectories from 2 to 5, 5 to 12, and 2 to 12 months postinjury.

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

Patients with TBI. The 75 patients with TBI in this study had been recruited to a larger study investigating the natural history of cognitive and motor recovery after TBI at the Neurorehabilitation Program of the Toronto Rehabilitation Institute. The clinical program is publicly funded, but it also receives patients who have motor vehicle collision insurance and other forms of private insurance. The catchment area for the program is province-wide. Overall, the program sees a broad cross-section of patients of differing age (≥ 17 y), socioeconomic status, and ethnicity.

Inclusion criteria for the study were as follows: (1) acute care medical diagnosis of TBI, (2) PTA of 1 hour or more and/or GCS of 12 or less either at emergency or the scene of accident and/or positive computed tomography or magnetic resonance imaging findings, (3) age between 17 and 80, (4) able to follow simple commands in English based on speech language pathologist intake assessment, and (5) competency to provide informed consent for study or availability of a legal decision-maker.

Exclusion criteria included the following: (1) orthopedic injuries affecting both upper extremities and/or both lower extremities (relevant to the larger study, which also examined motor recovery); (2) diseases primarily or frequently affecting the central nervous system, including dementia of Alzheimer type, Parkinsons disease, multiple sclerosis, Huntingtons disease, lupus, stroke-based on medical records, and screening of family members for patients older than 50 years; (3) history of psychotic disorder; (4) not emerged from PTA by 6 weeks postinjury, as measured by the Galveston Orientation Amnesia Test⁴³; (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)⁴⁴ at any of the assessments.

Table 2 provides demographic and injury characteristics of the sample, which is a typical sample of moderate to severe TBI: predominantly male, average estimated premorbid IQ, and preponderance of injuries caused by motor vehicle collisions. However, because the study excludes patients who were not out of PTA by 6 weeks postinjury, patients with the most severe injuries were not included in the study.

Seventy-eight patients were initially recruited. Of those, 3 were not included in the current analyses. One was suspected of having a comorbid dementia, and 2 developed new neurologic disorders during the course of the study (hydrocephalus and Korsakoff encephalopathy). Of the 75 patients included, 50 completed 3 assessments, 17 completed 2 assessments, and 8 completed 1 assessment.

Materials

Neuropsychological test battery. All of the tests were selected based on a priori clinical and experimental consensus regarding the cognitive domains most affected by TBI, and on the known validity and reliability of the tests for TBI. Cognitive domains assessed included the following:

Table 2: Injury and Demographic Characteristics of Sample (N=75)

Variable	Proportion	Range
Age (y)	37.37±15.49	(17–79)
Education (y)	12.71±2.78	(7–21)
Premorbid IQ (n=62)	100.43±12.51	(78–124)
Sex (% male:female)	80:20	
Socioeconomic status (%) (based on Hollingshead classification)		
1 (Major business/professional)	10.0	
2 (Medium business/minor professional, technical)	35.7	
3 (Skilled craftsperson, clerical, sales worker)	20.0	
4 (Machine operator, semiskilled worker)	31.4	
5 (Unskilled laborer, menial service worker)	1.4	
Type of injury (%)		
Motor vehicle collision	55.7	
Fall	32.9	
Assault	8.6	
Sports injury	2.9	
Acute care LOS (d)	38.03±17.17	(9–88)
GCS (lowest of recorded scores)	6.97±3.59	(2T–14)
Mild (13–15)	11.4	
Moderate (9–12)	15.7	
Severe (≤8)	58.6	
Missing data	14.3	
Length of PTA (%)		
<5min (very mild)	5.7	
1–24h (moderate)	2.9	
1–7d (severe)	17.1	
1–4wk (very severe)	38.6	
>4wk (extremely severe)	12.9	
Missing data	22.9	

NOTE. Values are means ± SDs or as otherwise noted.

1. Simple speed of processing. This domain was composed of Stroop reading (a test of speeded single word reading) and Stroop color naming (a test of speeded color naming).⁴⁵
2. Complex speed of processing. This domain included the following: TMT-B minus TMT-A³³ (connect-the-dots style, timed psychomotor tests; TMT-A measures speeded visual attention and scanning; TMT-B additionally measures speeded set shifting); the Hayling Sentence Completion Test (modified for computerized administration)⁴⁶ congruent minus incongruent conditions (a test of generative and inhibitory processes in which the former requires speeded completion of sentences missing the last word with a word that makes sense in the context of the sentence, and the latter requires speeded sentence completion with a word that does not make sense in the context of the sentence); choice reaction time (a test requiring a speeded decision made to a visual target—the orientation of an arrow) minus simple reaction time (a speeded presence/absence response to a visual target, ie, an arrow); and the Symbol Digit Modalities Test—Oral⁴⁷ (a timed test requiring pairing of symbols with digits).
3. Executive function. This domain included the digit and spatial spans backward tasks (tests requiring the immediate repetition backward of strings of digits or visual

sequences of increasing length)⁴⁸; and the Wechsler Adult Intelligence Scale, verbal abstraction test (a test requiring identification of common threads between pairs of words).^{49,50}

4. Simple attention. This was composed of the digit and spatial spans forward tasks (immediate repetition of strings of digits or visual sequences of increasing length).⁴⁸
5. Organized and unorganized verbal and visuospatial learning and memory. This last domain included the RAVLT³³ (a test of recall and recognition of an unorganized list of 15 words); the Rey Visual Design Learning Test³³ (a visuospatial analog to RAVLT); and the Wechsler Memory Scale—III, logical memory⁴⁸ (a test requiring the immediate and delayed recall of prose passages).

None of the neuropsychological tests have appreciable floor or ceiling effects for patients with moderate to severe TBI. Most tests (except for TMT-A and Symbol Digit Modalities) have alternate forms, which were administered on repeat testing to minimize practice effects.

In order to avoid contamination of findings by orthopedic injury or central motor deficits, all timed tests either did not have manual motor demands or had motor contributions parceled out through a subtraction approach (eg, TMT-B minus TMT-A) in order to measure mental processing speed and not manual motor speed. The test battery described was part of a larger comprehensive neuropsychological battery, which required approximately 4.5 hours to administer.

Collection of moderator variables, age, premorbid IQ, and years of education. Information about age and highest level of education attained was collected during a structured interview from patients, and corroborated by caregivers where necessary. Estimated premorbid IQ was estimated for each participant using the WTAR⁵¹ or the NAART.⁵² (Note that the study switched from the NAART to the WTAR because the latter has been demonstrated to show good reliability for moderate and severe TBI.⁵³)

Collection of control variables (injury severity), GCS, PTA, and acute care LOS. This information was abstracted from the hospital medical records wherever possible. The lowest GCS score recorded for each patient, either at the scene of injury or in the emergency department, was collected where available and used as a continuous, ordinal scale value. Where information related to PTA was not recorded in the medical record, questioning of the patient and caregivers was undertaken during a structured interview. Length of PTA was described according to the classification described by Lezak et al³³ and used as a continuous ordinal scale value. Acute care LOS, in days, was calculated based on admission and discharge dates from the acute care hospital.

Design and Procedures

The 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. When the same form was administered a second time (ie, where only 2 alternate forms were

available), this administration occurred no less than 10 months after the first administration in order to minimize practice effects. Order of alternate forms was counterbalanced across subjects. The 2-month testing window ranged from 1 to 3 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 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. In order to increase reliability of neuropsychological tests, all cognitive test scores were transformed to a common metric and combined into their respective larger aggregate. 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.) To combine tests without normative data, we used the means and SDs of the tests in the later stages of recovery (ie, 5mo and 1y postinjury) to generate a z score. 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.

Mixed-effects models. With longitudinal mixed models, it is possible to study whether expected values of the intercepts and slopes—that is, the level and shape of recovery trajectories—are affected by other variables. Participants were tested at approximately 2, 5, and 12 months after injury, and the rate of recovery may differ between the 2-month to 5-month period and the 5-month to 12-month period. A model for individual recovery trajectories that allows a possible change in rate around 5 months uses a linear spline. The model at the individual level for a response variable Y is given by the following:

$$Y_{it} = \beta_{0i} + \beta_{1i}T_{it} + \beta_{2i}(T_{it} - 5)_+ + \varepsilon_{it}$$

where Y_{it} is the measured response variable for subject i on occasion t , T_{it} is the number of months postinjury when testing was performed, measured to the nearest day, and the quantity $(T_{it} - 5)_+$ equals 0 if T_{it} and equals $T_{it} - 5$ if $T_{it} \geq 5$. The error term, ε_{it} , which is assumed to have a normative distribution with mean 0 and unknown variance σ^2_{ε} , represents the random variability in the measurement of the response for the i th subject.

These definitions for the variables representing time postinjury imply the following interpretations of the parameters β_{0i} , β_{1i} , and β_{2i} : β_{0i} is the intercept at time $T=0$, β_{1i} is the rate of change a month before the fifth month, $\beta_{1i} + \beta_{2i}$ is the rate of change a month after the fifth month, and β_{2i} is the difference between these 2 rates. The expected response level at time T postinjury is given by the following:

$$\beta_{0i} + \beta_{1i}T + \beta_{2i}(T - 5)_+$$

The parameters β_{0i} , β_{1i} , and β_{2i} of the individual-level model are then treated as outcomes in a between-individual model in which the relationship between trajectories and other variables, such as age, can be estimated.

For example, a model to study the relationship between age and the extent and speed of recovery could have the following form:

$$\beta_{0i} = \gamma_{00} + \gamma_{01}age.z_i + \delta_{0i}$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11}age.z_i + \delta_{1i}$$

$$\beta_{2i} = \gamma_{20} + \gamma_{21}age.z_i + \delta_{2i}$$

where $age.z_i$ is a z score for the age of subject i at injury. The error terms, δ_{0i} , δ_{1i} and δ_{2i} are assumed to have a multivariate normative distribution with mean 0 and a variance covariance matrix to be estimated or specified in the analysis. These error terms represent departures of the i th subject's trajectory from the trajectory predicted by age. If the variance of δ_{1i} or δ_{2i} is estimated to be very small, the variance and associated covariance may be treated as if they were 0.

For g equal to 1, 2, or 3, the parameters γ_{g0} are the mean population values of the corresponding β_{g0} for a subject whose age equals the sample average, and γ_{g1} is the expected difference in β_{g0} associated with a difference of 1 SD of age. If γ_{11} and γ_{12} are not both 0, then age acts as a moderator because there is an interaction between age and time in their effect on the response.

In short, mixed-effects models allow us to examine the impact of potential moderators on recovery trajectories as well as on the level of impairment (in this case, at 2 and 12mo postinjury). The purpose of these analyses is to identify which variables affect the shape of recovery trajectories. The mixed-effects model hypothesizes a recovery trajectory for each subject, where trajectories vary randomly from subject to subject in both height and shape, corresponding to differences in the degree and speed of recovery. Using the first 3 waves of the data in which subjects were measured at 2, 5, and 12 months postinjury, we studied the amount of recovery from 2 to 5 months, from 5 to 12 months, and from 2 to 12 months postinjury.

Five outcome measures (aggregates) were examined. The first (preliminary) analyses undertaken were simple predictor (or regression) models in which we sought those variables that accounted for the most variance at initial level of performance that were themselves not affected by performance level (as would be a behavioral measure, for example) and that were available for most subjects. Identifying these variables allowed us to then use them as covariates in the recovery models to control for differences between participants in terms of initial level of impairment (ie, different starting points). We included age, estimated premorbid IQ, years of education, length of PTA, GCS, and acute care LOS and looked at these potential control variables individually and interactively.

In the next set of analyses, the effects of the 3 moderator variables of interest (age, estimated premorbid IQ, and years of education) on the 5 cognitive outcome aggregates were initially examined. We adjusted for multiple comparisons, with an initial P value of .05, using a Bonferroni-Holm adjustment.⁵⁴ We then examined for each variable whether there was evidence of an overall effect—that is, the contribution of the moderator to the model through both main effects and interactions combined. Taking a conservative approach, only if an overall effect was present after adjusting for multiple comparisons did we then examine whether the predictor was significantly related to the slopes (ie, 2–5, 5–12, or 2–12mo) and/or levels (at 2mo or 1y) for the trajectory.

RESULTS

In preliminary models examined for all cognitive aggregates, moderators, and control variables, premorbid IQ was found to be a significant predictor of initial level of impairment and was used as a covariate in subsequent models, except those exam-

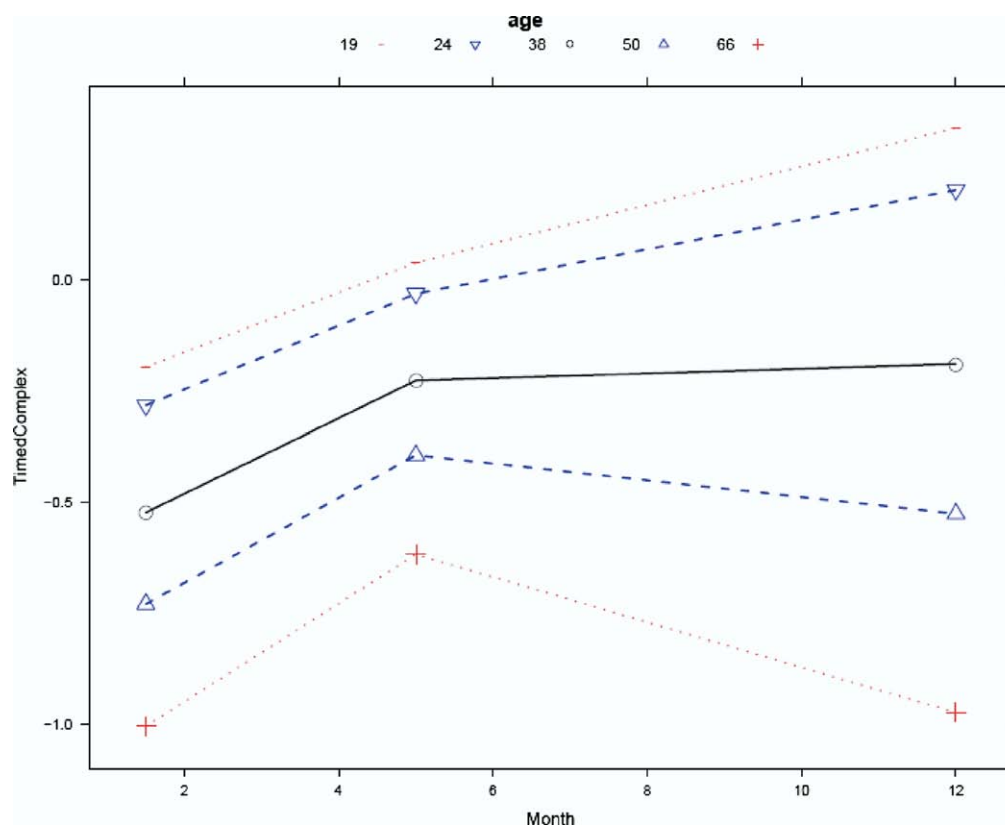


Fig 1. Relationship between age and recovery of complex speed of processing across time. Y-axis values are z scores. The 5 curves on the graph describe the data in quantiles representing age percentiles (eg, the top curve represents the average trajectory for a 19-year-old, which is located at the twentieth percentile, meaning that 20% of the participants are 19 years of age or younger).

ining premorbid IQ as a moderator. In some cases, an interaction between premorbid IQ and age as predictors of initial level of impairment was found (ie, untimed attention–years of education; untimed attention–acute care LOS; memory–premorbid IQ, memory–years of education, memory–acute care LOS), and in these cases, age was added as a covariate in the models.

In the main analyses, after the Bonferroni-Holm adjustment, the significance level for the overall effect was P equal to .013. The variables for which overall effects attained significance were age for the complex speed of processing and simple speed of processing aggregates, and premorbid IQ for the simple speed of processing, untimed executive, and memory aggregates. For these models, we were then able to examine the specific effects of the moderator on the recovery trajectories. Years of education showed no significant overall effects; indeed, none of the findings for years of education approached significance, even prior to adjustment for multiple comparisons.

Age and simple and complex speed of processing. Age moderated overall recovery of simple speed of processing ($F_{3,62}=4.259, P<.01$). On inspection of the specific recovery curves, there was a significant impact of age from 2 to 12 months postinjury ($z_{87}=-3.48, P<.001$).

Age also had a significant overall effect on complex speed of processing ($F_{3,61}=7.437, P<.001$). Figure 1 illustrates the relationship between differing levels of the moderator on the trajectory of complex speed of processing across time. As can be seen in figure 1, there was a significant impact of age on recovery trajectories for complex speed of processing from 2 to 12 months postinjury ($t_{81}=-2.221, P<.05$) and from 5 to 12 months postinjury ($t_{81}=-2.95, P<.005$).

In addition, age significantly predicted outcome at 2 months ($t_{61}=-3.03, P<.005$) and at 12 months postinjury for complex speed of processing ($t_{61}=-4.567, P<.001$).

Premorbid IQ, simple speed of processing tests. Premorbid IQ showed a significant overall effect for simple speed of processing tests ($F_{3,63}=11.27; P<.001$). It did not significantly impact recovery trajectories of the simple speed of processing tests; however, as can be seen in the parallel curves of figure 2, it did show a robust impact on levels of impairment at both 2 months postinjury ($t_{63}=5.613, P<.001$) and 12 months postinjury ($t_{63}=3.513, P<.001$), as illustrated by the differing heights of the curves as a function of premorbid IQ level.

Premorbid IQ, untimed executive tests. Premorbid IQ showed a significant overall effect for untimed executive functioning tests ($F_{3,63}=8.538; P<.001$). As with simple speed of processing, it did not significantly impact recovery trajectories of the untimed executive tests, but it did show a significant impact on levels of impairment at both 2 months postinjury ($t_{63}=4.627, P<.001$) and 12 months postinjury ($t_{63}=2.265, P<.05$).

Premorbid IQ, memory. Premorbid IQ showed a significant overall effect on memory tests ($F_{3,63}=7.89; P<.001$) with a highly significant impact on outcomes at 2 months postinjury ($t_{63}=4.837, P<.001$) and 12 months postinjury ($t_{63}=3.60, P<.001$), but no effect on trajectories.

DISCUSSION

Using mixed-effects models, we examined a series of clinically and theoretically relevant variables with the potential to moderate both the level of cognitive functioning and recovery slopes after TBI. We found that for speed of processing, age significantly moderated the trajectory of recovery as well as

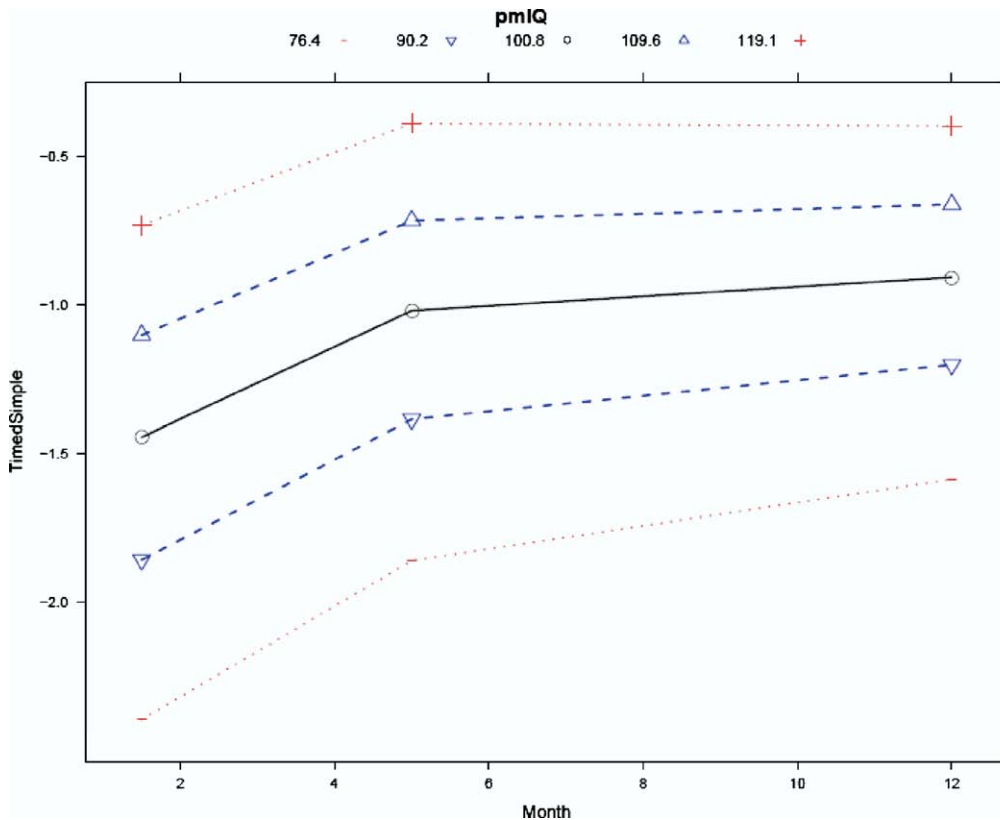


Fig 2. Relationship between premorbid IQ (pmIQ) and recovery of simple speed of processing across time. Y-axis values are z scores. The 5 curves on the graph describe the data in quantiles representing estimated premorbid IQ percentiles (eg, the top curve represents the average trajectory for an individual with an estimated premorbid IQ of 119.1, which is located at the twentieth percentile, meaning that 20% of the participants in our sample have an estimated IQ of 119.1 or higher).

levels of performance at discrete time points during the first year of recovery from TBI. Younger age fostered better recovery from 2 to 12 months postinjury for both simple and complex speed of processing; it also enhanced later recovery in particular (from 5–12mo postinjury) for complex speed of processing. Premorbid IQ influenced outcomes, but only for level of functioning. These results are broadly consistent with those of Chu et al,¹⁰ who, like us, found no moderating effects of age on memory recovery trajectories (1–5y postinjury), and Zwaagstra et al,²¹ who found moderating effects of age on recovery trajectory for speed of processing (3mo–4y postinjury) in a sample of 24 patients. There was no evidence in this study that years of education moderated either recovery trajectories or level of function.

Understanding whether a variable influences the degree of recovery is critical for our full understanding of the recovery process. For example, such information allows us to identify, at different stages of recovery, subgroups of people who are showing greater or lesser recovery. The current findings carry both favorable and unfavorable implications from a clinical point of view. Demographic and injury-related variables cannot be changed; therefore, as pointed out by Chu,¹⁰ it might be better if such factors did not have an impact on recovery. However, an understanding of these factors does allow for better scientific and clinical hypothesis testing on how to enhance outcome.

For example, the current findings revealed that older age was negatively associated with recovery for speed of processing, both simple and complex, but there was no evidence of an effect on memory, untimed executive function, or simple attention. This pattern of findings supports the theoretical possibility that a passive reserve capacity (ie, attributable to endogenous factors) is associated with white matter integrity. Thus,

these findings (together with those of Zwaagstra et al²¹) would support the investigation of treatments that entail targeted interventions to enhance white matter connectivity. From a clinical point of view, the present findings also suggest more selective targeting of therapy for older patients that focuses on speed of processing, particularly during the latter part of the first year postinjury.

It is interesting to note that premorbid IQ and years of education, which are strongly associated with the notion of reserve capacity,^{17,25} did not show any evidence of augmenting recovery in our study. There was some evidence of a buffering effect of premorbid IQ. However, this impact of premorbid IQ on outcome cannot be disentangled here from preinjury effects of IQ on cognitive test performance. Further research, using an IQ and education–matched control group, would enable better quantification of any buffering effects of premorbid IQ (and years of education) on brain injury.

Study Limitations

We sought to control those factors that influenced initial level of performance. For each variable, separate models were constructed to assess which control variables most strongly influenced initial level of performance. Using a single site, prospective design imposes limits on the number of participants that can be recruited over a given period; given sample size constraints, we could include a maximum of 2 control variables in our moderator models. Consequently, control of factors affecting initial level of performance may have been incomplete. A larger sample size is needed to replicate the current findings with more complex models. Stronger statistical evidence is needed, in particular, for acceptance of the null findings in this study, namely the absence of impact of premorbid IQ and years of education on recovery trajectories, and

on the circumscribed impact of age on recovery trajectories for speed of processing only. These null findings, if verified, would have significant clinical and scientific implications. We used a rigid criterion for allowing a close examination of the results from our models. We required that the predictor show a significant overall effect on recovery levels and trajectories, after adjusting for multiple comparisons, and only then would we examine the response levels, specific effects, and interactions. While this approach helped to protect from type I error, our study might have been at risk of missing bona fide moderators of recovery. Again, further research with a larger sample size would be valuable to ascertain whether acceptance of the null is valid.

CONCLUSIONS

Age appears to moderate recovery of speed of processing during the first year after severe TBI. Years of education and premorbid IQ showed no evidence of playing a recuperative role but the latter showed a possible buffering influence. The results have clinical implications and offer hypotheses for future research. Further research is needed using larger samples, which would allow the use of more complex statistical models with multiple control variables. Finally, rehabilitation research targeting white matter connectivity in older patients may be a promising area of future investigation.

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ORIGINAL ARTICLE

Postrecovery Cognitive Decline in Adults With Traumatic Brain Injury

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

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

Design: Observational cohort.

Setting: Inpatient rehabilitation hospital.

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

Interventions: Not applicable.

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

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

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

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

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

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

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

List of Abbreviations

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

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

Himanen et al¹⁵ studied changes in the cognitive performance levels of 61 patients with TBI who were tested twice over an almost 30-year interval. This study measured the evolution of cognitive impairment across 8 neuropsychological tests. Results revealed a significant increase in the overall index of cognitive impairment at approximately 30 years post-TBI relative to the baseline level, which was, on average, 2.5 years postinjury. However, not all patients contributed to this change: while 56% of participants showed decline, 23% showed improvement, and 21% remained at the same level as in the original examination. Again, older age was a risk factor for decline, as was male sex. However, this study too had a high attrition rate (>70%) as the authors pointed out, as well as a biased follow-up sample, consisting of patients who were "... referred to the neurology clinic or neuropsychologist because of a recent nontrivial injury or disability,"^{15(p187)} which would have inflated the true incidence of decline after TBI. Of note, this study controlled for age-related decline over the lengthy follow-up interval by comparing performances of their subjects at each time point to normative data. However, there is mounting evidence that the apolipoprotein E allele 4 increases the likelihood of premature dementia after TBI,¹⁹⁻²¹ which has important implications related to the underlying mechanisms of postrecovery cognitive decline in the aging brain. Therefore, the preponderance of decline in their study may partially reflect the deleterious interactions between aging and TBI.

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

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

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

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

METHODS

Participants

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

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

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

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

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

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

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

NOTE. Values are mean ± SD unless otherwise noted.

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

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

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

Materials

Neuropsychological and clinical psychologic test battery.

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

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

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

Design and Procedures

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

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

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

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

Analyses

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

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

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

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

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

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

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

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

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

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

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

RESULTS

Group Data

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

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

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

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

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

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

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

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

[‡]Based on the Wilcoxon signed-rank test.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* $P < .01$; [†] $P \leq .10$.

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

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

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

funding than decliners (4 of 9), and this difference approached significance ($\chi^2=2.75$, $P=.10$). Because having insurance coverage may explain in part why the nondecliners group received significantly more hours of therapy after discharge, we examined in the overall sample the difference in hours of therapy between individuals who received third-party insurance funding versus those who do not. This comparison confirmed our expectation: individuals who were insured ($n=22$) received more hours of therapy after discharge (mean ± SD, 6.69 ± 4.4 h) than those who were not insured ($n=11$; mean ± SD, 3.32 ± 5.2 h), and this difference approached significance ($t_{31}=1.96$, $P=.06$). Of note, all of the patients who received third-party insurance were patients after MVC.

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

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

DISCUSSION

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

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

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

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

substance abuse and decline would seem to warrant further investigation.

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

Mechanisms of Postrecovery Cognitive Decline

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

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

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

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

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

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

Study Limitations

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

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

Clinical Implications

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

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

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

CONCLUSIONS

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

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

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ORIGINAL ARTICLE

Magnetic Resonance Imaging Evidence of Progression of Subacute Brain Atrophy in Moderate to Severe Traumatic Brain Injury

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ABSTRACT. Ng K, Mikulis DJ, Glazer J, Kabani N, Till C, Greenberg G, Thompson A, Lazinski D, Agid R, Colella B, Green RE. Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2): S35-44.

Objective: To demonstrate subacute progression of brain atrophy (from 4.5–29mo postinjury) in moderate to severe traumatic brain injury (TBI) using structural magnetic resonance imaging (MRI).

Design: Within-subjects, repeated-measures design.

Setting: Inpatient neurorehabilitation program and teaching hospital (MRI department).

Participants: Adults (N=14) with moderate to severe TBI.

Interventions: Not applicable.

Main Outcome Measures: Neuroradiologist readings and volumetric measurements (total brain cerebrospinal fluid and hippocampus) at 4.5 months and 2.5 years postinjury.

Results: Ten of 14 patients showed visible atrophy progression. Significant increase in cerebrospinal fluid (CSF) volume ($t_{13} = -4.073$, $P < .001$) and decrease in right and left hippocampal volumes ($t_{13} = 4.221$, $P < .001$ and $t_{13} = 3.078$, $P < .005$, respectively) were observed from 4.5 months to 2.5 years. Compared with published normative data, patients with TBI showed significantly more pathologic percent annual volume change for the hippocampi ($t_{26} = -3.864$, $P < .001$, right; and $t_{26} = -2.737$, $P < .01$, left), and a trend for CSF ($t_{26} = 1.655$, $P = .059$).

Conclusions: This study provides strong MRI evidence for subacute progression of atrophy, as distinct from early, acute neurologic changes observed.

Key Words: Atrophy; Brain injuries; Magnetic resonance imaging; Follow-up studies; Rehabilitation.

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MODERATE TO SEVERE TBI has an incidence of approximately 200 per 100,000 in developed countries worldwide.¹ Because its prevalence is particularly high in

young adults,¹ TBI can cause decades of disability with associated emotional and financial hardships.² Disability is caused in large part by the cognitive consequences of TBI,³ which are the result of both focal and diffuse injury to the brain,^{4,5} often in combination.⁶ Neuroimaging studies of subacute patients show a range of sequelae that includes generalized atrophy, cortical atrophy, hippocampal atrophy, white matter degeneration, and ventricular dilatation.⁷⁻¹⁶

The natural history of cognitive and functional recovery has been widely studied.¹⁷⁻²⁵ Cognitive recovery is characterized by a period of rapid recovery in the first months postinjury, followed by a plateau in recovery by 6 to 18 months after injury.²⁶⁻³¹ After this period, it is assumed that patients maintain this level of recovery. There have been far fewer studies in TBI of neuroradiologic change over time. Here, research to date suggests that relative to cognitive plateau, the stabilization of neuroimaging findings occurs much earlier, after the acute effects of injury (eg, contusion, hematoma, and edema) have resolved.^{32,33}

There is suggestion in the literature, however, that some subsequent deterioration on cognitive and neuroradiologic indices may occur. A small number of studies on long-term cognitive recovery have shown delayed cognitive decline in 15% to 56% of patients in the samples examined,³⁴⁻³⁷ with 1 study³⁷ demonstrating cognitive decline from as early as 5 months postinjury. These findings raise the question whether observed cognitive decline might be underlain by atrophic changes to the brain.

A small number of human studies^{38,39} and animal studies^{40,41} have investigated the possibility of progressive atrophy of the brain. However, to date, a critical question that persists is whether the observation of change over time in past studies represents secondary atrophy, per se, or rather the natural history of the primary insult itself that takes place during the first months postinjury (eg, clearing of traumatized cells, with

List of Abbreviations

CSF	cerebrospinal fluid
FLAIR	fluid attenuated inversion recovery
FOV	field of view
GCS	Glasgow Coma Scale
GRE	gradient-recalled echo
ICC	intraclass correlation coefficient
IQ	intelligence quotient
IR	inversion recovery
MRI	magnetic resonance imaging
PD	proton density
TBI	traumatic brain injury
3D	three-dimensional
TE	echo time
TI	inversion time
TR	repetition time

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microglial proliferation and edema, hyperemia, global swelling, resolution of edema, hyperemia and loss of inflammatory cells, involuting hematoma, encephalomalacia). This question largely remains because of the timing of the initial examination in past studies, performed within the first months^{38,39} or even days of injury,⁴²⁻⁴⁴ precluding differentiation of secondary atrophy from stabilization of the brain; for example, in 1 longitudinal study, the timing of the first assessment ranged from 7 to 430 days postinjury.⁴⁵

In addition, neuroimaging studies speaking to the question of atrophy have employed different acquisition parameters at the initial and follow-up assessments⁴⁴ or have used experimental designs that were partially or fully cross-sectional.^{27,39,45} Consequently, comparisons across time were vulnerable to confounding by measurement or subject variability. Most past studies have also been retrospective, with sample bias as pointed out by the authors, and with time windows of initial and follow-up assessments that were not predetermined, and sometimes overlapping.⁴³⁻⁴⁵

Further research into the question of progression of atrophy is needed to ascertain whether these preliminary indications of secondary atrophy are bona fide or simply represent the natural progression of the initial lesion. Therefore, in order to build on previous research, we performed a prospective, within-subjects study with a predetermined time window after injury for the initial scan (3.5–5.5mo postinjury) and for the follow-up scan (2–3.5y postinjury), without overlap between the initial and follow-up time windows. Identical MRI parameters were employed across the assessments, and critically, the time window for the initial imaging session was selected to be late enough that brain changes caused by the acute injury would have resolved, but early enough to avert overlap with the onset of putative postrecovery atrophy.

We extended previous studies by including a combination of expert visual ratings of MRI with volumetric assessments, employing parameters of the latter that have been used in previous studies examining this question (ie, CSF and hippocampal volume).^{38,45} We compared volumetric change over time in our study to age-stratified and sex-stratified normative data published in the literature.^{10,46}

We hypothesized that there would be evidence of delayed progression of atrophy after the initial period of stabilization in a percentage of patients after TBI, detectable on both visual ratings and volumetric analyses, and that the extent of volumetric change would be greater than that estimated for healthy controls.

METHODS

Participants

The participants in this study were 14 patients recruited from a larger, ongoing prospective study of cognitive and motor recovery from TBI, which included 2 subacute phase structural MRI assessments.

Patients from the larger study were recruited from the Neurorehabilitation Program of the Toronto Rehabilitation Institute, in a large, urban rehabilitation hospital.

The study protocol was approved by the research ethics board at the Toronto Rehabilitation Institute, and the procedures of the study were in accordance with the standards of the research ethics board.

Eligibility for the neurorehabilitation program includes the potential to benefit from rehabilitation, age 16 years or older, willingness to participate in all components of the program, and medical stability. Patients may have minimal to severe physical deficits. Patients from the clinical program were eligible for inclusion in the larger TBI recovery study if they met the following

criteria: (1) acute care diagnosis of TBI, (2) posttraumatic amnesia 1 hour or more and/or GCS of 12 or less either at emergency room or the scene of accident (note that, if blood alcohol level was elevated and suspected to have suppressed GCS score, then the higher GCS score was used as the inclusion criterion), and/or positive acute care computed tomography or MRI findings (based on clinical records), (3) age between 18 and 80 years, (4) able to follow simple commands in English based on speech language pathologist intake assessment, and (5) competency to provide informed consent for the study or availability of legal decision-maker. Participants were excluded on the basis of the following criteria: (1) orthopedic injuries affecting both upper extremities and/or both lower extremities; (2) diseases primarily or frequently affecting the central nervous system, including dementia of Alzheimer type, Parkinson disease, multiple sclerosis, Huntington disease, systemic lupus erythematosus, or stroke, based on medical records and screening of family members for patients over 60 years regarding any definite or possible prior diagnosis of dementia; (3) history of psychotic disorder; (4) not emerged from posttraumatic amnesia by 6 weeks postinjury, as measured by the Galveston Orientation Amnesia Test⁴⁷; (5) TBI secondary to other brain injury (eg, a fall caused by stroke); and (6) metal implants that preclude MRI.

To be eligible for the current study, participants needed additionally to have completed the 4.5-month neuroimaging assessment, to have reached the long-term follow-up stage, and to have not developed further neurologic complications (eg, subsequent brain injury, hydrocephalus). There were 18 eligible patients. Four of these were lost to follow-up (unable to reach via their supplied contact details), leaving 14 patients available to participate in the follow-up assessment. Thus, the retention rate was 73.7%, which is very high compared with many longitudinal studies of TBI.^{2,34,36}

Table 1 shows the injury and demographic information of each participant in the study. Overall, the group was a typical group of patients with moderate to severe TBI, with a greater proportion of male subjects, average estimated premorbid IQ, and moving vehicle collisions the most common cause of injury, followed by falls.

Inspection of the mean values in table 1 reveals that the 4 patients who did not return for follow-up were slightly higher functioning as a group, although this was driven in large part by a single patient who was a top tier health care professional with 21 years of education. Unpaired, 2-tailed tests showed no significant differences between the 2 groups nor differences approaching significance for age ($t_{17} = -.40$, $P > .10$), premorbid intelligence ($t_{13} = 1.67$, $P > .10$), socioeconomic status⁴⁸ ($t_{17} = .37$, $P > .1$), years of education ($t_{17} = -1.3$, $P > .10$), and GCS score ($t_{15} = -.39$, $P > .10$). There were proportionately more female subjects and motor vehicle collisions in the tested group. However, the low attrition, the absence of significant differences (or trends), and overall similarity between the groups (aside from the 1 patient mentioned) indicates that the study did not suffer from selective attrition and that the sample tested at the 2 time points was a representative sample of Canadian patients referred for inpatient neurorehabilitation in an urban setting.

Imaging Protocol

MRI scans were acquired on a Signa-Echospeed 1.5 Tesla high definition scanner,^a using an 8-channel head coil. Sequences included the following: sagittal T1 (TR/TE=300/13ms), slice thickness equal to 5mm, space 2.5mm, matrix 256 × 128; axial GRE (TR/TE=450/20), flip angle equal to 20°, slice thickness equal to 3mm no gap, matrix 256 × 192; axial FLAIR TR/TE equal to 9000/45ms, TI equal to 2200ms, slice thickness equal to 5mm no gap, matrix 256 × 192; axial fast

Table 1: Demographic and Injury Data of Participants Included in the Study as Well as Those Lost to Follow Up

	Sex	Age	Injury	GCS (lowest)	Estimated PTA (wk)	SES*	Acute LOS	Years of Education	Estimated Premorbid Intelligence
Participants (N=14)									
1	Female	24	MVC (ped)	3	>2	4	24	8	NA
2	Male	58	MVC	13	>0.5	4	33	12	NA
3	Male	41	MVC	13	>0.5	3	35	9	78
4	Female	52	MVC (ped)	13	0.5	3	—	12	113
5	Male	21	MVC	8	3	4	17	9	NA
6	Male	22	Fall	4	2	2	29	9	85
7	Male	42	Fall (bike)	5	1	4	24	17	119
8	Male	20	MVC	5	>1	2	17	13	80
9	Male	32	Fall	13	>1	2	37	16	83
10	Male	42	MVC	3	>3	4	45	11	99
11	Male	19	MVC	—	1.2	4	14	9	103
12	Female	43	MVC	3	NA	—	88	13	108
13	Male	31	MVC	6	4-6	2	53	16	97
14	Female	44	Fall (bike)	6	NA	2	24	16	120
Mean (totals)	(10 Male/4 female)	35.1	(9 MVCs, 4 fall)	7.3		3.08	33.9	12.1	98.6
Lost to follow-up (n=4)									
1	Male	49	Sport fall	13	1	1	38	21	123
2	Male	36	MVC	11	2	4	21	9	81
3	Male	41	MVC	6	1	2	37	15	108
4	Male	20	Fall	3	>1.5	2	49	12	108
Mean (totals)	(4 Male)	36.5	(2 MVCs/2 falls)	8.25	1.33	2.25	36.25	14.25	105

Abbreviations: LOS, length of stay; MVC, motor vehicle collision; NA, not applicable; ped, pedestrian; PTA, posttraumatic amnesia. *SES denotes socioeconomic status, as measured by the Hollingshead⁴⁸ classification: 1 (major business/professional); 2 (medium business/minor professional, technical); 3 (skilled craftsperson, clerical, sales worker); 4 (machine operator, semiskilled worker); 5 (unskilled laborer, menial service worker).

spin-echo PD/T2 TR/TE equal to 5500/30.90ms, slice thickness equal to 3mm no gap, matrix 256 × 192. All aforementioned sequences were obtained with a 22-cm FOV. The high-resolution isotropic T1-weighted, 3D IR prepped radio-frequency spoiled-GRE images (TI/TR/TE=300/12/5, TI, flip angle=20°, slice thickness=1mm no gap, matrix=256 × 256) were acquired in the axial plane using a 25-cm FOV. The entire scanning session lasted approximately 55 minutes.

Design and Procedures

The study was a within-subjects, repeated-measures design. All participants were required to pass a rigorous clinical screening procedure prior to the first MRI assessment. All MRIs were conducted at the same center, a teaching hospital in an urban setting. All equipment and acquisition parameters were identical for the initial and follow-up assessments. One of 2 MRI technologists performed all MRIs. The first assessment was conducted at a mean ± SD of 4.5±0.5 months postinjury. Participants were contacted by telephone to arrange the date of the follow-up scan, which took place at a mean ± SD of 29.3±4.1 months postinjury. The mean time ± SD between scans was 24.8±4.4 months (range, 20.2–34.5mo).

Once all data were collected, the images were analyzed by 2 different methods, as follows, in order to ascertain change over time.

Classification of images based on expert reader ratings. Three experienced staff neuroradiologists reviewed all pairs of imaging studies for each patient. They were informed that all patients had sustained a TBI and that each patient had been scanned at 2 different times after injury. The early and late scans were then randomized to the top and bottom rows of a workstation, with the readers kept blinded to the temporal sequences of the scans and all clinical data.

Readers were asked to use all available sequences including sagittal T1, axial T1 3D IR prepped radio frequency spoiled-GRE, axial PD and T2, axial FLAIR, and axial GRE in order to independently document whether the scans were the same or if 1 scan showed deterioration or improvement, based on the following key criteria: extent of T2 signal abnormalities seen on FLAIR, volume extent of tissue loss, and generalized volume in CSF spaces. Note that the GRE sequence was not used for assessment of progression, but just to direct attention to areas of injury because changes in iron deposition over this time frame were not observed.

For each of the 14 subjects, an ordinal scale was used by the neuroradiologists to rate change between the 2 MRI scans (ie, deterioration, no observable change, improvement). Interrater reliability for the coding of MRI change by each radiologist was assessed by using the ICC. Because there exists no widely accepted method for investigating interrater agreement using ordinal data, it was necessary to choose between methods for determining interrater agreement for continuous data (ie, ICC) and those used for nominal data (ie, Fleiss κ). While it can be argued that our data more closely approximate nominal data, the appropriate kappa statistic for studies with nominal data and more than 2 raters, Fleiss multirater kappa, is known to be influenced by prevalence (ie, the true proportion of cases of various types in a population) and bias (ie, the bias of 1 rater relative to another),⁴⁹ which can lead to the paradox of high agreement but low kappa.⁵⁰ It also assumes that raters are restricted in how they can distribute cases across categories, which is not a typical feature of many agreement studies, including the current study.⁵¹ Furthermore, much controversy surrounds the appropriate use and interpretation of kappa statistics in general.^{50,52} Although ICC is used for continuous

data, it was chosen for the current study because it would provide a conservative estimate of interrater agreement because the main problem that results from treating ordinal data as continuous is that it makes correlations smaller than they should be, so any value obtained would underestimate the actual ICC. ICC was calculated in a 2-way random model based on consistency agreement, in which each MRI is rated by each rater with a confidence interval of 95%.⁵³ Level of clinical significance was defined according to conventional criteria (>.74, excellent; .60–.74, good; .40–.59, fair; <.40, poor).⁵⁴ A random-effects model was used under the assumption that the raters represent a random sample of a larger pool of raters.

Volumetric data analysis. The high-resolution isotropic axial T1 3D IR prepped radio frequency spoiled-GRE images were submitted for volumetric analysis. CSF and hippocampal volumes were obtained for all 14 patients. The MRIs were transferred to an external workstation, with image processing and image data analysis carried out at the Sunnybrook Health Sciences Centre by a technician blinded to the clinical findings. The scans were received in the Digital Imaging and Communications in Medicine file format and were subsequently converted into Medical Imaging Network Common Data form.⁵⁵

A number of image processing steps were performed in order to make the MRI data usable for image analysis. The first step was the intensity nonuniformity correction.⁵⁶ The images were linearly registered (aligned) into stereotaxic coordinates⁵⁷ based on the Talairach atlas.⁵⁸ The linear registration to Talairach coordinates was accomplished through 3D cross-correlation between a given volume and an average brain MRI previously converted into the Talairach coordinate system.⁵⁷ After the registration, the images had the same size and orientation, allowing for direct anatomical comparisons between subjects. A second nonuniformity correction was performed after the registration, which helped to remove any residual nonuniformity artifacts.

Every voxel was then classified into CSF, gray matter, or white matter using an automated tissue classification algorithm.⁵⁹ Subsequently, cortical surface extraction from the tissue-classified images was performed, resulting in a 3D reconstruction of the cortical surface.

Both hippocampi were segmented manually using DISPLAY software.^{60,6} This tool allows for viewing images simultaneously in the sagittal, coronal, and horizontal planes. The details of manual segmentation for each structure have been described by Pruessner et al.⁶¹ The structures were labeled on each slice of an image using coronal, sagittal, and horizontal views, and their individual volumes were calculated automatically in DISPLAY. The same well-trained technician performed the manual segmentation for both the initial and follow-up scans for each patient.

Use of normative data. We compared our CSF volume changes to the normative data from Blatter et al.⁴⁶ that were published for the purpose of a reference standard. (Absolute change across assessments could not be compared because parameters of the acquisition differed across our 2 studies.) The data from Blatter⁴⁶ include mean CSF volumes for male and for female subjects across five 10-year stratifications, from ages 16 to 25, 26 to 35, 36 to 45, 46 to 55, and 56 to 65. Mean education \pm SD of the normative sample was 15.5 ± 2.7 years.

In order to control for differences in the test interval between scans in our study versus the intervals in the study by Blatter,⁴⁶ we computed the annual percent change from the 2 studies. For data from our study, we divided the percent change by the time interval between the 2 scans for each patient. To compute the annual percent increase from the normative data,⁴⁶ we computed a separate value for the sex and age-band stratifications

that matched each patient in our sample. We first calculated a change score taking the mean CSF volume in the age band after the age band of interest and subtracted the mean CSF volume of the age band preceding the age band of interest. We then divided the change score by 20 (because the mean span across these stratifications was 20 years) and then calculated the annual percentage change from this. For example, for a 40-year-old female patient in our sample, the normative data of relevance would be the mean CSF volumes for female patients from 26 to 35, 36 to 45, and 46 to 55 years. We would therefore subtract the mean CSF volume for the 46 to 55 year age-band from the 26 to 35 year age-band, divide by 20, and then calculate the annual percentage change. Note that where the age of a patient within our study fell within the first age-band (such that there were no prior age-band normative data), we calculated the annual percent volume using the first age-band CSF volume and the one after it, and dividing by 10. Where the age of the patient within our study fell within the last age-band, such that there were no subsequent age-band normative data, we computed the annual percent volume using only the last age-band and the one preceding it, and again dividing by 10.

In short, for each patient's annual percent change score, there was an annual percent change score computed from an age-matched and sex-matched normative sample. This allowed us to examine whether the CSF increases observed in patients in the present study were greater than those expected for people of comparable age and sex.

The annual percent change for each hippocampal volume was computed in the same way as above, using the normative data from Bigler et al.¹⁰

Statistical analyses. Based on specific hypotheses, all within-subjects comparisons of CSF and hippocampal volumes from the first to the second assessment were carried out with 1-tailed paired *t* tests. All comparisons of computed annual percent change in our patients versus the computed annual percent change from published normative data were conducted with 1-tailed Student *t* tests without equal variance assumed.

Spearman rank correlations were used to compare expert ratings (progression vs no progression) to the volumetric scores (annual percent change scores). Pearson moment correlations were used to compare the volumetric change scores to one another (ie, CSF to hippocampus; hippocampus right to hippocampus left).

RESULTS

Visible Lesion Changes

The average measure ICC (ie, reliability of all raters averaged together, also known as Cronbach α) was .797, which indicates excellent interrater reliability. For 9 of 14 pairs of scans, all 3 blinded readers showed unanimous agreement (8 progression of atrophy; 1 stable); for 2 of the scans, there was agreement by 2 of the 3 reviewers (progression of atrophy); for 3 scans, there was no agreement. All individual ratings are presented in table 2.

The number of scans for which 2 of 3 raters identified the follow-up MRI as displaying increased progression of lesion was 10 (71.43% of the pairs), with 8 of these receiving unanimous agreement. Two pairs of scans illustrating visible lesion progression are shown in figure 1. There were no instances in which 2 or 3 of the readers selected the early MRI as showing progression of atrophy.

Volumetric Changes

Cerebrospinal fluid volume increase. Table 3 shows that, as expected, there was a mean increase in CSF volume from the

Table 2: Comparison of Expert Rating and Volumetric Analyses on Progression of Atrophy

Subject	Expert Rating				Volumetric Analysis			
	Rater 1	Rater 2	Rater 3	Consensus Rating	CSF Volume Increase Greater Than Normative Increase	Hippocampal Volume Loss Greater Than Normative Loss		
						Right	Left	
1	A	A	A	Atrophy	No	Yes	No	
2	A	A	I	Atrophy	No	No	Yes	
3	A	A	A	Atrophy	Yes	Yes	Yes	
4	A	A	A	Atrophy	Yes	Yes	No	
5	A	I	S	No consensus	Yes	Yes	Yes	
6	A	A	A	Atrophy	Yes	Yes	Yes	
7	A	A	A	Atrophy	Yes	Yes	Yes	
8	I	A	S	No consensus	No	Yes	Yes	
9	A	A	A	Atrophy	No	Yes	Yes	
10	A	A	I	Atrophy	Yes	Yes	Yes	
11	S	A	I	No consensus	Yes	Yes	No	
12	A	A	A	Atrophy	Yes	Yes	Yes	
13	S	S	S	No atrophy	No	No	Yes	
14	A	A	A	Atrophy	Yes	Yes	Yes	

Abbreviations: A, atrophy; I, improvement; S, stable.

first to the second scan. This increase in volume was highly significant ($t_{13} = -4.073, P < .001$). In order to ascertain the clinical significance of this change, and to provide evidence that this change was not attributable to age-related decline over the test-retest period, we compared the magnitude of change to that computed from age-stratified normative data⁴⁶ as described. The mean annual percent increase \pm SD in CSF volume in the present study was $4.25 \pm 4.18\%$ per year compared with only $2.33 \pm 1.15\%$ in the normative sample. This difference approached significance ($t_{26} = 1.655, P = .059$).

Hippocampal volume loss. The data for the hippocampal volumetric analyses are presented in tables 4 (right hippocampus) and 5 (left hippocampus). Table 4 illustrates that, as predicted, the right hippocampus showed an overall loss of volume over the study period that was statistically significant ($t_{13} = 4.221, P < .001$). Table 5 shows that the left hippocampus also showed a significant decrease in volume ($t_{13} = 3.078, P < .005$).

In order to provide evidence that these changes, too, were not attributable to age-related decline over the test-retest period, we compared the hippocampal volume change in our study to normative data.¹⁰ The mean annual percent decrease \pm SD in right hippocampal volume was $-2.30 \pm 2.12\%$, which was markedly larger than the average annual percent change computed from the normative data ($-0.098 \pm 0.20\%$). This difference was highly significant ($t_{26} = -3.86, P < .001$). For the left hippocampus, the mean annual percent volume decrease was $-2.11 \pm 2.67\%$, while the average annual percent decrease computed from the normative data was only $-0.15 \pm 0.11\%$, a difference that was statistically significant ($t_{26} = -2.73, P < .01$).

Comparison of Visual and Volumetric Changes

Table 2 illustrates the results of expert rater and the respective CSF and hippocampal volume changes. There was some concordance between the 2 types of ratings. Seven of the 10 patients rated as showing progression of atrophy by the expert raters also showed CSF volume increase greater than that of healthy controls. For the remaining 2 patients rated as showing atrophy across the study period, there was hippocampal volume loss greater than observed in the normative data in 1 or both hippocampi.

Two of the 4 patients without evidence of atrophy on the visible ratings showed no overall increase in CSF volume greater than that of controls, though 1 did show increased hippocampal volume loss in 1 hippocampus, and the other showed hippocampal volume loss (greater than healthy controls) in both hippocampi.

Using Spearman rank correlations, there were no significant correlations between the expert ratings (atrophy vs no evidence of atrophy) and annual percent change for the CSF or hippocampal volumes; effect sizes were small and nonsignificant ($r = .04, P > .1$, CSF; $r = .28, P > .1$, right hippocampus; $r = .24, P > .1$, left hippocampus). Correlations among volumetric measures were stronger. Pearson correlations between annual CSF volume change and hippocampal volume change (individually) were very small and not significant, but Pearson correlation between the annual hippocampal volume change for the left and right hippocampus was statistically significant ($r = 0.61, P < .05$).

DISCUSSION

The natural history in patients with TBI after the initial period of rapid recovery is not completely understood. Most patients appear to remain at this new, recovered baseline level of cognition, with many showing further improvement; however, there are scattered reports of delayed cognitive decline.³⁴⁻³⁷

We prospectively compared imaging performed at 4.5 months postinjury with follow-up imaging at 2.5 years postinjury. We found strong evidence of secondary progression of encephalomalacia that was visible to expert neuroradiologist readers. For 8 of 14 patients, there was unanimous agreement for progression of atrophy. For 2 further patients, there was majority (2 of 3) agreement of atrophy. For the remaining 4 patients, there was consensus of stability for 1 patient, and a lack of consensus for the other 3. Thus, a substantial proportion of our sample demonstrated visible progression of lesions during this subacute period. The volumetric analyses were globally consistent with these findings in that significant atrophy was observed. There was significant CSF volume increase over the same period. The annual CSF volume increase in our

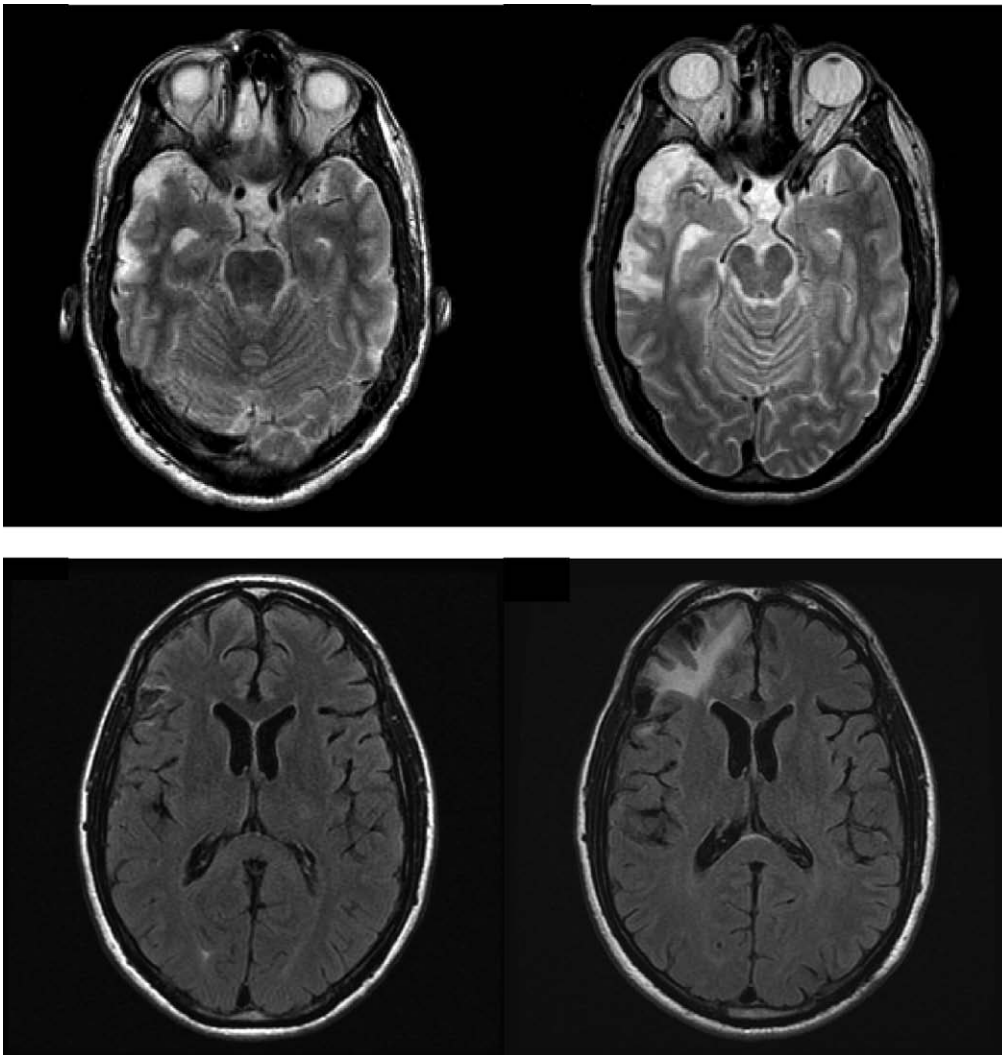


Fig 1. Example of lesion progression from 4.5 months postinjury (left) to 2.5 years postinjury (right) in 2 different patients. Top, T2 axial images demonstrate significant progression of localized atrophy of the right temporal pole extending posteriorly to the mid right temporal lobe that lies superior to the petrous temporal bone. There is also localized dilatation of the right temporal horn. Bottom, FLAIR axial images demonstrate marked progression of localized atrophy in the right frontal lobe with associated adjacent gliosis, where there were only subtle changes on the initial MRI.

patients was nearly double that estimated for healthy controls.⁴⁶ Hippocampal shrinkage showed the same pattern relative to control data,¹⁰ and even more dramatically.

However, it was of interest to note that the 2 patients with the highest increase in total CSF volume (23.95% and 20.43%) did not show visible progression of atrophy based on the expert rater observations. Moreover, several patients with overt progression of lesions on consensus agreement demonstrated no greater CSF increase than that of controls. Finally, there were no significant correlations between expert ratings and volumetric findings. These disparities in the findings offer several possible explanations.

The most probable explanation for disparity between CSF volume and visible lesion progression is that visible lesion volume changes may contribute only minimally to overall CSF volume changes. CSF volume increases reflect global atrophy of the brain, which may be associated with global loss of healthy neurons (or loss of dendritic arborization) resulting from gradual loss of functional connectivity caused by brain injury-related disuse (ie, negative neuroplasticity)⁶² or by delayed apoptosis (see further discussion of this topic below) which has been observed in animal models of brain injury.^{40,63}

Another explanation is that the expert raters may not have been able to see changes detected by the computerized volu-

metric measurements. For example, it is not easy to see hippocampal change with the naked eye, especially in the axial plane (high-resolution coronal images—not employed in the current study—are needed to detect changes in hippocampal volume visible to naked eye), unless exceedingly obvious. Furthermore, the relationship between gliosis and local atrophy may not be as strong as expected in all cases. This underscores the clinical importance of volumetric analysis of scans.

Still another possible explanation concerns a limitation of the study. The normative data from outside of our study, show wide individual differences in CSF volumes, and were derived from cross-sectional samples. The age stratifications were across decades. To compute annual change in volumes, we treated annual change as a linear increment; however, the relationship between age and CSF increase is nonlinear. Taken together, it is possible that the normative data employed may not have provided a valid comparator for our sample. Future research employing longitudinal, control data from within the same study at the same time intervals would provide a better reference for change.

Compatibility with previous studies. A confounding issue from previous studies was their very early initial scanning within days or weeks of injury in most cases. This precluded definitive differentiation of atrophy caused by the natural his-

Table 3: Change in CSF Volume From Assessment 1 to Assessment 2

Subject no.	CSF Absolute Volumes (mm ³)		CSF Volume Change	CSF % Volume Change	Computed Annual % Change	Normative Annual % Change
	Scan 1	Scan 2	Scan 2-1	Scan 2-1		
1	201,900	207,951	6051	3.00	1.04	1.35
2	223,733	236,918	13,185	5.89	2.42	3.71
3	220,550	241,038	20,488	9.29	3.49	1.17
4	188,913	205,854	16,941	8.97	4.06	1.76
5	217,311	269,364	52,053	23.95	11.96	3.42
6	188,090	215,112	27,022	14.37	7.12	3.42
7	206,627	213,372	6745	3.26	1.69	1.17
8	216,945	222,475	5530	2.55	1.16	3.42
9	226,944	232,539	5595	2.47	1.32	3.28
10	254,047	272,612	18,565	7.31	3.95	1.17
11	164,002	197,505	33,503	20.43	11.58	3.42
12	251,124	290,025	38,901	15.49	9.09	1.04
13	268,176	258,174	-10,002	-3.73	-2.15	3.28
14	226,752	237,316	10,564	4.67	2.76	1.04
Mean ± SD	218,222.4±27,950.61	235,732.50±28,026.87*	17,510.07±16,086.06	8.42±7.68	4.25±4.18	2.33±1.15†

NOTE. Total percent CSF change between scan 1 and scan 2, computed annual percent change, and normative annual percent change are presented.
 *Difference between scans 1 and 2 significant at $P<.001$.
 †Difference between computed versus estimated normative change approached significance, $.05<P<.10$.

tory of the primary insult itself from true delayed secondary atrophy.⁴²⁻⁴⁴

A small number of studies conducted neuroimaging assessments more than a month postinjury. One study by van der Naalt et al³⁹ reported that atrophy can be observed from early postinjury to the latter part of the first year of injury (6-12mo postinjury). In this case, the initial MRI was performed within 1 to 3 months of the injury, later than in the aforementioned studies, but perhaps again too early to be confident that the initial insult had not yet resolved. Indeed, 1 of their cases was reported as showing a persistent contusion with surrounding edema at the time of the first scan. This provides some evidence that acute lesion effects had not yet resolved in at least

some of the patients in their study. Similarly, Trivedi et al³⁸ showed significant decrease in percent brain volume change (%BVC) in patients with TBI compared with healthy controls. They, too, acknowledged that "... it is possible that the clearing of brain edema over time might be responsible for the substantial %BVC observed in the TBI group ..."^{38,p770} Their first scan took place at more than 2 months postinjury on average, but some patients were seen as early as 39 days postinjury. MacKenzie et al⁴⁵ examined progression of atrophy on measures of volume of brain parenchyma, total CSF, and percent volume of brain parenchyma (an index of brain volume that incorporates CSF volume) in mild and moderate TBI across the first year of brain injury. In this retrospective study,

Table 4: Volume Change in Right Hippocampus From Assessment 1 to Assessment 2

Subject no.	Hippocampus Absolute Volumes (mm ³)		Absolute Hippocampal Volume Δ	% Hippocampal Volume Δ	Computed Annual % Change	Normative Annual % Change
	Scan 1	Scan 2	Scan 2-1	Scan 2-1		
1	2708	2545	-163	-6.02	-2.09	0.15
2	3467	3470	3	0.086	0.04	-0.24
3	3152	2854	-298	-9.45	-3.55	-0.28
4	3602	3506	-96	-2.67	-1.21	-0.14
5	3607	3458	-149	-4.13	-2.06	0.15
6	2701	2656	-45	-1.67	-0.83	0.15
7	2873	2496	-377	-13.12	-6.78	-0.28
8	3287	3037	-250	-7.6	-3.47	0.15
9	3870	3743	-127	-3.28	-1.76	-0.19
10	3349	3157	-192	-5.73	-3.10	-0.28
11	3439	3421	-18	-.52	-0.30	0.15
12	3711	3337	-374	-10.08	-5.91	-0.28
13	4159	4199	40	0.96	0.56	-0.19
14	2463	2393	-70	-2.84	-1.69	-0.28
Mean ± SD	3313.43±486.63	3162.29±525.77*	-151.14±133.97	-4.72±4.16	-2.30±2.12	-0.098±.20†

NOTE. Total percent change from scan 1 to 2 is presented. Computed annual percent change is provided for each participant as well as estimated annual percent change of age and sex-matched normative sample.
 *Difference between scans 1 and 2 significant at $P<.001$.
 †Difference between computed versus estimated normative change significant at $P<.001$.

Table 5: Volume Change in Left Hippocampus From Assessment 1 to Assessment 2

Subject no.	Hippocampus Absolute Volumes (mm ³)		Absolute Hippocampal Volume Δ	% Hippocampal Volume Δ	Computed Annual % Change	Normative Annual % Change
	Scan 1	Scan 2	Scan 2-1	Scan 2-1		
1	2298	2486	188	8.18	2.84	-0.08
2	3194	2988	-206	-6.4	-2.65	-0.47
3	3279	3020	-259	-7.90	-2.97	-0.13
4	3729	3791	62	1.66	0.75	-0.25
5	3681	3620	-61	-1.66	-0.83	-0.08
6	3081	3005	-76	-2.47	-1.22	-0.08
7	3130	2806	-324	-10.35	-5.35	-0.13
8	3302	3051	-251	-7.6	-3.46	-0.08
9	3713	3513	-200	-5.39	-2.88	-0.15
10	3295	2976	-319	-9.68	-5.24	-0.13
11	2947	3033	86	2.92	1.65	-0.08
12	3431	3051	-380	-11.08	-6.5	-0.13
13	4119	3952	-167	-4.05	-2.34	-0.15
14	2384	2332	-52	-2.18	-1.29	-0.13
Mean \pm SD	3255.93 \pm 497.43	3116 \pm 459.65*	-139.93 \pm 170.12	-4.00 \pm 2.65	-2.11 \pm 2.67	-0.15 \pm 0.11 [†]

NOTE. Total percent change from Scan 1 to 2 is presented. Computed annual percent change is provided for each participant as well as estimated annual percent change of age and sex-matched normative sample.

*Difference between scans 1 and 2 significant at $P < .005$.

[†]Difference between computed versus estimated normative change significant at $P < .01$.

7 patients were observed longitudinally and compared with 4 controls, who were also assessed at 2 time points. The authors found no change in volume of brain parenchyma or CSF, but did observe change in percent volume of brain parenchyma relative to the controls. However, because the first examination ranged from 7 to 430 days postinjury, again, it is not clear whether the change represents bona fide secondary atrophy or resolution of acute mass effect and swelling associated with edema, hemorrhage, and tissue hyperemia.

In another retrospective study designed to examine brain-behavior relationships in chronic TBI, Blatter et al²⁷ studied 123 patients with TBI and measured the volume of brain and CSF using MRI. Patients were divided into subgroups based on time since injury to the MRI. However, MRI was performed on the basis of clinical indications. Thus, while patients scanned at a later date showed more atrophy compared with patients scanned earlier (as well as compared with healthy controls)⁴⁶ the sample may have been a biased one selected for poor clinical recovery. As well, the comparisons were cross-sectional.

We therefore believe this study provides the most conclusive evidence to date for chronic lesion progression and atrophy in TBI. Our study is also consistent with findings from animal studies, which show preliminary indications of subacute progression of atrophy. Smith et al,⁶³ for example, demonstrated progressive tissue loss with associated ventricular dilatation in rats at multiple intervals up to a year after injury. Dixon et al⁶⁴ showed behavioral deficits that progressed over the course of the first year after injury.

Mechanisms of decline. Some studies have looked at potential mechanisms of this delayed decline, and several possibilities have been proposed. Using the terminal deoxynucleotidyl transferase-mediated biotinylated deoxyuridine triphosphate nick-end labeling histochemical technique, Williams et al⁴¹ demonstrated long-term deoxyribonucleic acid fragmentation within white matter up to 12 months after TBI in humans. Delayed apoptosis appears to occur in rats after TBI^{40,63} and progressive, delayed, and remote damage has been focally observed in the thalamus,^{65,66} presumably because of the apoptotic removal of axonal projections and subsequent deafferentation of remote relay stations.

The presence of delayed inflammation has also been examined. Gentleman et al⁶⁷ reported persisting inflammation associated with the interleukin-1 genotype. Rodriguez-Paez et al⁶⁸ observed persistent edema with an associated inflammatory infiltrate using light and electron microscopy 6 months after TBI in various structures. Active inflammation as long as 1 year after TBI has also been reported.⁶⁹ In addition, abnormal protein accumulation, such as β -amyloid precursor protein, in damaged axons and other neuronal compartments^{66,70,71} has also been implicated.

Understanding the mechanisms underlying this delayed neuroanatomical and cognitive decline is an important area of further research, because potential treatment regimens such as various neuroprotective agents⁷² can be targeted to these areas. For example, mild hypothermia has been shown to target multiple injury cascades after acute brain injury in humans.⁷³ Importantly Bramlett et al⁶⁵ showed that post-TBI hypothermia conveyed significant improvement in lateral ventricular dilation in animal models, indicative of its chronic neuroprotective properties. Schouten et al⁷⁴ have suggested cellular transplantation strategies to promote recovery in animal models.

Study Limitations and Future Directions

There were several limitations of this study. First, sample size was only 14, thus limiting the reliability of the findings, particularly given the demographic and neurologic heterogeneity of the sample. We did not include cognitive or functional findings in the current study. Future research, with larger sample size, should address the clinical implications of progression of atrophy. For example, changes in cognitive and motor assessment findings could be correlated with changes in neuroradiologic findings. Functional outcomes in patients who do and do not demonstrate progression of atrophy could be compared. Single case studies correlating cognitive and/or motor findings to discrete lesion changes would be informative for both clinical and scientific purposes.

CONCLUSIONS

There is compelling visual and volumetric evidence that delayed progressive atrophy occurs in patients with TBI after

the presumed initial period of stabilization and recovery, and long after the direct mechanical effects of the traumatic event have resolved. Our prospective study showed that 85.71% of our cohort of patients showed robust signs of delayed progressive atrophy on MRI after the initial scan at 4.5 months after injury. The extent of decline was more than we anticipated, and much more than is generally accepted.

These findings are in agreement with various other studies that have employed different design parameters with less conclusive findings. The findings are also compatible with the appearance of new symptomatology and the reports of cognitive decline during the same time frame. The exact reasons and nature of this further decline are not yet entirely known, but various theories seem plausible and are potential targets for new treatment regimens.

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Suppliers

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- b. Brain Imaging Centre of the Montreal Neurological Institute, Montreal Neurological Institute and Hospital, 3801 University St, Montreal, QC, Canada H3A 2B4.

ORIGINAL ARTICLE

Use of Diffusion Tensor Imaging to Examine Subacute White Matter Injury Progression in Moderate to Severe Traumatic Brain Injury

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ABSTRACT. Greenberg G, Mikulis DJ, Ng K, DeSouza D, Green RE. Use of diffusion tensor imaging to examine subacute white matter injury progression in moderate to severe traumatic brain injury. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S45-50.

Objective: To demonstrate subacute progression of white matter (WM) injury (4.5mo–2.5y postinjury) in patients with traumatic brain injury using diffusion-tensor imaging.

Design: Prospective, repeated-measures, within-subjects design.

Setting: Inpatient neurorehabilitation program and teaching hospital MRI department.

Participants: Brain-injured adults (N=13) with a mean Glasgow Coma Scale score of 7.67 ± 4.16 .

Interventions: Not applicable.

Main Outcome Measures: Fractional anisotropy (FA) values were measured at 4.5 and 29 months postinjury in right and left frontal and temporal deep WM tracts and the anterior and posterior corpus callosum.

Results: FA significantly decreased in frontal and temporal tracts: right frontal ($.38 \pm .06$ to $.30 \pm .06$; $P < .005$), left frontal ($.37 \pm .06$ to $.32 \pm .06$; $P < .05$), right temporal ($.28 \pm .05$ to $.22 \pm .018$; $P < .005$), and left temporal ($.28 \pm .05$ to $.24 \pm .02$; $P < .05$). No significant changes were in the corpus callosum.

Conclusions: Preliminary results demonstrate progression of WM damage as evidenced by interval changes in diffusion anisotropy. Future research should examine the relationship between decreased FA and long-term clinical outcome.

Key Words: Brain injuries; Follow-up studies; Magnetic resonance imaging; Rehabilitation.

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TRAUMATIC BRAIN INJURY refers to an injury caused by externally inflicted trauma to the brain and can result in significant cognitive, motor, and psychosocial impairments.¹⁻⁴ A large proportion of patients with moderate and severe TBI

are young adults⁵; consequently, these patients often face decades of disability, with associated emotional, social, and financial difficulties.⁶ This chronic period of disability has received only limited scientific attention, particularly with respect to neuroimaging research. Clinically, it is generally assumed that ongoing disability is attributable to the residual deficits from the original injury; however, recent findings suggest that some degree of neurological deterioration may occur after the initial acute injuries have resolved.⁷⁻¹² Chronic disability could be caused by a combination of acute injury and chronic progressive damage.

Recovery from TBI has been widely studied with the general finding that recovery is asymptotic. Maximal behavioral recovery occurs during the early months postinjury followed by a plateau at approximately 6 to 18 months post-TBI,^{13,14} with plateau variations largely attributable to differences in outcome measures¹⁵ and other methodologic differences across studies.^{16,17} Recent findings have suggested, however, that behavioral recovery curves may be characterized—for some patients in some areas of functioning—by a more parabolic shape, with a decline in cognitive status after initial recovery.^{8,10,12} There is neurophysiologic evidence of this long-term decline from neuropathologic investigations in animals^{7,9} and neuroimaging studies in humans; the latter studies have employed both volumetric MRI measurements^{11,15,18} as well as visual inspection of lesions by experts.¹¹

Much of the neurophysiologic evidence to date is equivocal, however. Many of the observed changes over time may be attributable to the resolution of early acute effects of the primary injury. In most studies, the baseline (comparator) scan was undertaken early post-TBI, when acute changes were resolving (eg, reduction of inflammatory cells, edema, and hyperemia; involution of hematoma). In some studies, both the first and the second scan were conducted during the acute phase¹⁹⁻²²; in others, the second scan was conducted in the chronic phase,^{23,24} but the first was carried out during the acute phase. Therefore, with the exception of the study in this issue

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List of Abbreviations

CT	computed tomography
DAI	diffuse axonal injury
DTI	diffusion-tensor imaging
FA	fractional anisotropy
FLAIR	fluid-attenuated inversion recovery
MRI	magnetic resonance imaging
NS	not significant
PTA	posttraumatic amnesia
ROI	region of interest
SPGR	spoiled gradient recalled
TBI	traumatic brain injury
WM	white matter

by Ng et al,¹¹ it is unclear whether the interval change in these studies was attributable to atrophy or rather to the full, neuro-radiologic manifestations of the original injury.

Previous human neuroimaging studies that have examined the question of progression of atrophy have employed conventional MRI techniques such as proton, T2-weighted, and SPGR imaging. To date, there are no studies that have used DTI. However, this technique is highly sensitive to the neuropathology of TBI, more so than conventional imaging,^{19,25-27} and therefore represents a valuable tool for examining this question.

DTI is a relatively recent development in MRI technology. It is an ideal tool for investigating progression of atrophy in TBI because of its sensitivity to abnormalities in the microstructure of WM (eg, Naganawa et al²¹), which is extensively disrupted after TBI,^{28,29} and because correlations have been observed between DTI and TBI outcome.^{23,30} DAI lesions are frequently microscopic and often underestimated by conventional MRI and typically invisible on CT^{19,22,31} compared with DTI. In 1 study, Huisman et al¹⁹ found that approximately 16% of DAI lesions were identifiable exclusively by DTI compared with conventional MRI (T2/FLAIR and T2-weighted gradient echo sequences).

In general, DTI works by incorporating pulsed magnetic field gradients into a standard MRI sequence that characterizes the local diffusivity of water.³¹ In healthy WM, there is greater diffusion along the long axis of axonal bundles than along the radial axis because of hindrance from the myelin sheath.^{22,32} Two key measures associated with water diffusion are diffusivity, the magnitude of diffusion; and anisotropy, the directionality of water diffusion.³² DTI data can be used to generate images of FA,²² an index comparing the preferred direction of water diffusion with its orthogonal component. Accordingly, a decreased FA value has been shown to be largely the result of selected increases in diffusion along the radial axis of axonal bundles. FA is sensitive to changes in WM integrity^{33,34} and provides pertinent information regarding the degree of WM damage including factors such as myelin sheath thickness and axonal membrane integrity.^{22,35} Given that WM damage is a predominant feature of TBI, it is not surprising that a number of studies have demonstrated decreases in FA values in severe TBI.^{21,22,24,27,32}

The aim of the current study was to determine whether there is evidence of increasing WM injury after moderate and severe TBI using DTI-derived FA values. This is based on previous findings from our group that showed robust progression of atrophy, often adjacent to the site of original lesions. Thus, based on the findings by Ng et al,¹¹ we predicted significant declines in FA values in the selected ROIs, which were selected for the high probability of damage from the initial injury. Six preselected ROIs were examined. These include frontal and temporal deep WM tracts, and the anterior and posterior regions of the corpus callosum. These regions were selected because previous studies have identified them as particularly susceptible to WM injury after TBI.^{21,22,25,27,32,36-39} Thirteen patients underwent neuroimaging at 2 time points: the first was undertaken at 4.5 months postinjury, after resolution of acute injury; and the second was completed at 2.5 years postinjury. ROI maps were generated at both time points, and the change in FA values was compared within subjects for each ROI.

METHODS

Participants

The study protocol was approved by the research ethics board at the Toronto Rehabilitation Institute, and the procedures of the

study were in accordance with the standards of the research ethics board.

Thirteen adult patients (10 men, 3 women) with TBI were enrolled in the study. As indicated in table 1, this group was in the severely impaired range, had a high school education, was of average estimated premorbid intelligence, and had the expected high male to female ratio. All patients had been admitted to the Inpatient Neurorehabilitation Program of the Toronto Rehabilitation Institute, a large, urban inpatient hospital, between 2004 and 2007. They were recruited from a larger, ongoing prospective study of cognitive and motor recovery from TBI.

Patients were eligible for the larger study if they met the following criteria: (1) acute care diagnosis of TBI, (2) PTA 1 hour or more and/or Glasgow Coma Scale of 12 or less either at the emergency department or the scene of accident and/or positive acute care CT or MRI findings, (3) age between 18 and 80 years, (4) able to follow simple commands in English, and (5) competency to provide informed consent for study or availability of legal decision-maker. Exclusion criteria were (1) orthopedic injury affecting both upper extremities and/or both lower extremities, (2) diseases primarily or frequently affecting the central nervous system, (3) history of psychotic disorder, (4) not emerged from PTA by 6 weeks postinjury, (5) TBI secondary to other brain injury (eg, a fall because of stroke), and (6) metal implants precluding MRI.

To be eligible for the current study, participants needed additionally to have completed the 4.5-month MRI, to have reached the long-term follow-up stage, and to have not developed further neurological complications (eg, subsequent brain injury, hydrocephalus). There were 18 eligible patients. Four patients were unreachable by telephone or mail; 1 had compromised MRI acquisition data. Thus, 13 patients participated in the current study, representing a retention rate of 72%. (Note that this sample of patients, minus 1, was also tested in the study by Ng¹¹). As shown in table 1, those participating were highly similar to those lost to follow-up, with the possible exception of estimated premorbid intelligence quotient, for which the mean was more than 4 points higher in the latter group. This was attributable to 1 patient with 21 years of education, however.

Design and Procedures

Baseline MRI was performed at a mean \pm SD of $4.5 \pm .40$ months postinjury. Follow-up MRI was conducted at a mean \pm SD of 29.3 ± 4.0 months postinjury.

Magnetic Resonance Imaging Acquisition

All patients were scanned on a GE 1.5-Tesla HD MRI system^a using a series of conventional sequences. These included sagittal T1, axial gradient-recalled echo, axial FLAIR, axial proton density/T2, and axial 3D fast spoiled gradient-echo. DTI parameters were echo time 1 equals minimum, repetition time equals 8300, field of view equals 30 cm, frequency equals 128, phase equals 128, number of excitations equals 1, 30 contiguous sections, 5-mm section thickness, and diffusion gradients set in 25 directions.

Diffusion-Tensor Imaging Processing and Region of Interest Measurements

All images were processed on a GE Advantage Workstation 4.2_06^a using the Functool software 3.1.22.^a Corrections were made to remove echo-planar imaging distortions from the raw images. For each patient, 6 preselected ROIs were examined including the anterior corpus callosum (including genu), posterior corpus callosum (including splenium), deep frontal WM of anterior frontal lobes (deep frontal WM), and deep temporal

Table 1: Demographic and Injury Data of Participants Included in the Study as Well as Those Lost to Follow-Up

	Sex	Age	Injury	Glasgow Coma Scale (Lowest)	Estimated PTA (wk)	SES	Acute Length of Stay	Years of Education	Estimated Premorbid Intelligence Quotient
Participants (N=13)									
1	Female	24	MVC (ped)	3	>2	4	24	8	NA
2	Male	58	MVC	13	>0.5	4	33	12	NA
3	Male	41	MVC	13	>0.5	3	35	9	78
4	Female	52	MVC (ped)	13	0.5	3	—	12	113
5	Male	21	MVC	8	3	4	17	9	NA
6	Male	22	Fall	4	2	2	29	9	85
7	Male	42	Fall (bike)	5	1	4	24	17	119
8	Male	20	MVC	5	>1	2	17	13	80
9	Male	32	Fall	13	>1	2	37	16	83
10	Male	42	MVC	3	>3	4	45	11	99
11	Male	19	MVC	—	1.2	4	14	9	103
12	Male	31	MVC	6	4–6	2	53	16	97
13	Female	44	Fall (bike)	6	NA	2	24	16	120
Mean:(totals)	(10 males/3 females)	34.46	(9 MVC, 4 fall)	7.67		3.08	29.33	12.07	97.70
Lost to follow-up (n=5)									
1	Male	49	Sport, fall	13	1	1	38	21	123
2	Male	36	MVC, Fall	11	2	4	21	9	81
3	Male	41	MVC	6	1	2	37	15	108
4	Male	20	Fall	3	>1.5	2	49	12	108
5	Female	43	MVC	3	NA			13	108
Mean:(totals)	(4 males/1 female)	37.8	(3 MVC, 2 fall)	7.2		2.25	36.25	14.0	105.6

Abbreviations: GCS, Glasgow Coma Scale; IQ, intelligence quotient; LOS, length of stay; MVC, motor vehicle collision; NA, not applicable; ped, pedestrian; SES, socioeconomic status, as measured by the Hollingshead⁴⁸ classification: 1 (major business/professional); 2 (medium business/minor professional, technical); 3 (skilled craftsperson, clerical, sales worker); 4 (machine operator, semiskilled worker); 5 (unskilled laborer, menial service worker).

WM bilaterally. An ROI in the range of 32 to 34mm² was manually copied and pasted to each region using the reference voxel grid generated by the software ensuring symmetry. ROI mapping was carried out as follows: for the anterior corpus callosum, the genu of the corpus callosum was centered in the axial plane; for the posterior corpus callosum, the splenium of the corpus callosum was centered in the axial plane; for deep frontal WM, a slice contained the corpus callosum and the ROI was centered in WM diagonal to the tip of anterior horn of the lateral ventricle; for deep temporal WM, the slice contained the temporal horns, and the ROI was centered anterior to the cap of the temporal horn (fig 1).

RESULTS

Paired, 1-tailed *t* tests were used to compare the initial and follow-up scans. A Bonferroni-Holm adjustment was applied to the 6 comparisons, giving an initial Bonferroni significance level of *P* equal to .008 (all 6 comparisons) and a final Bonferroni-Holm adjusted significance of *P* equal to .013. This revealed no significant differences in the corpus callosum ($t_{12}=1.00$, NS [anterior corpus callosum]; $t_{12}=-.02$, NS [posterior corpus callosum]). Findings from the frontal and temporal lobes, presented in figure 2, were significant. For the frontal lobes, mean FA values at time 1 and time 2 for the right

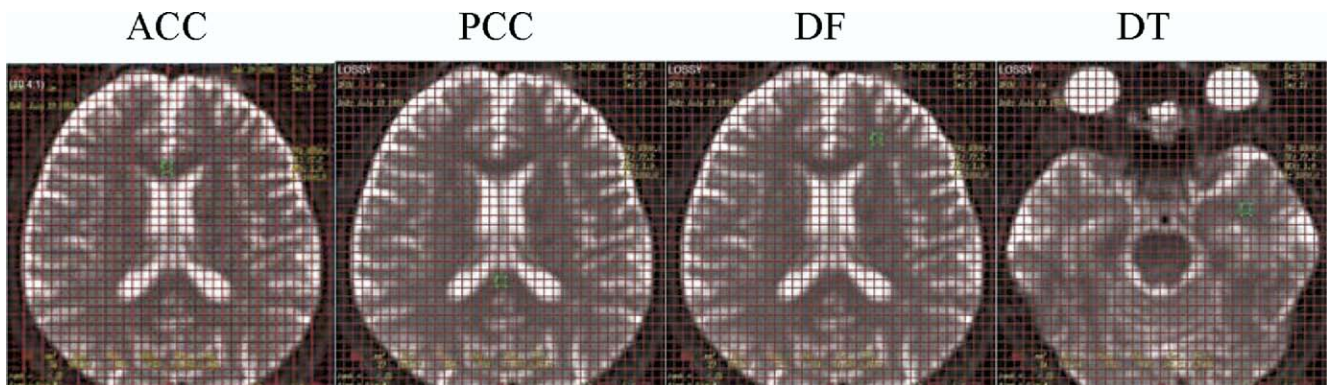
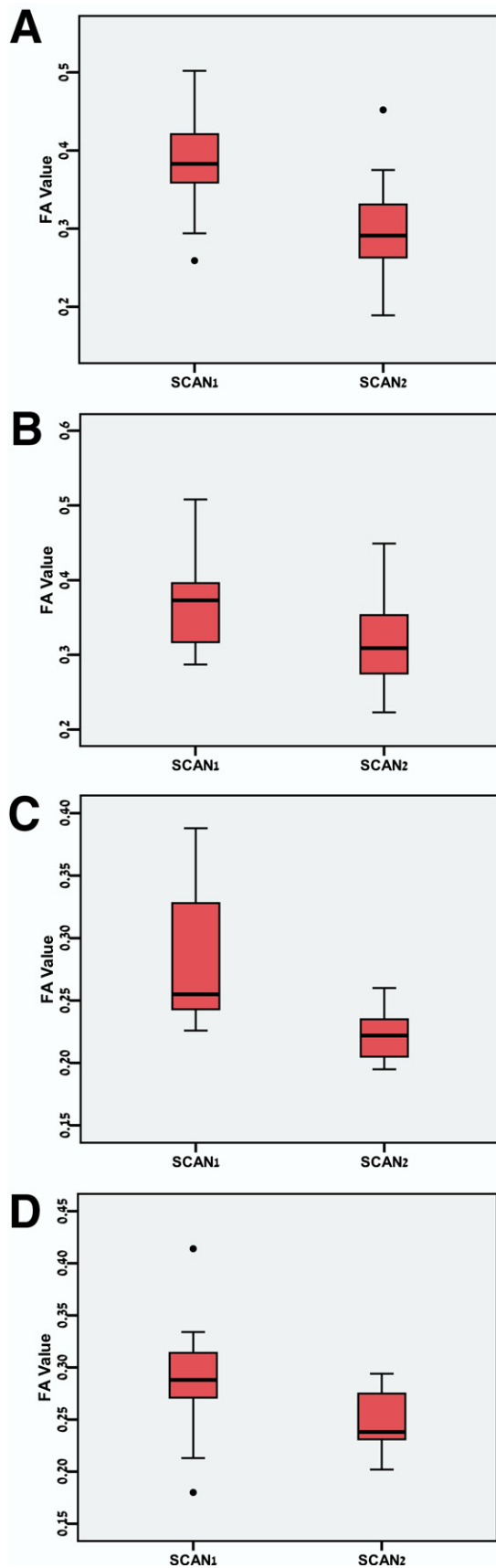


Fig 1. T2-weighted images with overlying grid from Functool software, showing the ROI selection. Abbreviations: ACC, anterior corpus callosum; DF, deep frontal white matter; DT, deep temporal white matter; PCC, posterior corpus callosum.



hemisphere were, respectively, $.38 \pm .06$ and $.30 \pm .06$, with a significantly smaller FA at time point 2 ($t_{12}=3.21$, $P<.005$). For the left hemisphere, means \pm SDs were $.37 \pm .06$ and $.32 \pm .06$ across the 2 time points, and were significantly different ($t_{12}=2.67$, $P<.013$). For deep temporal lobe WM, mean FA values \pm SDs at time 1 and time 2 for the right hemisphere were $.28 \pm .05$ and $.22 \pm .02$, respectively ($t_{12}=3.62$, $P<.005$). For the left hemisphere, the means \pm SDs were $.28 \pm .05$ and $.24 \pm .02$ ($t_{12}=2.68$, $P<.013$).

DISCUSSION

Because of its unique sensitivity to DAI,^{19,27,40,41} we employed DTI to examine fiber tract changes during subacute and chronic TBI.

Analysis of ROIs at follow-up DTI (≈ 29 months postinjury) showed that FA had significantly decreased in the frontal and temporal lobes bilaterally. These abnormalities are concordant with a small number of previous reports^{7,9,11,15,18} and are likely to reflect demyelination, edema, and persistent axonal injury as described in a mouse model.⁴² Progression of injury was not observed in the corpus callosum, either anteriorly or posteriorly, although previous studies that investigated injured subjects at a single point of time after TBI, such as Nakayama et al,³⁸ have shown decrease in callosal FA compared with healthy subjects. MacDonald et al⁴² suggest that DTI signals at the contusion site are affected by pericontusional wallerian degeneration secondary to cell loss, as depicted in their mouse model. According to their study, this is a result of axonal injury at acute time points and primarily demyelination and edema at subacute time points. The underlying cause of the decreased FA may represent apoptosis, and indeed, several studies have shown that neurons are affected by apoptotic pathways after TBI.⁴³ The neuronal apoptosis was described in both postmortem and *in vivo* studies,⁴⁴⁻⁴⁶ and Cernak et al⁴⁷ have demonstrated diffusion signal changes in areas of apoptosis in their rat model.

To date, only 1 previous human study examining progression of atrophy in humans (this issue) has examined patients prospectively, within subjects, and solely after the acute period has resolved.¹¹ Thus, this is the second study to offer strong evidence of atrophy unconfounded by the effects of acute injury.

This is the first study published to date to use DTI to examine the question of progression of WM damage during the subacute period. There are only 2 previous longitudinal studies^{21,37} that have employed DTI in TBI; however, neither of them was designed to address the question of progression of injury, and neither conducted all assessments after the acute injury period. In 1 study,²¹ a single case design, the subject was scanned 3 times, but within 2 months of injury. In the second study,³⁷ there was a long-term follow up at 18 months postinjury, but the first scan was done at 6 days postinjury; here, FA improved over time.

CONCLUSIONS

Our results show that interval decline in diffusion anisotropy in frontal and temporal lobes was present in a group of patients

Fig 2. Box plot diagrams showing FA reduction in right and left frontal lobes (A, B) and right and left temporal lobes (C, D), respectively. Mean, first to third quartiles and minimum and maximum scores are indicated. For each pair of box plots, the left box plot contains values from the 4.5 month postinjury scan; the right box plot contains 2.5 year postinjury scan values. FA values, presented on the Y axis, range from .2 to .5 (A, B); .15 to .4 (C), and .15 to .45 (D).

with moderate-severe, subacute TBI. The location of this progression is concordant with increasing frontotemporal atrophy observed in our previous study that also included these patients.¹¹ It is of interest, however, that the corpus callosum, another frequently affected area, did not show progression of WM damage. Further research is needed on a larger sample to replicate this pattern of findings. It remains to be determined how these measurements correlate with clinical outcome in larger populations.

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Prediction of Return to Productivity After Severe Traumatic Brain Injury: Investigations of Optimal Neuropsychological Tests and Timing of Assessment

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ABSTRACT. Green RE, Colella B, Hebert DA, Bayley M, Kang HS, Till C, Monette G. Prediction of return to productivity after severe traumatic brain injury: investigations of optimal neuropsychological tests and timing of assessment. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S51-60.

Objectives: (1) To examine predictive validity of global neuropsychological performance, and performance on timed tests (controlling for manual motor function) and untimed tests, including attention, memory, executive function, on return to productivity at 1 year after traumatic brain injury (TBI). (2) To compare predictive validity at 8 weeks versus 5 months postinjury. (3) To examine predictive validity of early degree of recovery (8wk–5mo postinjury) for return to productivity.

Design: Longitudinal, within subjects.

Setting: Inpatient neurorehabilitation and community.

Participants: Patients (N=63) with moderate to severe TBI.

Interventions: Not applicable.

Main Outcome Measures: Primary outcome: return to productivity at 1 year postinjury. Primary predictors: neuropsychological composite scores. Control variables: posttraumatic amnesia, acute care length of stay (LOS), Glasgow Coma Scale score, age, and estimated premorbid intelligence quotient.

Results: Return to productivity was significantly correlated with global neuropsychological performance at 5 months postinjury ($P < .05$) and showed a trend toward significance at 8 weeks. Performance on the untimed composite score, and more specifically executive and memory functions, mirrored this pattern. Logical Memory performance significantly predicted return to productivity, but not other memory tests. Timed tests showed no significance or trend at either time point. Early degree of recovery did not predict return to productivity. Among control variables, only acute care LOS was predictive of return to productivity.

Conclusions: Findings validate utility of early neuropsychological assessment for predicting later return to productivity. They also provide more precise information regarding the optimal timing and test type: results support testing at 5 months postinjury on untimed tests (memory and executive function),

but not simple attention or speed of mental processing. Findings are discussed with reference to previous literature.

Key Words: Outcome assessment (health care); Rehabilitation; Brain injuries; Work.

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MODERATE AND SEVERE TBI are associated with cognitive, physical, and emotional impairments that can impede one's ability to engage in productive activities, such as work, school, parenting, and leisure pursuits. One of the more urgent early questions of brain-injured persons and their family members is whether return to prior activities will be possible. However, because of the variability across brain injuries and the wide range of factors that influence return to prior activities, our ability to predict accurately such clinical outcomes is limited, despite extensive research to date.

Indeed, the literature examining prediction of functional outcome is vast. The many predictors that have been examined fall largely into 1 of 2 categories: injury-related variables, such as severity of injury,¹⁻¹⁰ mechanism of injury,¹⁰⁻¹⁷ and cognitive impairment,^{9,18-33} and demographic/premorbidity variables, such as age,^{1,3,6,10,34-39} education,^{1,3,4,7,34,36-38,40} and preinjury employment.^{3,32,40-46} The functional outcomes predicted by these variables are most frequently measured with broad composite scales, such as the FIM^{1,2,7,35,39,42,47-50} and the GOS,^{1,4,5,6,10,36,51-54} among a variety of others.^{1-3,7,13,15-17,35,39,44,50,55-62} Many of these global assessment tools are widely employed clinically, making them good candidates for retrospective studies. Moreover, their frequent use in the literature facilitates cross-study comparison. However, the limited sensitivity of these measures—particularly to the more subtle deficits that persist in the later stages of recovery^{55,63,64}—likely explains some of the discrepancies in the literature, where significant associations are found between a given predictor and an outcome (eg, age and the Community Integration Questionnaire) in some studies,^{11,21,59,61} but not others.^{3,44}

A more specific functional outcome measure—for which outcome prediction becomes more reliable the further from

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List of Abbreviations

GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
LOS	length of stay
NAART	North American Adult Reading Test
PTA	posttraumatic amnesia
RAVLT	Rey Auditory Verbal Learning Test
RTW	return to work
RVDLT	Rey Visual Design Learning Test
TBI	traumatic brain injury
WTAR	Wechsler Test of Adult Reading

injury—is return to work,^{3,7,37-39,44,65-68} where the passage of time allows for differences in recovery rates to exert less of an influence on outcome. In addition to the obvious financial benefits, returning to paid employment has been shown to improve motivation to integrate back into society, increase the opportunity for social interaction, enhance self-esteem and perceived status, and even reduce the likelihood of secondary complications such as physical disability and substance abuse.^{69,70} An increased interest in RTW in recent years has been noted by Shames et al,⁷¹ who attribute this in part to a change in the World Health Organization's *International Classification of Functioning, Disability and Health*, where RTW was included as a key component of rehabilitation in 2001.⁷¹ One limitation of RTW as a clinical outcome measure, though, is that it does not subsume clinically and personally relevant vocational and avocational activities, such as parenting, leisure pursuits, and school. Ascertaining such premorbid productivity information, against which to compare postinjury return to productivity, is not straightforward because of the need for an available, reliable historian. Nonetheless, a small number of recent studies have been able to examine return to productivity after TBI.⁶⁸

Although RTW and return to productivity are more reliable outcome measures than composite scales such as the FIM and GOS, prediction studies have still shown inconsistencies. For example, many studies employing demographic predictors have shown significantly better outcomes with younger age,^{25,29,37,39,45,46,72-77} but a number have not.^{12,23,44,65,78,79} Some studies have shown positive correlations with higher income,²³ lower preinjury education level,^{12,32,37,46,66,74,80,81} and lower preinjury substance use,^{12,16,82} but, again, conflicting findings have been observed.⁴⁴ With regard to injury-related predictors, previous studies have demonstrated that, overall, injury severity is an important predictor of RTW and return to productivity^{3,7,8,15,19-21,31-33,37-39,48,60,83-84}; however, many studies have found weak or no evidence of an association between RTW/return to productivity and length of coma, depth of coma (as measured by the GCS), or length of PTA,^{15,37,44,45,76,80,84} although length of coma and length of PTA are consistently found to be stronger predictors of outcome than GCS.^{19-21,29,72,81,84,85}

Inconsistencies across studies may be attributable, in part, to differences in the quality of predictor variable data across studies. For example, length of coma and length of PTA are often unrecorded,^{3,44,73,86} resulting in high rates of missing data in studies.^{3,73,86} GCS scores may be confounded by intoxication at time of injury,^{87,88} which is prevalent but unreliably reported in medical records.⁸⁶⁻⁸⁸ Moreover, the collection of these variables is not required to be undertaken in a fully standardized fashion by a trained clinician, which can itself affect the reliability of data. Finally, these injury severity scores are only indirectly related to functional outcome; thus, variance accounted for would logically be limited.

There is a growing literature examining the relationship between neuropsychological test performance and RTW or return to productivity.^{9,18-33} Cognitive predictors are injury-related, but have the advantage of being more directly related to functioning (eg, school and most jobs require a minimum level of attention and memory). Neuropsychological tests require standardized administration, and many neuropsychological tests require administration by trained examiners under expert supervision. It is therefore not surprising that correlations between cognitive functions and RTW and return to productivity have been observed not only in studies of concurrent correlation,^{76,89-93} but also in studies employing clinically valuable predictive designs, where neuropsychological assessment has been conducted at 6 months or earlier.^{9,18,20,23,25-28,30-32}

Sherer et al,³² for example, found a significant contribution to return to productivity at 1 year postinjury of neuropsychological testing conducted on resolution of PTA.

The cognitive functions that have been most strongly associated with RTW or return to productivity are speed of processing,^{9,12,23,24,26,27,29,33} memory,^{12,18,20,22,24,27,31} and intellectual status.^{12,19,23,33,79,93,94} However, as with other predictor variables, some inconsistencies have been observed. For example, regarding memory function, Dawson et al²⁰ found that recovery of memory during acute care (3 words at 24 hours) was the sole predictor of return to productivity at 4 years postinjury.²⁰ Boake et al¹⁸ found that all 3 memory tests employed in their study (ie, Logical Memory Immediate and Delayed Recall; RAVLT) significantly predicted return to productivity. Cifu et al³¹ found that memory (Logical Memory Delayed Recall) was the only domain among several examined that predicted later return to productivity. On the other hand, Rassovsky et al⁹ observed no mediating effect of memory performance (at 6 months postinjury) for injury severity and RTW (at 1 year postinjury), and in an earlier study, Fraser²⁷ showed a relationship between return to productivity and a range of cognitive functions, with the exception of memory (and problem-solving). Critical differences across studies in the number and type of memory tests and subtests, as well as in the injury severity and demographic control variables employed, likely explain some of these discrepancies. Speed of processing also has shown disparate findings, with most studies demonstrating significant predictive validity of early cognitive processing speed for later return to productivity,^{9,32} but a small number of studies showing no relationship.^{18,31} Lack of control for manual motor impairments across studies (either orthopedic or centrally mediated) may explain observed disparities. Another important methodologic difference across these studies, as well as the wider literature on prediction of return to productivity, concerns sample bias. For example, some studies have employed retrospective designs,^{3,19,22,65,66,79,93,95,96} which are more vulnerable to sample bias as well as constraints on choice of predictor and outcome measures. Others studies have employed prospective designs, though it should be noted that even large, multisite prospective studies using database registries have been vulnerable to selective attrition and consequent sample bias, with attrition rates reaching upwards of 75% in some studies.^{31,46,76,97,98}

Given the clinical value of predicting return to productivity, the important findings to date, but also the inconsistencies of past research, further research is clearly warranted. In the current study, we attempted to build on the strengths of previous research, to obviate past methodologic limitations, and to address some novel questions. We recruited patients prospectively from a large, urban neurorehabilitation facility where we had the opportunity to follow every patient clinically over the course of the study, providing clinical assessment and feedback at each assessment. Consequently, recruitment and retention were high, which minimized threat to reliability from sample bias. Family involvement in the study was extensive; therefore, access to reliable historians was available, and it was possible to obtain very specific premorbid and current information regarding roles and activities. As well, we had full control over our choice, timing, and collection of predictor and outcome variables.

We examined early neuropsychological performance as a predictor of return to productivity at 1 year postinjury, comparing the predictive validity of neuropsychological performance at 8 weeks postinjury with performance at 5 months postinjury. To our knowledge, no studies have compared more than 1 early subacute neuropsychological assessment within

the same study in the prediction of return to productivity, and only 1 study has examined RTW: Spikman et al⁹⁹ found that from a battery of attention, speed of processing, and executive function tests, only early performance on the Stroop Color-Word test (a timed test of selective attention) predicted RTW at 2 to 5 years postinjury. However, the variable accounted for only a small amount of variance. A determination of the optimum earliest time point at which to assess cognitive functioning in order to predict return to productivity reliably, along with an understanding of which tests are most predictive, would be of marked clinical and practical utility. Indeed, only a handful of studies have examined early cognitive assessment and later return to work (see Sherer et al³² for review).

We also examined whether the degree of early subacute recovery (8wk–5mo postinjury) was a better predictor of outcome than performance level at either of the 2 time points. Again, only the study by Spikman⁹⁹ has addressed this question, to our knowledge, and specifically for RTW rather than return to productivity. They found a circumscribed and small effect: that early recovery across the first and third occasion of testing (\approx 1–6mo postinjury) on the Stroop Color-Word test was predictive of 2-year to 5-year RTW. It is clinically intuitive that a rapid early recovery would predict a better productivity outcome than a slow early recovery. However, this question has had only minimal empirical investigation and there is scope for misinforming patients if this intuitively compelling possibility is actually incorrect.

At each time point, we examined global neuropsychological performance on a composite of cognitive tests from a range of cognitive domains that are commonly disrupted in TBI. Although a large cognitive battery offers the advantage of increased reliability, a more parsimonious battery offers greater feasibility. We therefore subdivided the global composite into a timed test aggregate made up of tests of simple and complex speed of processing, and an untimed test aggregate made up of tests of memory, attention, and executive function. We also examined a series of demographic and injury control variables to identify any variables that might account for significant return to productivity outcome variance, and that would be included in analyses.

Previous studies have identified both timed and untimed tests as predictors of RTW and return to productivity. We were interested in distinguishing timed from untimed processing for several reasons. First, speed of processing is arguably the most ubiquitous and persisting complaint after moderate and severe TBI.¹⁰⁰ Second, whether speed of processing should be disruptive to return to productivity is not self-evident. While many activities involve time constraints, speed of processing impairments can be compensated for by allotting extra time to complete activities. Last, previous studies examining speed of processing as a predictor of return to productivity have employed tasks with manual motor demands, without any reported control for central or orthopedic injuries to motor function; in 1 study,⁹ 3 of 4 speed of processing tests had manual motor requirements, for example. Consequently, it has not been clear how much outcome variance in these studies might be attributed to persisting peripheral or central motor damage. In the present study, we employed tests of speed of processing without manual motor demands or where the contribution of manual motor function/dysfunction could be parceled out using a subtraction approach (eg, Trail Making Test Part B minus Trail Making Test Part A).

Finally, in addition to multivariate logistic regression models to examine global predictor (timed vs untimed) and control variables, we also conducted nested regression analyses of the smaller cognitive domains, focusing in particular on memory

because of the ubiquitous, but also conflicting findings in this domain. Here, we examined the respective contributions of memory for verbal information (organized and unorganized), and memory for visuospatial (unorganized) material.

In summary, we used regression models to identify relevant control variables, and then examined the predictive validity of cognitive performance for return to productivity at 1 year, comparing 2 early, subacute time points and also using early degree of recovery as a predictor. Composite scores of clinically meaningful domains (eg, timed test aggregate, memory test aggregate) were used; these provide greater reliability than individual test performances, but have been little used in previous studies. We re-examined speed of processing—a predictor with somewhat inconsistent previous findings—controlling for motor impairments that may have confounded previous research. In addition, we examined memory using two approaches to analysis (aggregate, individual test contributions) in order to explain previous inconsistencies with this variable.

METHODS

The study protocol was approved by the research ethics board at the Toronto Rehabilitation Institute, and the procedures of the study were in accordance with the standards of the research ethics board.

Participants

The 63 patients with TBI in this study were part of a larger study conducted at the Neurorehabilitation Program of the Toronto Rehabilitation Institute investigating the natural history and mechanisms of cognitive and motor recovery after TBI. The neurorehabilitation program has a province-wide catchment area, is located in an urban center, and sees patients both with and without motor vehicle or private insurance. Therefore, there is a wide range of socioeconomic status and ethnicities represented in the program. Participants in the larger study underwent prospective neuropsychological assessments at 1 to 3 months postinjury, 3.5 to 5.5 months postinjury, and 11 to 13 months postinjury and met the following inclusion criteria: (1) acute care medical diagnosis of TBI, (2) PTA 1 hour or more and/or GCS of 12 or less either at emergency or the scene of accident and/or positive computed tomography or magnetic resonance imaging findings, (3) age between 17 and 80 years, (4) ability to follow simple commands in English based on speech language pathologist intake assessment, and (5) competency to provide informed consent for study or availability of a legal decision-maker.

Exclusion criteria included the following: (1) orthopedic injuries affecting both upper extremities; (2) diseases primarily or frequently affecting the central nervous system, including dementia of Alzheimer type, Parkinson's disease, multiple sclerosis, Huntington's disease, lupus, and stroke; (3) history of psychotic disorder; (4) not emerged from PTA by 6 weeks postinjury, as measured by the Galveston Orientation Amnesia Test¹⁰¹; (5) TBI secondary to another neurologic event (eg, a fall caused by stroke); and (6) failure on a symptom validity test (Test of Memory Malingerer)¹⁰² at any of the assessments.

Participants were eligible for the current study if they were at least 1 year postinjury. Of a total of 70 eligible participants from the larger study, 5 could not be reached at 1 year postinjury, and 2 declined to participate. The sample therefore included 63 participants, representing a 90% retention rate.

Table 1 shows the demographic and injury characteristics of the study sample. The study sample was severely impaired on average, with a typically high ratio of male to female subjects,

Table 1: Injury and Demographic Characteristics of Sample (N=63)

Variable	Proportion	Range
Age (y)	36.98±14.91	17–79
Education (y)	12.84±2.75	8–21
Premorbid intelligence quotient (n=58)	99.93±12.90	78–124
Sex (% male/female)	82.5/17.5	
Socioeconomic status (%) (based on Hollingshead Classification)		
1 (Major business/professional)	11.1	
2 (Medium business/minor professional, technical)	38.1	
3 (Skilled craftsperson, clerical, sales worker)	19.0	
4 (Machine operator, semiskilled worker)	30.2	
5 (Unskilled laborer, menial service worker)	1.6	
Type of injury (%)		
Motor vehicle collision	58.7	
Fall	30.2	
Assault	7.9	
Sports injury	3.2	
Acute care LOS	37.10±16.45	9–88
GCS (lowest of recorded scores)	6.77±3.43	2–13
Mild (13–15) (%)	11.1	
Moderate (9–12) (%)	15.9	
Severe (≤8) (%)	63.5	
Missing data (%)	9.5	
Length of PTA (%)		
<5min (very mild)	3.2	
1–24h (moderate)	1.6	
1–7d (severe)	21.0	
1–4wk (very severe)	40.3	
>4wk (extremely severe)	11.3	
Missing data	22.6	

NOTE. Values are means ± SDs unless otherwise noted.

and with the most frequent cause of injury being motor vehicle collisions.

Materials

Predictor variables: neuropsychological test aggregates. All of the tests were selected based on a priori clinical and experimental consensus regarding the cognitive domains most affected by TBI,¹⁰⁰ and on their known validity and reliability for TBI. Cognitive domains assessed included executive function (working memory and abstract intellectual functioning)^{103–105}; attention span¹⁰⁶; speed of processing^{100,107,108}; verbal and visuospatial learning, recall, and recognition^{100,106}; and verbal intellectual function^{104,105} (see table 2 for a list of neuropsychological tests and the functions they measure). None of the neuropsychological tests have appreciable floor or ceiling effects for patients with moderate to severe TBI. Tests with alternate forms were administered on repeat testing to minimize practice effects.

Classification of tests into aggregates was based on known clinical classifications and expert knowledge. The main aggregate was a global neuropsychological aggregate, made up of all neuropsychological tests in the battery (see table 2). This aggregate was then subdivided into timed tests and untimed tests, with the former composed of measures of simple and complex speed of processing (ie, parallel processing or speed of decision-making) and the latter composed of untimed tests

of attention, executive function, and verbal and visuospatial memory, for both organized and unorganized material.

In order to avoid contamination of findings by orthopedic injury or central motor deficits, all timed tests either did not have manual motor demands or had motor contributions parceled out through a subtraction method (eg, Trail-Making Test Part B minus Trail-Making Test Part A). The battery required 2 to 2.5 hours to administer on average.

Control variables: preinjury demographic characteristics and injury severity variables. Information about age, productivity, and highest level of education attained was collected during a structured interview from patients, and corroborated by caregivers where necessary. Estimated premorbid intelligence quotient was estimated for each participant using the WTAR¹⁰⁹ or the NAART.¹¹⁰ (Note that for the larger study from which participants were drawn, the NAART was replaced by the WTAR, which has been shown to demonstrate good psychometric properties for this population.¹¹¹)

Information about severity of injury (ie, GCS, PTA, acute care LOS) was abstracted from the rehabilitation hospital records wherever possible. Where information related to PTA was not recorded in the medical record, questioning of the patient and caregivers was undertaken during a structured

Table 2: Neuropsychological Assessment Battery

Aggregate	Cognitive Domain and Test	
Untimed	SIMPLE ATTENTION: Auditory-verbal and visuospatial span forwards ¹⁰⁶	
	EXECUTIVE FUNCTION (WORKING MEMORY): Auditory-verbal and visuospatial span backwards ¹⁰⁶	
	EXECUTIVE FUNCTION (VERBAL ABSTRACTION): Similarities Test (Wechsler Adult Intelligence Scale-III and Wechsler Abbreviated Scale of Intelligence) ^{104,105}	
	MEMORY VERBAL (UNORGANIZED): Rey Auditory Verbal Learning Test: total learning, immediate and delayed recall, recognition subtests ¹⁰⁰	
	MEMORY NONVERBAL (UNORGANIZED): Rey Visual Design Learning Test: total learning and recognition subtests ¹⁰⁰	
	MEMORY VERBAL (ORGANIZED): Logical Memory (Wechsler Memory Scale-III) ¹⁰⁶ : immediate and delayed recall	
	Timed	SPEED OF PROCESSING: SIMPLE: Stroop Test: Speeded word reading and speeded color naming subtests ¹⁰⁸
		SPEED OF PROCESSING: COMPLEX: Symbol Digit Modalities Test-Oral ¹⁰⁷ (speeded pairing of visual symbols with digits with responses given orally)
		Hayling Sentence Completion Test (modified for computer administration): congruent minus incongruent conditions ¹⁰³ (speeded oral generation of words, either congruent or incongruent with a series of target words)
		Choice reaction time minus simple reaction time (speeded, psychomotor tests of decision making and simple response to stimulus)
	Trail Making Test Part B ¹⁰⁰ minus Trail Making Test Part A ¹⁰⁰ (speeded visual scanning and attention and set shifting [B] and speeded visual scanning and attention [A]; both psychomotor tasks)	

interview to ascertain length of PTA. PTA was described according to the classification described by Lezak et al.¹⁰⁰ Acute care LOS was calculated from admission and discharge dates from the acute care hospital.

Outcome variable: return to productivity. A dichotomous classification of return to productivity was made for all patients. Activities included paid employment (full or part-time), volunteer employment, school, parenting, home-making, and active retirement (ie, participation in cultural and physical activities). Information on premorbid and current activities was collected from patients and corroborated by caregivers. Two trained clinicians ascertained the match, or lack thereof, between current and previous level of productivity. In all cases, clear consensus was reached, with patients either returning to prior type and level of productivity or not.

Design and Procedures

The study employed a prospective, repeated-measures design. During the neuropsychological assessments at time 1 (8.0 ± 2.7 weeks postinjury) and time 2 (4.8 ± 1.2 months postinjury), a clinical interview of the patient was followed by the neuropsychological assessment, which was followed by a clinical feedback session with the patient and family/professional caregivers. Detailed information concerning premorbid role and activities was collected in the interview and feedback at the time 1 assessment from patients and their caregivers. Return to productivity information was collected in person at 1 year postinjury.

The neuropsychological test battery was divided into 5 blocks of tests, with a fixed order of tests within each block, and with test blocks counterbalanced across subjects (but consistent within subjects across assessments). The battery was designed to minimize interference between tests (eg, the verbal memory tests 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. Alternate forms, used to minimize practice effects, were counterbalanced across subjects.

Data Analysis

All raw test scores obtained from standardized neuropsychological measures were transformed into normative scores using published normative data for the test. Cognitive test scores were transformed to a common metric and combined into larger aggregates in order to increase reliability and maximize power; there was insufficient sample size to allow for an examination of every test of cognitive functioning. 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.) To combine tests without normative data, we used the means and SDs of the tests in the later stages of recovery (ie, 5mo and 1y postinjury) to generate a z score. 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.

Logistic regression models were then undertaken. To build our models, we took a conservative approach based on our sample size and knowledge of factors that might influence outcome. First, logistic regression models regressing return to productivity on each of the control variables in separate regression models were carried out in order to determine which would be included as control variables in the cognitive models. Based on findings from previous studies, variables examined

were acute care LOS, premorbid intelligence quotient, age, years of education, GCS, and length of PTA. Only acute care LOS was significantly related to return to productivity; it was therefore included in the subsequent models. For each aggregate, separate logistic regressions on the time 1 results, on the time 2 results, and, finally, on the improvement (recovery) from time 1 to time 2 were conducted to study whether any of these significantly predicted return to productivity at the end of 1 year postinjury.

Analyses were performed with the R Programming Language version 2.6.2.^a

RESULTS

Classification of participants into those who did versus did not return to prior level of productivity revealed that 30.2% (or 19 subjects) had returned to their prior level of productivity by 1 year postinjury, whereas 69.8% participants (44 subjects) had not.

Early recovery as a predictor of outcome. Recovery of cognitive function (ie, change in performance from time 1 to time 2) did not significantly predict return to productivity for any of the aggregates nor show a trend toward significance. Therefore, this variable is not discussed further in the Results section.

All cognitive tests. Global neuropsychological performance at time 2 significantly predicted return to productivity at 1 year ($\beta=0.940$, $z_{51}=2.135$, $P<.05$, estimate of SE=0.44). At time 1, this aggregate did not significantly predict return to productivity; however, a trend toward significance was observed ($\beta=0.53$, $z_{51}=1.69$, $P=.09$, estimate of SE=0.31).

Timed neuropsychological tests. In contrast to the findings of global neuropsychological testing, no significant effects or effects approaching significance were observed at either time 2 ($\beta=0.47$, $z_{52}=1.16$, $P=.25$, estimate of SE=0.41) or time 1 ($\beta=0.36$, $z_{49}=1.04$, $P=.30$, estimate of SE=0.35). In order to ensure that we were not masking an effect of 1 subdomain by another, we examined simple versus complex subaggregates separately. However, again, no significant effect or trend toward significance was observed at either time 1 or time 2 for either of these timed subaggregates.

Untimed neuropsychological tests. Findings from these analyses mirrored those of the global aggregate and suggested that outcome variance for the global aggregate was likely attributable largely to this domain. At time 2, this aggregate significantly predicted return to productivity ($\beta=0.95$, $z_{51}=2.18$, $P<.05$, estimate of SE=0.43) and showed a trend at time 1 ($\beta=0.53$, $z_{51}=1.71$, $P=.09$, estimate of SE=0.31).

In order to understand better the source of outcome variance at time 2, the 3 smaller aggregates were examined. Memory performance significantly predicted return to productivity ($\beta=0.98$, $z_{51}=2.15$, $P<.05$, estimate of SE=0.45). In more fine-grained, separate analyses for each of the 3 memory recall tests: Logical Memory (immediate plus delayed recall) significantly predicted return to productivity ($\beta=0.70$, $z_{51}=1.97$, $P<.05$, estimate of SE=0.35). RAVLT (total learning plus short delay recall plus long-delay recall) showed a trend toward significance ($\beta=0.49$, $z_{51}=1.70$, $P=.09$, estimate of SE=0.29). RVDLT (total learning) showed no significant effect or trend toward significance: ($\beta=0.31$, $z_{51}=1.48$, $P=.14$, estimate of SE=0.21). For discrimination (RAVLT plus RVDLT recognition hits minus false alarms), a trend toward significance was observed ($\beta=0.80$, $z_{51}=1.87$, $P=.06$, estimate of SE=0.43).

We next examined the contribution of executive function and attention span subaggregates to the prediction of return to productivity. While attention span at time 2 did not show

evidence of predictive validity for return to productivity ($\beta = -0.11$, $z_{52} = -0.38$, $P = .70$, estimated SE = 0.30), executive function significantly predicted return to productivity ($\beta = 0.89$, $z_{51} = 2.24$, $P < .05$, estimated SE = .040).

DISCUSSION

We examined the predictive validity of early cognitive performance after moderate and severe brain injury for return to prior level of productivity at 1 year postinjury while controlling for severity of injury. We found that prediction of return to productivity was stronger at 5 months postinjury than at 8 weeks postinjury, and that while performance on global neuropsychological functioning significantly predicted return to productivity, untimed tests rather than tests of speed of processing appeared to account for the outcome variance. More specifically, memory function (both as a composite measure) and individually for Logical Memory (but not RAVLT or RVDLT) at 5 months postinjury significantly predicted return to productivity at 1 year, as did executive function, but not attention span. We found no evidence that early degree of recovery was predictive of eventual return to productivity.

Return to productivity, particularly employment, is highly valued by society.³² Our ability to predict whether or not TBI survivors can return to their prior type and level of productivity is critically important for clinical and economic planning, as well as the process of adjustment to disability for patients and their families. Our findings validate the utility of neuropsychological testing to predict return to prior type and level of productivity, and shed more light on the timing and type of tests that are most and least predictive for return to productivity.

The current results differ slightly from previous studies. As in our study, Rassovsky et al⁹ (at 6 months postinjury) found that cognitive deficits significantly influenced return to productivity in a study using structural equation modeling to explore mediators of the relationship between severity of injury and return to productivity at 1 year postinjury. However, they observed that speed of processing, but not memory (using the RAVLT), accounted for significant outcome variance. This discrepancy may be explained by the outcome measures employed. Using a more reliable index of memory comprising multiple tests, memory predicted return to productivity in our study. As well, we found that RAVLT contributed less outcome variance to return to productivity than Logical Memory. Arguably, Logical Memory (a measure of story recall) has greater ecologic validity than RAVLT (a test requiring the recall of a list of 15 words presented in an unorganized fashion). Most verbal information in everyday life is presented in a more meaningful, structured manner (eg, stories, tasks, anecdotes). In addition, in everyday life, there may be greater expectation and less accommodation for persons to learn and retain this type of information: the inability to recall a personal anecdote, a short story, the contents of a movie, or the elements of a structured task might be quite debilitating in many settings and therefore highly predictive of success or failure. On the other hand, in circumstances in which a long list of unorganized information is presented (eg, a task with many unrelated steps), there might be greater tolerance for and accommodation of compensatory aids to be used, like note-taking. Thus, ability to recall this type of information may be less closely tied to success in returning to prior activities. We did not find any evidence for the predictive validity of visual memory. However, nonverbal memory might play a predictive role for the return to some kinds of activities that depend more heavily on memory for visual information.³³ It would be of value for future research to examine larger samples that would enable

subgroups analyses; in this way, activities that specifically depend on visual memory (eg, engineering, taxi-driving, architecture, designing) could be separately examined.

With regard to timed tests, a critical difference between the current study and that of Rassovsky⁹ among others that found predictive validity of speed of processing^{32,99} was that we designed the present study to minimize the contribution of manual motor capacity in order to avert contamination from manual motor dysfunction. The timed tests either had no manual motor demands or allowed for the use of a subtraction technique to parcel out motor contributions. In the Rassovsky⁹ study, for example, 3 of 4 tests had manual motor demands, and orthopedic injury, a common occurrence in TBI, was not an exclusion criterion. By 6 months postinjury, the time of assessment in their study, acute effects of orthopedic injury would have resolved; but many patients can have persisting weakness, pain, and slowness associated with orthopedic injury,^{112,113} and there was no evidence presented to rule out the persistence of centrally mediated motor impairments at 6 months postinjury. Consequently, the relationship between speed of processing and return to productivity in past studies could be attributable to manual motor factors (either orthopedic or central), rather than speed of mental processing per se. Why might there be a lack of correlation between speed of processing and return to productivity? One possibility is that there are straightforward, self-evident adaptations that can accommodate slower speed of processing, such as planning and allocating more time for tasks/activities. In many jobs, staying late at work or taking work home is possible. For school, studying for longer hours is within the control of the student. Active retirement activities (eg, cultural, gardening) are not obviously impeded by slower speed. Because speed of processing impairment is so prevalent even many years postinjury, a lack of correlation between speed of processing impairments and return to productivity would be a welcome outcome. Further research with a larger sample size, similarly low attrition, and similar controls for manual motor impairment would be clinically valuable.

Our results also differed somewhat from those of Sherer et al,³² who found that 1-month performance predicted 1-year postinjury vocational outcome. We found only trends toward significance at our early time point. One explanation is that the Sherer³² study had more power because of its larger sample size. Another explanation is that in the current study, while attrition was only 10%, the attrition rate in the Sherer³² study, which was a larger, multisite study, was greater than two thirds. Therefore, it is possible that their study was vulnerable to selective attrition, rendering the sample biased. For example, it is possible that those with milder impairments and greater independence and/or those with more severe impairments and poorer outcomes (with greater need of support) were more able or motivated to return for follow-up examination.

Finally, we did not find any evidence that early, subacute recovery from time 1 to time 2 was predictive of return to productivity, in contrast with Spikment et al,⁹⁹ who found that early recovery (1–6mo postinjury only) accounted for a small but significant amount of outcome variance for RTW. From a clinical point of view, it is an intuitively appealing possibility that a good early recovery bodes well for the future and that conversely, a slow early recovery bodes poorly. On the basis of these 2 studies, it would appear that degree of early recovery is not a robust prognosticator of RTW/return to productivity. If this interpretation is verified in future research, then it would be important for clinicians to avoid such an assumption.

Study Limitations

The current study was limited in its power because of sample size. Greater power would have allowed for a more nuanced analysis of the contributions to outcome variance of individual tests. It would have also allowed for subgroup analyses of patients returning to different types of activities that might have been differentially affected by cognitive tests. As well, while only acute care LOS predicted return to productivity, it is possible that interactions between control variables may have had an impact on return to productivity. Again, a more powerful model would have included all control variables and possible suppressor variables within the model. Similarly, while it was necessary to conduct separate regression analyses to examine aggregates, greater power would have permitted the examination of all aggregates within the same model. The absence of significance at 8 weeks postinjury may also be explained by a dearth of power, especially because we observed trends toward significance for some variables. Knowing whether earlier performance is predictive of return to productivity would be clinically valuable. In this regard, while we decided that reliable change indices were beyond the scope of this study, future research might include this level of analysis to determine whether variables are predictive at the individual as well as group levels.

An additional limitation of the current study is the differences in task demands of the tests in the timed and untimed aggregates. Thus, factors other than speed of processing may have differed across the aggregates. A better means of investigating the impact of speed of processing on return to productivity would be to have timed versus untimed analogs of the same tasks.

In the present study, we did not find a relationship between degree of early recovery and return to productivity. Because a higher level of initial performance leaves less room for recovery, the absence of an observed relationship may have been partially attributable to this factor if acute care LOS did not fully control for severity of injury. Again, further research with more powerful statistical models would help to minimize this limitation.

In examining the predictive validity of early neuropsychological testing, one cannot escape the alternative interpretation of the findings that differences in findings across tests may be explained by differences in recovery rates of tests. For example, if speed of processing and attention span impairments recover more quickly or more completely than memory and executive function deficits, this would provide an alternative explanation of the lack of correlation between the former domains and return to productivity. This explanation is rendered less likely by the finding that speed of processing recovers more slowly than other cognitive functions, however.¹⁰⁰

Finally, our results cannot be generalized to patients with the most severe impairments because we employed as an exclusion criterion patients whose PTA had not resolved by 6 weeks postinjury.

CONCLUSIONS

The current study replicates previous research demonstrating that early neuropsychological testing is a useful predictor of return to productivity at 1 year. Our results extend previous findings by indicating that testing at 5 months postinjury is more effective at predicting return to productivity than testing at 8 weeks postinjury. However, further research with a larger sample size would be valuable to confirm or disconfirm this finding and, moreover, to ask the more nuanced question of whether earlier neuropsychological testing might be predictive

of later return to productivity for specific subgroups of people with TBI (eg, those with milder injuries). Our results also extend previous research by suggesting that a more parsimonious battery based on untimed tests—rather than a comprehensive neuropsychological battery—may allow for effective prediction of return to productivity. In particular, our findings indicate that an optimal test battery would be made up of (1) either a variety of memory tests or several tests of verbal memory for organized information (such as Logical Memory) and (2) tests of executive function. Also of clinical relevance was the finding that the magnitude of early recovery did not appear to be a useful predictor of return to productivity; if future research confirms this finding, it will be important for clinicians not to speculate on future outcomes based on early recovery. Finally, our results suggest that speed of processing—whether simple or complex—does not play a significant role in return to productivity. If confirmed, the lack of prognostic value of this prevalent and persisting impairment would be a welcome finding.

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ORIGINAL ARTICLE

The Efficacy of Cognitive Behavior Therapy in the Treatment of Emotional Distress After Acquired Brain Injury

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ABSTRACT. Bradbury CL, Christensen BK, Lau MA, Ruttan LA, Arundine AL, Green RE. The efficacy of cognitive behavior therapy in the treatment of emotional distress after acquired brain injury. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S61-8.

Objective: To evaluate the efficacy of cognitive behavior therapy (CBT), adapted to meet the unique needs of individuals with acquired brain injury (ABI), and modified for both group and telephone delivery.

Design: Matched-controlled trial, with multiple measurements across participants, including pretreatment baseline assessment plus posttreatment and 1-month follow-up.

Setting: Outpatient community brain injury center.

Participants: Participants (N=20) with chronic ABI. Ten were assigned to the CBT treatment group and 10 to education control. All were experiencing significant emotional distress at the onset of the study.

Intervention: Eleven sessions of CBT (or education control), including 1 introductory individual session plus 10 further sessions administered in either group format or by telephone. The CBT was designed to decrease psychologic distress and improve coping. Specific adaptations were made to the CBT in order to better accommodate individuals with cognitive difficulties.

Main Outcome Measures: Primary outcome measures included the Symptom Checklist-90-Revised (SCL-90-R) and the Depression Anxiety Stress Scales (DASS-21). Secondary outcome measures included the Community Integration Questionnaire (CIQ) and the Ways of Coping Scale, Revised.

Results: Significant CBT treatment effects (in both group and telephone formats) were observed on the SCL-90-R and the DASS-21, whereas no significant effects were observed in the education control group. No significant effects of treatment were observed on the CIQ or Ways of Coping Scale, Revised.

Conclusions: Results suggest that adapted CBT—administered by telephone or in a face-to-face group setting—can significantly improve emotional well-being in chronic ABI.

Key Words: Anxiety; Brain injuries; Depression; Psychotherapy; Rehabilitation.

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PEOPLE WITH ABI are at increased risk for the development of psychiatric disturbance; many have extreme and protracted emotional disturbances in the months and years after injury.¹ However, the emotional consequences of ABI have historically received little attention. Although physical and cognitive symptoms are often the focus of inpatient rehabilitation programs, the emotional impact of ABI is frequently undertreated.^{2,3} For people in the chronic stages of ABI, outpatient treatment for psychiatric sequelae may be inaccessible because of geographic remoteness, financial barriers, or physical disability limiting travel to treatment facilities.⁴ Moreover, to date, there have been no validated treatments tailored to meet the specific needs of people with ABI.

The most common post-ABI psychiatric symptoms are depression^{5,6} and anxiety,⁵ with the prevalence of depression estimated to be upwards of 40%.⁷ Importantly, the presence of psychologic symptoms, particularly depression and anxiety, places individuals at increased risk for poorer outcomes after brain injury.⁸⁻¹¹ For example, during rehabilitation, the severity of depressive symptoms has been shown to be a robust determinant of poorer functional outcomes after TBI, even after controlling for demographic variables, cognitive deficits, and injury severity.⁹ Emotional distress has also been shown to have a similar direct and negative impact on life satisfaction.^{10,12} The consequences of prolonged, poor psychosocial adjustment after ABI can be profound, with suicide risk estimated to be 3 to 4 times greater than in healthy individuals.^{11,13} Importantly, if left untreated, clinically significant depressive symptoms do not appear to remit over time,^{8,10,11} suggesting that psychiatric symptoms represent a long-term consequence of ABI.

The persistence of emotional distress in ABI underscores the importance of both early identification and effective treatment interventions. However, traditional psychiatric treatments (pharmacologic and supportive) have been largely ineffective with clients with ABI.²

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List of Abbreviations

ABI	acquired brain injury
ANOVA	analysis of variance
CBT	cognitive behavioral therapy
CIQ	Community Integration Questionnaire
DASS-21	Depression Anxiety Stress Scales, short form
GSI	Global Severity Index
RBANS	Repeatable Battery of Adult Neuropsychological Status
SCL-90-R	Symptom Checklist-90-Revised
TBI	traumatic brain injury
WTAR	Wechsler Test of Adult Reading

To be effective, psychological treatments designed for ABI populations need to address the complex relationship between the various sequelae of ABI, including compromised self-awareness and coping. Poor coping (eg, emotion-focused coping) has been widely associated with adjustment problems, anxiety, and depression postinjury.^{14,15} Conversely, adaptive coping (ie, problem-focused coping) has been recognized as a precursor to better adjustment and overall well being,¹⁶ yet it may require intact executive function, often compromised after brain injury.¹⁷ Reduced self-awareness has been associated with adjustment difficulties post-ABI.¹⁸ Individuals with higher levels of self-awareness endorse greater levels of emotional distress and may also show greater motivation to change, translating into better outcomes.^{19,20} Yet, the opposite is true for patients with lower levels of self-awareness, often resulting in an underestimation of symptoms and difficulties articulating and recognizing their own impairments. One promising psychological treatment that may improve both effective coping and self-awareness is CBT.²¹

CBT is one of the most empirically validated short-term interventions aimed at decreasing psychological distress, improving coping, and enhancing psychological well being in a wide range of clinical populations²² with demonstrated efficacy in both the individual therapy modality and the group therapy modality, which is more cost-effective.²³ There is an emerging literature detailing the benefits of CBT in medical populations,²² where improved coping and overall quality of life have been observed in patients with breast cancer²⁴ and other chronic conditions.²⁵ CBT has also been shown to promote behavioral activation in patients with stroke²⁶ and to decrease depressive symptoms in an Alzheimer's population.²⁷

Despite the proven benefits of CBT for both the general and medical population, there is a paucity of treatment with demonstrated efficacy for ABI, and the few existing studies evaluating efficacy contain methodologic limitations.²⁸⁻³¹ Intuitively, CBT represents a promising intervention for individuals with ABI, given its efficacy among other populations with mood and anxiety symptoms. Nonetheless, there are strong suggestions that psychological interventions may need modifications to meet the unique needs of persons with ABI. Recently, Mateer and Sira³² also emphasized the importance of addressing the emotional sequelae in brain injury and developed several guidelines for tailoring CBT to a brain-injured population.

Until recently, though, there were only case study accounts of the effectiveness of CBT in the treatment of patients with ABI.²⁹ For example, Tiersky et al³⁰ evaluated the efficacy of an intensive neuropsychiatric rehabilitation program (cognitive remediation and CBT 3 times a week for 11 weeks) aimed at treating mild to moderate psychological symptoms and postconcussive symptoms in patients with TBI. The intervention was effective in reducing psychological distress in patients compared with wait list controls. The benefit of this evaluation was the inclusion of CBT as the primary treatment. Yet, methodologic limitations (eg, confounding of CBT with cognitive remediation, intensity and proximity of care) make it impossible to ascertain the underlying mechanism of improvement and likely precluded outpatients from rural communities or patients with mobility constraints from participating. Anson and Ponsford³¹ also found that group CBT improved coping strategies among patients with TBI, yet failed to impact mood or anxiety symptoms. Again, several methodologic limitations (no control group, small sample size, concurrent cognitive remediation) should be noted.³¹ Nevertheless, these preliminary positive findings are promising and support further investigations into the efficacy of CBT for the ABI population.

An additional major barrier to the delivery of postacute health care to people with ABI is accessibility.⁴ Financial circumstances, mobility issues, and geographic remoteness can impede access to services,⁴ which has led some (eg, Tam et al)³³ to advocate the development of telerehabilitation for ABI. Emerging research investigating the efficacy of telephone-administered psychotherapy have shown telephone therapy to be beneficial in the treatment of depression in patients with multiple sclerosis³⁴ and for terminally ill patients with cancer.³⁵ CBT has demonstrated efficacy for telephone delivery in medical populations, allowing for administration of therapy regardless of the patient's geographic location; however, the efficacy of telephone CBT in ABI has yet to be examined.

Finally, although CBT has been identified as the treatment of choice for the psychiatric sequelae of ABI, there is little research on its efficacy when adapted for patients with cognitive impairments.

The objective of this study was to evaluate the efficacy of a CBT protocol for reducing emotional distress and improving coping in a group of patients with chronic ABI that (1) has been adapted for people with ABI, (2) can be delivered in conventional group format or by telephone, and (3) is benchmarked against an education control group. We hypothesized, first, that CBT, administered by group or telephone modality, would improve the emotional wellness, coping skills, and community integration for individuals with chronic ABI. Second, we hypothesized that improvements in emotional wellness would be maintained at 1 month after cessation of treatment.

METHODS

Participants

The study protocol was approved by the research ethics board at the institution at which the study was conducted, and the procedures of the study were in accordance with the standards of the research ethics board.

A total of 20 patients were initially recruited from a community-based ABI treatment organization for patients with the chronic effects of ABI. Inclusion criteria were as follows: (1) age between 18 and 65 years, (2) greater than 1 year postinjury, (3) able to provide informed consent, (4) on stable dosage of psychoactive medication and being monitored by a physician or psychiatrist, and (5) scored at least 1 SD above the published mean on the SCL-90-R.³⁶ GSI.

Individuals were excluded from the study if they (1) were endorsing significant suicidal ideation at the time of evaluation, (2) were currently engaged in another CBT or other psychotherapeutic intervention (not including sporadic support from social work, psychiatry, case manager, or other counselor), (3) had a concurrent neurological or psychotic disorder, or (4) were diagnosed with a communication disorder that would preclude participation.

Twenty-nine patients were approached to participate in the study. Of these, 7 declined. Of the 22 who agreed to participate, 20 met the SCL-90-R cutoff. From these patients, 2 groups were created who were matched on SCL-90-R scores, age, sex, and years of education. All participants in the groups had sustained significant brain injuries. Patients with TBI had initial GCS scores in the moderate or severe range. All patients with nontraumatic injuries were currently operating in the moderate to severe range of cognitive impairment in at least 1 cognitive domain and/or had remained in inpatient treatment for more than double the provincial average length of stay (27 days).

Within each group, half of the participants were assigned to a conventional group format for their sessions, and half were

assigned to a telephone-administered format; this latter assignment was based on logistical considerations, with patients traveling the farthest distances or without reliable transportation to the treatment facility receiving the telephone administration. (After the study commenced, 1 participant in the telephone-administered CBT condition withdrew and was subsequently replaced by a new recruit.) Table 1 shows the demographic, medical, and injury variables of the 2 groups. The CBT and education control groups did not differ significantly across any of the following parameters: age, years of

education, time since injury, estimated premorbid intelligence quotient as measured by the WTAR,³⁷ or current cognitive functioning as measured by the RBANS.³⁸

There were 4 subgroups in total. The treatment group comprised a telephone-administered subgroup (telephone CBT; n=5) and a face-to-face, group format subgroup (group format CBT; n=5). The education control group was composed of a telephone-administered subgroup (telephone education control; n=5) and a group-administered subgroup (group education control; n=5).

Materials

Prior to treatment, all participants were administered the following neuropsychological tests to confirm similar levels of premorbid intellectual functioning and current cognitive functioning, and to provide clinical information with which to tailor therapy: (1) the WTAR,³⁷ an estimate of premorbid intelligence; and (2) the RBANS,³⁸ a brief, valid, and reliable measure of neuropsychological functioning that evaluates performance across a range of cognitive domains, providing summary index scores for each.

Primary Outcome Measures

Symptom Checklist-90-Revised.³⁶ This is a 90-item self-report questionnaire that measures a broad range of psychological symptoms, including a global severity index of psychological distress, the GSI. The GSI captures overall levels of emotional distress by calculating an aggregate score across clinical scales, allowing the comparison of overall emotional well being of participants with differing diagnoses. The SCL-90-R has robust psychometric properties and has been normed for the ABI population.³⁹

Depression Anxiety Stress Scales.⁴⁰ The DASS-21 is a 21-item self-report measure, shown to be a valid and reliable measure of depression and anxiety.⁴¹ The DASS-21 consists of a total score that evaluates overall emotional distress from all 3 clinical scales, as well as subscale scores of depression, anxiety, and stress.

Secondary Outcome Measures

The Ways of Coping Scale, Revised.⁴² The Ways of Coping Scale, Revised is a 66 item self-report measure used to assess the cognitive and behavioral strategies that individuals implement in order to cope with a situation that they perceive to be stressful. Factor analysis of the Ways of Coping Scale, Revised has generated 8 dimensions of coping, and the current study focused on planful problem-focused coping (Ways of Coping Scale, Revised, Planful Problem Focused subscale; planning, strategizing, and perspective-taking considered more adaptive)⁴³ and escape/avoidance coping (Escape Avoidance subscale; emotional method of coping, considered less adaptive).⁴²

Community Integration Questionnaire.⁴⁴ The CIQ is a 15 question self-report measure aimed at evaluating an individual's level of community reintegration after brain injury. It is a widely used measure of community reintegration after brain injury and has been shown to be a valid and reliable measure for the ABI population.

Design and Procedures

The design was a pre/posttreatment, education controlled design, comparing the effects of CBT to education both within and between groups. The modalities were commensurate on pretreatment SCL-90-R means, with no significant differences, similar distributions, and minimal effect sizes. Prior to treat-

Table 1: Demographic, Medical, and Injury Variables

	CBT Group (n=10)	Education Control (n=10)
Age, mean \pm SD (y)	39.8 \pm 10.44	42.50 \pm 13.01
Sex, n (%)		
Female	5 (50)	5 (50)
Male	5 (50)	5 (50)
Years postinjury, mean \pm SD	7.00 \pm 6.15	11.40 \pm 9.42
Injury type		
Trauma, n (%)	7 (70)	3 (30)
MVC	5	1
Pedestrian MVC	1	1
Fall	1	1
Nontrauma, n (%)	3 (30)	7 (70)
Aneurysm/AVM/stroke	2	3
Hypoxia/anoxia	1	1
Anaphylaxis	0	1
Tumor	0	2
Psychotropic medication, n (%)		
No medication	4 (40)	3 (30)
Antidepressant	5 (50)	6 (60)
Antipsychotic/mood stabilizer	3 (30)	6 (60)
Benzodiazepine	2 (20)	2 (20)
Stimulant	0 (0)	2 (20)
Marital status, n (%)		
Single	8 (80)	4 (40)
Married/common law	1 (10)	4 (40)
Divorced/separated	1 (10)	2 (20)
Years of education, mean \pm SD	13.10 \pm 1.66	14.00 \pm 1.89
Preinjury employment, n (%)		
Employed	8 (80)	6 (60)
Student	2 (20)	2 (20)
Unemployed	0 (0)	2 (20)
Postinjury employment, n (%)		
Employed	1 (10)	0 (0)
Student	0 (0)	1 (10)
Unemployed	9 (90)	9 (90)
Estimated premorbid IQ, mean \pm SD		
WTAR standard score	95.40 \pm 11.58	102.8 \pm 13.47
Cognitive functioning, mean \pm SD		
RBANS total index	66.10 \pm 16.37	73.20 \pm 15.62
Immediate memory	71.10 \pm 20.96	75.80 \pm 17.64
Attention	68.50 \pm 21.10	73.00 \pm 20.36
Language	79.50 \pm 13.06	83.00 \pm 16.55
Visuospatial	76.50 \pm 19.80	86.70 \pm 16.67
Delayed memory	64.30 \pm 25.29	75.40 \pm 20.38

Abbreviations: AVM, arteriovenous malformation; MVC, motor vehicle collision; IQ, intelligence quotient.

ment commencing, neuropsychological tests and baseline psychologic outcome measures were administered. Then, the first session for all participants took place in person, 1-on-1, with their therapist or educator. At this time, all procedures were explained and materials were distributed.

The subsequent 10 treatment/education sessions were conducted either over the telephone (1-on-1 format) or in the face-to-face, group format. The sessions took place on a weekly basis with some sessions occurring twice weekly because of time constraints and scheduling. All sessions were completed within a 9-week time frame, with sessions ranging from 45 to 75 minutes as required. All participants completed the DASS-21 at the beginning of each weekly session to monitor progress and suicide risk. After completion of the eleventh session, all participants completed the posttreatment outcome measures. Participants in both groups also received 1-month follow-up sessions, at which time only the primary outcome measures (SCL-90-R and DASS-21) were administered.

CBT protocol (telephone CBT and group format CBT). The CBT was tailored to meet the unique needs of the ABI population, while adhering to proven treatment protocols. To address cognitive difficulties, specific alterations were made to conventional CBT, including repetition of important materials and frequent breaks.³² To expand and refine the recommendations of Mateer and Sira,³² specific cognitive information about each patient was obtained from neuropsychological assessment results. Specifically, the presence and severity of current cognitive deficits were identified in the following areas: memory, attention, initiation/activation, language, and speed of processing. For each patient, (1) their ability to benefit from repetition, (2) their capacity to learn and retain information, and (3) speed of information processing were identified and provided the therapist with information that helped determine the rate and complexity of speech and amount of repetition and summarization that might be required to optimize retention of information for each patient. In groups, the cofacilitator (master's-level graduate student) played a key role in assisting patients with higher needs (eg, reminders to complete homework). The master's-level student also administered telephone CBT to 1 participant under the direct supervision of the supervising psychologist. The 2 CBT therapists were clinical psychologists who also specialized in clinical neuropsychology, with a minimum of 5 years of clinical experience in the administration of CBT.

Education control protocol (telephone education control and group education control). The education control was administered by a trained clinician educator (master's-level graduate student). The purpose of the education group was to control for general aspects of therapeutic contact. Participants in both the telephone education control and group education control subgroups were provided wide-ranging information regarding the normative functioning of the brain, brain injury, and ABI sequelae. The content of the sessions was entirely educational, and if patients solicited counseling directly or indirectly, the educator was trained to explain that she was there to provide general information, but not counseling. Subsequent to the completion of the study, all control participants who continued to endorse significant emotional symptoms at their 1-month follow-up were offered CBT.

Statistical Analyses

Hypothesis 1. Pretreatment outcomes were compared with posttreatment outcomes using 2 (group: CBT vs education control) by 2 (time: pretreatment vs posttreatment) repeated-measures ANOVAs for each of the primary and secondary outcome measures. Subgroup analyses were also conducted, using paired *t* tests

(with primary outcome measures only) in order to evaluate the efficacy of both the group format CBT and the telephone CBT.

Hypothesis 2. (1) To evaluate retention of treatment gains, a 2 (group: CBT vs education control) by 2 (time: pretreatment vs 1-month follow-up) repeated-measures ANOVA was conducted, with the SCL-90-R GSI and DASS-21 as the dependent variables. We also examined effect sizes (Cohen's *d*) to compare the magnitude of the effect in this analysis to the equivalent analysis from hypothesis 1, with the expectation that participants in the CBT group would demonstrate commensurate pretreatment/1-month follow-up changes, compared with pre/posttreatment changes. (2) Paired *t* tests (CBT group) from posttreatment to follow-up were also undertaken, including effect size calculations (with no significant differences and small effect sizes expected).

RESULTS

Hypothesis 1

A significant group by time interaction was observed for the SCL-90-R ($F_{1,18}=7.03$, $P<.05$), with planned comparisons showing no significant pretreatment differences ($t_{18}=-0.40$, $P=.69$, 1-tailed, Cohen's $d=-0.18$), but significant posttreatment differences ($t_{18}=-2.95$, $P<.01$, 1-tailed Cohen's $d=-1.32$). Further, the CBT group showed a significant reduction in distress ($t_9=4.11$, $P<.01$) with a large effect size (Cohen's $d=1.30$). Similarly, with the DASS-21 total score as a dependent variable, a significant group by time interaction was observed ($F_{1,18}=7.56$, $P<.05$), with nonsignificant pretreatment differences between the 2 groups ($t_{18}=-1.01$, $P=.33$, although a moderate effect size was observed, Cohen's $d=-0.48$), but significant posttreatment differences ($t_{18}=-0.93$, $P<.001$, with a very large effect size Cohen's $d=-1.76$). Significant improvement on the DASS-21 was also observed from pretreatment to posttreatment in the CBT group ($t_9=6.27$, $P<.001$, Cohen's $d=1.79$). Moreover, although the mean pretreatment DASS-21 scores indicated a moderate range of emotional disturbance, relative to normative data, posttreatment DASS-21 total scores for the CBT group fell within the normative range for emotional disturbance. See figure 1 for group differences on DASS-21 scores across all sessions.

Table 2 displays the descriptive statistics for the subgroups on the primary outcome measures. On the SCL-90-R GSI, the group format CBT patients showed significant improvement over time as predicted ($t_4=3.67$, $P<.01$, 1-tailed, with a large Cohen's *d* effect size: Cohen's $d=1.45$) as did the telephone CBT patients ($t_4=2.20$, $P<.05$, 1-tailed, with a large effect size: Cohen's $d=1.06$). On the DASS-21 total score, significant reductions in emotional distress with large effect sizes were observed for both the group format CBT subgroup ($t_4=5.03$, $P<.01$, 1-tailed, Cohen's $d=1.91$) and the telephone CBT subgroup ($t_4=3.07$, $P<.05$, 1-tailed Cohen's $d=1.46$). Further, there were no significant between-group differences at posttreatment, when the group format CBT and telephone CBT groups were compared on either the SCL-90-R ($t_8=0.19$, $P=.85$, Cohen's $d=0.12$) or the DASS-21 ($t_8=-0.78$, $P=.46$, Cohen's $d=-0.49$). Last, there were no significant improvements, or trends toward improvement, after treatment in either of the education control groups on either test.

Scores on the secondary outcome measures for community integration, emotion-focused coping, and problem-focused coping, all changed in the expected directions—that is, improvements were noted for the most part in the CBT group, but not the education control group. Most of these results were trends toward significance. On total CIQ score, results revealed a trend toward a group by time interaction ($F_{1,18}=4.34$,

Between Group Differences on DASS Total Score Over Time

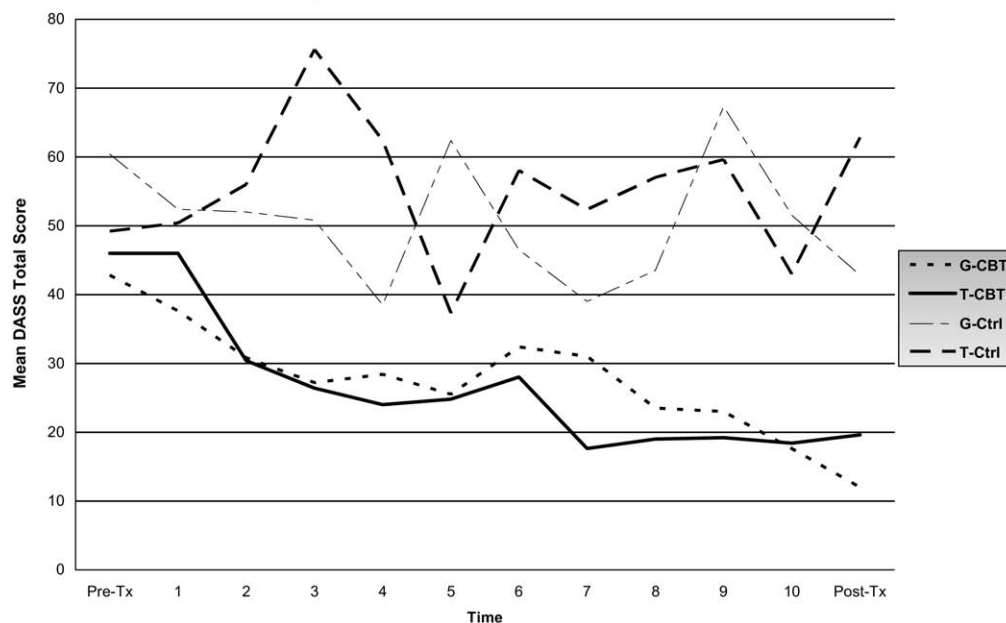


Fig 1. Group differences on DASS-21 total score over time. Performances in each of the 4 groups are presented across the 10 treatment/education sessions. A lower score represents less emotional distress. G-CBT, Group CBT; T-CBT, telephone CBT; G-Ctrl, group education control; T-Ctrl, telephone education control; Pre-TX, pretreatment; Post-TX, posttreatment.

$P=.052$), and similar results were revealed on the Ways of Coping Scale, Revised, Escape Avoidance subscale ($F_{1,18}=3.94$, $P=.063$). No group by time interaction effect was revealed on the Ways of Coping Scale, Revised, Planful Problem Focused subscale ($F_{1,18}=0.22$, $P=.65$), but a main effect of time was shown ($F_{1,18}=7.81$, $P<.05$). Therefore, both groups seemed to improve their problem-solving approach by being involved in CBT or learning about brain injury. However, only the CBT group showed trends toward declines in emotion-focused coping.

Hypothesis 2

As shown in figure 2, when pretreatment and 1-month follow-up outcomes on the SCL-90-R GSI were examined, a significant group by time interaction was observed ($F_{1,18}=18.60$, $P<.001$). As previously stated, the groups had commensurate

pretreatment scores. However, significant differences were revealed at follow-up on a 1-tailed t test ($t_{18}=-3.38$, $P<.01$, Cohen's $d=-1.51$), with the treatment group showing significantly better functioning than the control group. As well, significant improvement within the CBT group from pretreatment to follow-up was observed ($t_9=5.17$, $P<.001$, 1-tailed, Cohen's $d=1.30$).

As shown in figure 3, similar results were revealed for the DASS-21, with a significant group by time interaction observed ($F_{1,18}=12.65$, $P<.01$). The CBT group demonstrated significant reductions in distress (DASS-21 total score) compared with the control group ($t_{18}=-4.65$, $P<.001$, Cohen's $d=-2.08$), and significant improvement within the CBT group from pretreatment to 1-month follow-up was also found ($t_9=7.01$, $P<.001$, 1-tailed, Cohen's $d=1.85$).

Table 2: Individual Group Analyses for Primary Outcome Measures

Outcome Measures	G-CBT (n=5) Mean \pm SD	T-CBT (n=5) Mean \pm SD	G-Ctrl (n=5) Mean \pm SD	T-Ctrl (n=5) Mean \pm SD
SCL-90-R, GSI				
Pre	71.00 \pm 7.84	68.40 \pm 8.26	72.40 \pm 9.15	69.80 \pm 6.98
Post	59.20 \pm 8.41	58.00 \pm 11.11	68.00 \pm 7.97	72.80 \pm 9.28
DASS-21				
Total score				
Pre	42.80 \pm 21.15	46.00 \pm 13.41	60.40 \pm 36.89	49.20 \pm 17.81
Post	12.00 \pm 8.60	19.60 \pm 19.97	42.80 \pm 25.00	62.80 \pm 24.68
Depression				
Pre	21.20 \pm 14.87	13.60 \pm 7.67	23.20 \pm 10.35	18.40 \pm 7.80
Post	6.80 \pm 6.57	5.20 \pm 5.76	16.00 \pm 11.31	22.80 \pm 10.26
Anxiety				
Pre	8.00 \pm 3.74	11.20 \pm 8.07	16.00 \pm 14.63	14.80 \pm 5.93
Post	2.00 \pm 3.46	3.60 \pm 3.58	7.60 \pm 6.69	16.80 \pm 8.44
Stress				
Pre	13.60 \pm 9.94	21.20 \pm 3.03	21.20 \pm 13.31	16.00 \pm 6.78
Post	3.20 \pm 3.35	10.80 \pm 11.28	19.20 \pm 11.19	23.20 \pm 8.44

Abbreviations: G-CBT, Group CBT; T-CBT, telephone CBT; G-Ctrl, group education control; T-Ctrl, telephone education control.

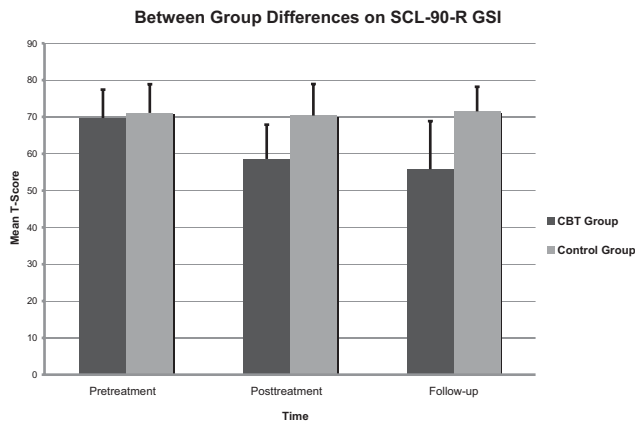


Fig 2. Differences on SCL-90-R GSI from pretreatment to follow-up across collapsed CBT groups and education control groups.

Importantly, no change was found between posttreatment and 1-month follow-up measures for the CBT group on either the SCL-90-R GSI ($t_9 = -0.89, P = .20$, Cohen's $d = 0.25$) or the DASS-21 total score ($t_9 = -0.06, P = .48$, Cohen's $d = -0.02$), demonstrating the stability of group effects over time. The stability of positive change was also upheld, on both outcome measures, for subgroup analyses. The group format CBT participants showed commensurate posttreatment and follow-up scores on the SCL-90-R GSI ($t_4 = 0.44, P = .34$, Cohen's $d = 0.19$), and the DASS-21 total score ($t_4 = -0.12, P = .45$, Cohen's $d = -0.05$). The telephone CBT participants showed similar results on the SCL-90-R GSI ($t_4 = 0.75, P = .25$, Cohen's $d = 0.27$) and DASS-21 ($t_4 = 0.00, P = .50$, Cohen's $d = 0.00$).

Importantly, there were no significant differences between the group format CBT and telephone CBT groups at follow-up on either the SCL-90-R GSI ($t_8 = .32, P = .76$, Cohen's $d = -0.20$), or the DASS-21 ($t_8 = -.82, P = .44$, Cohen's $d = -0.52$). See table 3 for individual change scores and clinical impact for individual participants.

DISCUSSION

As predicted, results of the current study revealed statistically significant improvements in emotional distress for the CBT group, compared with the control group, from pretreat-

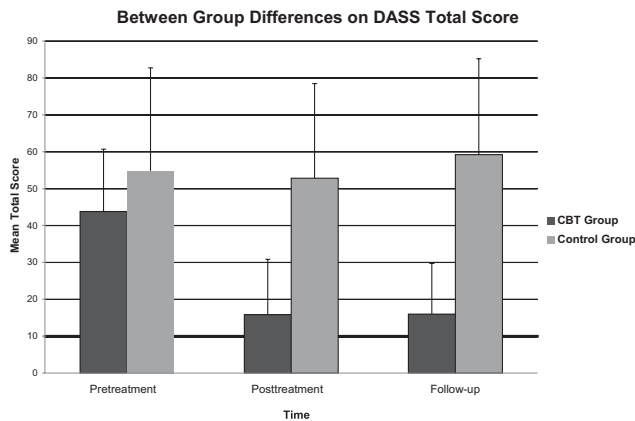


Fig 3. Differences on DASS-21 total score from pretreatment to follow-up across collapsed CBT groups and education control groups.

Table 3: Individual Scores on SCL-90-R GSI and DASS-21, Pretreatment Versus Posttreatment Versus 1-Month Follow-Up

Patient	GSI Pre	GSI Post	GSI Follow-Up	DASS-21 Pre, Total Score	DASS-21 Post, Total Score	DASS-21 Follow-Up
CBT treatment group						
1*	63	55	41	16	0	8
2*	81	58	71	62	22	14
3*	74	68	64	56	18	26
4*	63	48	50	24	8	4
5*	74	67	60	56	12	10
6	65	66	58	44	38	18
7	72	71	72	62	44	44
8	81	59	60	56	10	30
9	60	50	30	40	0	0
10	64	44	52	28	6	6
Education control group						
1*	65	60	58	54	20	12
2*	74	66	68	24	26	48
3*	81	81	81	88	82	90
4*	81	69	73	108	52	70
5*	61	64	67	28	34	50
6	72	61	71	58	82	76
7	65	65	74	38	32	32
8	64	81	72	24	40	44
9	67	76	70	68	78	86
10	81	81	81	58	82	84

*Group-administered subgroup patients for group cognitive behavior therapy and group education control.

ment to posttreatment and at a 1-month follow-up. Upwards of 60% of the CBT participants showed meaningful improvements in their pre-post treatment reports of emotional distress on the SCL-90-R GSI (ie, a t score < 1 SD above the mean), compared with 0% of control group participants. Similar benefits were observed on the DASS-21, with 80% of the CBT group reporting normative levels of emotional distress post-treatment, compared with only 20% of controls. Therefore, they may have been experiencing a greater number of symptoms, and this may have impacted the current findings.

Results also demonstrated the lasting benefits of CBT at 1 month postinjury, with 50% of CBT participants continuing to show meaningful positive change on the SCL-90-R GSI compared with only 10% of the control group. Similar findings were found on the DASS-21, with 80% of participants in the CBT group reporting normative levels of emotional distress at their 1-month follow-up, compared with only 10% of controls. Importantly, the efficacy of treatment cannot be attributed to higher estimated premorbid intelligence quotient or higher current cognitive functioning in the treatment group because there were no significant differences between the groups on the WTAR or the RBANS. This suggests that CBT adapted to meet the unique cognitive and emotional needs of ABI survivors can be successful at improving emotional well being, even in patients who are years postinjury.

Importantly, individual subgroup analyses showed commensurate improvements on the SCL-90-R GSI and on the DASS-21 total score for both the group format CBT and the telephone CBT subgroups. Given the small sample size, it is difficult to interpret preliminary findings regarding treatment modality with confidence. Nonetheless, these results support

the notion that adapted CBT for ABI could have equivalent efficacy when administered in either traditional group or adapted telephone modalities. This important finding, if replicated in a larger, randomized controlled trial, would allow for greater accessibility to individuals with ABI who, because of either mobility or geographic restrictions, would have otherwise been precluded from participation in treatment. However, the current findings should still be considered preliminary, given the small sample size, and the fact that the study was a case matched design and not a more rigorous design, such as a randomized controlled trial.

Secondary outcomes including coping and community integration still require further investigation. Both the CBT and the control group showed significant improvements (pretreatment to posttreatment) in their implementation of problem-focused (adaptive) coping, but only the CBT group showed concurrent declines (trend) in their emotion-focused (maladaptive) coping. Findings suggest that providing structure, organization, and learning opportunities may have a global positive impact on planning and problem-solving in ABI, but that to elicit positive emotional change, the problem-solving must be related to psychologic/psychosocial issues. Community integration results were inconclusive, with both groups showing some changes over time and no significant effects revealed, despite trends in the direction of improved integration. Additional research into the secondary benefits of CBT for ABI is required. The current findings are nevertheless compelling, suggesting that individuals with ABI have the potential to improve their emotional well being, which in turn may have a widespread and positive impact on other aspects of functioning.

The emotional sequelae of ABI are not under debate. Emotional distress has unequivocally been identified as a significant contributing factor to poorer community functioning and decreased quality of life after brain injury.⁹⁻¹¹ That emotional distress does not receive more attention in traditional rehabilitation programs is a concern. Although significant rehabilitation efforts are devoted to the cognitive and motor sequelae of ABI, the emotional sequelae often receive limited attention, particularly during acute rehabilitation. Yet, psychologic services are often expensive and inaccessible for people in the subacute and chronic stages of brain injury. Moreover, few psychologic interventions are tailored to the specific cognitive needs and content issues of brain-injured patients. Of the previous findings, improvements in emotional well being³⁰ and coping strategies³¹ had been suggested, but the current study, to our knowledge, is the first of its kind that documents the efficacy of adapted CBT for individuals with ABI, and also investigates CBT efficacy for both group and telephone treatment modalities. Moreover, the current findings delineate the specific mechanisms underlying change, showing that education and socialization are insufficient to evoke change and that the necessary component is an adapted psychotherapeutic intervention that individuals with ABI can learn and retain over time.

Study Limitations

There are obvious limitations to the current study. First, the current study was an education-matched study, not a randomized controlled trial; therefore, caution should be applied in the extrapolation and generalization of the findings outside the context of the current study. Another very pertinent limitation was the small sample size, again making it difficult to interpret the current findings confidently. Results were nevertheless compelling, and given the current strength of the findings, additional investigations are warranted.

An additional limitation of this study was the representativeness of the sample. All individuals who participated in the current project were connected to a community ABI program and lived in urban areas with access to high-quality health care. Therefore, the sample tested is not representative of all individuals with ABI. Finally, sample bias is a potential limitation. Individuals who chose to participate in the current study may have been more psychologically minded or at a stage in their recovery at which they were more receptive to psychologic intervention. Results suggest that for individuals motivated to participate, the intervention has the potential to be efficacious and that the results can be lasting.

Clinical Implications

Overall, these findings are very promising. Efficacy of the adapted CBT protocol for people with ABI was observed on the primary outcome measures even with very small numbers. Although there was diminution of emotional dysfunction in the CBT subgroups and the CBT collapsed group, there was no significant change to symptoms in the education control group. These preliminary results strongly support the value of a larger randomized controlled trial, especially given that the current protocol is unique in that it is universally applicable to all patients with ABI regardless of accessibility restrictions that may be present. Moreover, research has shown that patients with ABI do not necessarily respond as well to traditional therapeutic interventions when their unique cognitive and rehabilitative needs are not formally recognized and addressed.² The current approach adheres to proven CBT treatment protocols aimed at reducing emotional distress and improving adjustment and coping, but critically, it has been adapted to address the specific needs of the ABI population. An additional potential benefit of this research is that CBT has the potential to promote cognitive and physical functioning, either by enhancing mood (which when significantly disrupted can reduce cognitive functioning) or by promoting greater motivation for and engagement in rehabilitation. This in turn may further enhance coping and adjustment after ABI. The current line of research has the potential to influence standard rehabilitation practices positively by demonstrating the benefits of allocating appropriate resources to emotional recovery after ABI.

CONCLUSIONS

Emotional distress in ABI is a pertinent concern for patients, families, and health care professionals. To our knowledge, the current project is the first matched controlled study demonstrating both the potential feasibility and efficacy of CBT in the treatment of emotional dysfunction after ABI. The results of our study showed significant treatment effects when a modified CBT for the treatment of emotional distress in ABI was compared with an education control group. Specifically, the CBT group reported significantly lower levels of emotional distress posttreatment compared with their pretreatment scores. No changes were observed in the education control group's reports of emotional distress over time. Importantly, the current results identify that CBT, not simply socialization, is the necessary component for positive change. However, prospective randomized controlled trials with longer-term follow-up are needed to determine further the specific individual, personality, and injury variables that may mediate the effectiveness of CBT in the treatment of emotional distress in ABI.

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ORIGINAL ARTICLE

Long-Term Cognitive Outcome in Moderate to Severe Traumatic Brain Injury: A Meta-Analysis Examining Timed and Untimed Tests at 1 and 4.5 or More Years After Injury

Lesley Ruttan, PhD, CPsych, Krystle Martin, MA, Anita Liu, HBSc, Brenda Colella, MA, Robin E. Green, PhD, CPsych

ABSTRACT. Ruttan L, Martin K, Liu A, Colella B, Green RE. Long-term cognitive outcome in moderate to severe traumatic brain injury: a meta-analysis examining timed and untimed tests at 1 and 4.5 or more years after injury. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S69-76.

Objectives: To examine long-term outcome of moderate to severe traumatic brain injury (TBI) on timed and untimed cognitive tests using meta-analysis.

Design: Meta-analysis examining outcome at 2 epochs, 6 to 18 months postinjury (epoch 1) and 4.5 to 11 years postinjury (epoch 2).

Setting: Data source was published articles (1966–2007) identified through electronic and manual search.

Participants: A total of 1380 subjects with moderate to severe TBI participated in the 16 studies meeting inclusion criteria.

Interventions: Not applicable.

Main Outcome Measures: Timed and untimed neuropsychologic tests with quantitative results (means, SDs, *t*, and *df* tests) from studies containing a healthy comparison group and a mean time since injury falling within 1 of the 2 epochs.

Results: Patient versus control weighted effect sizes were medium to large at epoch 1 for both untimed tasks ($r = -.46$; confidence interval [CI], $-.32$ to $-.65$) and timed tasks ($r = -.46$; CI, $-.35$ to $-.59$). At epoch 2, effect sizes were slightly smaller for untimed tasks ($r = -.38$; CI, $-.25$ to $-.60$) and timed tasks ($r = -.40$; CI, $-.32$ to $-.62$).

Conclusions: Patients showed robust, persisting impairments on both timed and untimed tests at recovery plateau (ie, 6–18mo postinjury) and many years later. These findings converge with previous studies, though using an alternative approach that obviates some of the methodologic problems of longitudinal studies, such as selective attrition.

Key Words: Brain injuries; Neuropsychology; Rehabilitation.

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ACCORDING TO THE World Health Organization, TBI will surpass many diseases as the major cause of disability (and death) by the year 2020, with approximately 10 million

people affected annually worldwide.¹ The magnitude of the problem is caused in large part by the persistence of cognitive impairments,²⁻¹⁰ which may cause decades of disability as a result of the young demographic that TBI afflicts.¹¹⁻¹⁴ In moderate and severe TBI, cognitive deficits are associated strongly with the ongoing disruption of social networks, employability, and return to work.¹⁵⁻¹⁷ Therefore, gaining an understanding of the long-term course of cognitive functioning is of marked clinical importance: knowing whether some or all cognitive functions show persisting deficits into the longer term would allow better prognostication, planning, and the likelihood of developing targeted prophylactic treatments; the last is particularly important given the small but growing number of findings that some people even show a regression of some cognitive functions over time.^{8,18-20} Because some research has demonstrated that information processing impairments may mediate the relationship between TBI severity and post-TBI adaptive functioning,²¹ in the present study, we compared performance at 2 subacute time points on timed versus untimed tests.

Prospective studies examining early cognitive recovery after moderate and severe injury^{2,22,23} have generally found that most recovery occurs within the first 6 to 18 months of injury^{2,23} and that some improvement may continue thereafter at a slower pace.^{8,24,25} There has been considerable variability in findings on the rate and pattern of recovery of different functions,^{22,26} with the exception of speed of processing, which shows the most consistent findings after moderate to severe TBI.²⁷⁻³⁷ Studies have shown a higher prevalence of compromise^{36,38,39} and slower speed and extent of recovery^{40,41} on timed versus untimed tests, suggesting that speed of processing is uniquely vulnerable to the effects of moderate and severe brain injury.

With regard to longer-term outcomes, prospective studies of long-term cognitive recovery are relatively few. As pointed out by Dikmen et al,⁴² longitudinal cognitive recovery studies have also contained significant methodologic limitations, with a follow-up period rarely exceeding 2 years, biased samples (eg, those referred for clinical care),¹⁹ and even in prospective, well defined samples, very high attrition rates.^{8,19,20} As well, test

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List of Abbreviations

CI	confidence interval
ES	effect size
GCS	Glasgow Coma Scale
LOC	loss of consciousness
PASAT	Paced Auditory Serial Addition Test
PTA	posttraumatic amnesia
TBI	traumatic brain injury
TSI	time since injury

batteries have often included only 1¹⁸ or 2 tests.⁴² As such, other approaches to studying long-term outcome are warranted.

Overall, long-term recovery studies have not yet shown clear-cut patterns of findings across tests,^{8,18,19} although persisting impairments to speed of processing seem to be a common thread across studies. Dikmen et al,⁴² who maintained an 80% retention rate (but with 60% of the sample in the mild TBI range), prospectively examined long-term outcome at 3 to 5 years postinjury on a test of verbal learning and recall, and on the PASAT, a challenging timed test of sustained attention requiring serial calculations.⁴³ Clinically impaired performances (2–3 SDs below average) were observed on the PASAT⁴³ at all degrees of severity. However, for verbal learning, clinically significant impairment was observed only at the most severe level of injury, and impairment was still only 1.35 deviations below average. Moreover, prior neurologic disorders were present in some patients, and therefore, even this level of impairment may have been an overestimate. Thus, definitive persisting deficits on the timed PASAT test were observed, while the persisting deficits in verbal learning were milder and more circumscribed.

Salmond et al⁴⁴ reported persistence of deficits across 2 time points a minimum of 6 months apart, ranging from 6 months postinjury to 3 years postinjury. While not explicitly mentioned, 6 of the 8 variables showing significant differences between patients and controls were timed variables, and of the variables showing no between-group differences, only 1 of 6 was a timed variable. These results, too, suggest that performance on timed variables may be more significantly affected in the longer term. These results are consistent with Spikman et al,⁴⁵ who examined 51 patients with TBI several years postinjury and whose findings underscored the persistence of impairments in speed of processing.

A small number of long-term outcome studies have also shown a regression in functioning over time. The finding does not appear to be attributable to age-related decline given the use of age-scaled normative data or age-matched control groups in studies. Again, clear patterns in the data have yet to emerge in this branch of research; also, methodologic weaknesses limit the inferences that can be drawn. In a 30-year follow-up study of 210 patients with TBI, Himanen et al¹⁹ observed slight cognitive decline in 56% of patients on learning, memory, visuospatial construction, and arithmetic, and improvement only in semantic memory. However, attrition was 70%, and the study sample was composed of patients specifically referred for neuropsychologic or neurologic follow-up and thus likely showed disproportionate impairments. Salmond⁴⁴ found a decline in their battery in spatial recognition only; however, interestingly, it was the latency (ie, timed) measure of spatial recognition on which the decline was observed. Finally, in a study of 182 people with mild to severe TBI carried out by Millis et al,⁸ 15.2% showed a decline, 22.1% showed improvement, and 62.2% were unchanged over a 5-year period. Although the authors reported that most improvement was observed on measures of cognitive speed, visuoconstruction, and verbal memory, it is of interest to note that 2 of the 3 tests showing the highest decline (grooved pegboard and Trail-Making Test Part B) were also timed tests. However, this study, too, had very high attrition (>90%), rendering the observations regarding patterns across tests somewhat tenuous.

Taken together, previous studies suggest that cognitive deficits—particularly speed of processing—may persist or even worsen in the longer term, but that a clear pattern of findings across functions has yet to be identified. One explanation for variability in findings, as Mathias and Wheaton²⁷ have pointed

out, is that past studies of recovery may be confounded by the conflation of timed with untimed tests,⁴⁶ whereby speed of processing deficits compromise performance on tests that are purportedly measuring other cognitive functions (eg, spatial recognition), but nonetheless contain a timed dependent measure.

In sum, cognitive processing is consistently impaired by moderate and severe TBI, and there is evidence that deficits persist into the longer term. However, the patterns of persisting deficits are uncertain to date, because of methodologic limitations of the relatively few studies undertaken, including the confounding of untimed cognitive processes (eg, memory) with timed dependent variables. Therefore, further research is warranted to disentangle the contribution of speed of processing from untimed tests as well as to examine speed of processing on its own.

The current study employed meta-analysis to examine the long-term cognitive recovery of timed and untimed processes at approximately 1 year postinjury and at greater than 4.5 years postinjury. We were interested in how patients performed toward the end of the early recovery period versus how they fared many years postinjury, long after therapies would have stopped for most patients⁴⁷ and after a return to prior role would have been attempted. Meta-analysis has the advantage of allowing integration of a collection of studies on a particular topic for the purpose of synthesizing the findings. The method calculates standardized mean differences or ESs (ie, the difference between 2 means relative to the pooled SD, resulting in a *z* score) to provide a common metric on which to compare studies, with higher ES reflecting stronger differences between groups than lower ES. Researchers have noted that meta-analysis can minimize errors and heighten understanding of neuropsychologically meaningful patterns in data by integrating the findings from multiple studies.^{48,49} To our knowledge, there are no published meta-analytic studies in moderate to severe TBI specifically examining the performances of people with TBI versus healthy controls on timed and untimed neuropsychologic tasks at 2 postinjury epochs.

METHODS

Literature Search and Study Selection

A comprehensive search of PsycINFO and Medline electronic databases was undertaken in order to identify published studies examining cognition and TBI. Key words used in the search included *brain injury*, *traumatic brain injury*, *TBI*, and *head injury*. These words were combined with *cognition*, *neuropsychology*, and *neurocognition*. Search constraints included articles published in English and those printed after 1966 (after the inception of the Medline database) and indexed up until June 2007. For all articles identified as relevant, a manual search of the articles' reference lists was conducted to see whether there were any cited works that were missed by the search engines.

Original studies were included in the meta-analysis if they met the following criteria: (1) neuropsychologic tasks were administered to patients with TBI who were reported to have sustained either moderate or severe nonpenetrating brain injuries (ie, GCS score <13, LOC >1h, and/or duration of PTA >1h); (2) the mean TSI was reported for patients with TBI that allowed classification of studies into 2 nonoverlapping epochs (epoch 1: mean TSI, 6–18mo; epoch 2: mean TSI, ≥4.5y); (3) the research design included a comparison group composed of healthy, age-matched control subjects; (4) study statistics amenable for conversion to conventional ESs that reflect group differences were available (these measures included group

means and SDs, *t*, and *df*); and (5) the cognitive tasks included in the study were adequately described so that a determination could be made about whether the cognitive task was timed or untimed. A test was classified as timed if the dependent variable was timed or if exposure to test material was timed, necessitating speeded processing. All classifications were agreed on by 3 experts in the field of neuropsychology.

The titles of articles and abstract content obtained in the literature search were perused for indications that the study met the inclusion criteria. Copies of the full text of these studies were obtained and the articles were reviewed to determine whether they met the inclusion criteria for the study. Each article was examined by a minimum of 2 of the coauthors to determine its eligibility for the meta-analysis, and a total of 16 appropriate studies were identified.

Data Collection

For each study included in the meta-analysis (table 1), the journal name, title, authors, and date of publication were recorded. Several sample characteristics were also noted, including sample size, mean age, mean education, and sex for patient

and control samples when available; plus, severity of brain injury, as measured by GCS, duration of PTA, and length of LOC for the patient group were recorded, as was TSI at testing.

For some studies, adjustments to the published data were required in order to allow inclusion of the data in the meta-analysis. For example, for longitudinal studies of recovery, in which patients were tested more than once, only data from the first occasion of testing were included (to avoid contaminating the results with practice effects). Also, if more than 1 neuropsychologic test was used to measure a cognitive domain within a study, the mean ES was used so that each study had only 1 ES estimate per grouping of tasks, timed or untimed. Also, in the case of separate articles conducted by the same authors in which participants overlapped substantially, the findings were combined and treated as 1 study.^{50,51}

All cognitive tasks and test variables were included in the meta-analytic database. Pooling of the numerous and various cognitive measures for purposes of analysis can raise methodologic and theoretical challenges because of the heterogeneity of test batteries across studies. For the purpose of this study, we were interested only in examining the global difference be-

Table 1: Demographic Details for the TBI and Control Groups: Injury Data for the TBI Group

Studies	TBI and Controls (n)	TBI (n)	Controls (n)	Mean Age TBI (y)	Mean Age Controls (y)	Mean YOE TBI	Mean YOE Controls	Mean TSI (mo)	Injury Severity (tests used for classification)
Untimed—Epoch 1									
Ariza et al ⁵⁸	40.0	20.0	20.0	25.6	25.4	11.4	12.0	6.0	Mod/Sev (GCS)
Dikmen et al ²²	395.0	274.0	121.0	28.9	31.2	12.0	12.0	12.0	Mod/Sev (GCS)
Formisano et al ⁵⁵	45.0	25.0	20.0	22.3	Matched	NA	NA	11.2	Sev (GCS)
Mathias et al ⁵²	50.0	25.0	25.0	28.6	28.4	11.8	12.0	7.0	Sev (GCS, LOC)
Salmond et al ⁴⁴	41.0	21.0	20.0	33.0	36.0	NA	NA	9.8	Sev (NA)
Mean untimed epoch 1	114.2	73.0	41.2	27.7	28.7	11.7	12.0	9.2	
Untimed—Epoch 2									
Larson et al ⁸³	50.0	26.0	24.0	40.7	35.9	13.9	13.8	110.0	Mod/Sev (GCS, LOC, PTA)
Schmitter-Edgecombe et al ⁵⁹	40.0	20.0	20.0	29.5	29.3	14.1	14.5	64.8	Sev (LOC)
Schmitter-Edgecombe et al ⁵⁴	54.0	27.0	27.0	32.4	32.6	14.0	14.4	60.0	Sev (GCS, LOC)
Schmitter-Edgecombe et al ⁵⁰	48.0	24.0	24.0	34.4	35.4	14.1	14.2	126.0	Sev (GCS, PTA)
Simpson et al ⁵³	40.0	20.0	20.0	32.4	32.2	14.3	14.8	72.0	Sev (GCS)
Vickery et al ⁵⁶	40.0	20.0	20.0	34.1	38.7	12.5	12.7	64.8	Sev (GCS, LOC)
Mean untimed epoch 2	45.3	22.8	22.5	33.9	34.0	13.8	14.1	63.4	
Mean epoch 1 and 2	76.6	45.6	31.0	31.1	31.6	13.1	13.4	38.8	
Timed—Epoch 1									
Ariza et al ⁵⁸	40.0	20.0	20.0	25.6	25.4	11.4	12.0	6.0	Mod/Sev (GCS)
Dikman et al ²²	395.0	274.0	121.0	28.9	31.2	12.0	12.0	12.0	Mod/Sev (GCS)
Formisano et al ⁵⁵	45.0	25.0	20.0	22.3	Matched	NA	NA	11.2	Sev (GCS)
Mathias et al ⁵²	50.0	25.0	25.0	28.6	28.4	11.8	12.0	7.0	Sev (GCS, LOC)
Periáñez et al ⁶⁴	313.0	90.0	223.0	34.6	38.9	12.9	13.3	12.5	Sev (GCS, PTA)
Spikman et al ⁶⁵	104.0	44.0	60.0	29.8	28.5	NA	NA	12.0	Sev (GCS, PTA)
Vakil et al ⁷³	52.0	25.0	27.0	27.0	25.4	NA	NA	4.9	Sev (GCS, LOC)
Mean timed epoch 1	142.7	71.9	70.9	28.1	30.3	12.0	12.3	9.4	
Timed—Epoch 2									
O’Keeffe et al ⁶²	36.0	18.0	18.0	31.3	32.9	NA	NA	38.6	Sev (GCS, PTA)
Park et al ⁶³	24.0	12.0	12.0	53.2	51.5	15.3	15.9	62.4	Sev (NA)
Schmitter-Edgecombe et al ⁵⁹	40.0	20.0	20.0	29.3	29.5	14.1	14.5	64.8	Sev (PTA)
Schmitter-Edgecombe et al ⁵⁰	48.0	24.0	24.0	34.4	35.4	14.1	14.2	126.0	Sev (GCS, PTA)
Simpson et al ⁵³	40.0	20.0	20.0	32.3	32.2	14.3	14.8	72.0	Sev (GCS)
Vickery et al ⁵⁶	48.0	23.0	25.0	34.1	38.7	12.5	12.7	61.7	Sev (GCS, LOC)
Mean timed epoch 2	39.3	19.5	19.8	35.8	36.7	14.0	14.4	51.4	
Mean epoch 1 and 2	95.0	47.7	47.3	31.7	33.2	13.1	13.5	28.8	

NOTE. Severity ratings are based on self-description of mean severity level provided by author of article. Abbreviations: LOC, loss of consciousness; Mod, moderate; NA, not available; YOE, years of education; Sev, severe.

tween timed and untimed neuropsychologic tests, so the various cognitive measures were simply divided into these 2 categories based on the researchers' specific knowledge of neurocognitive tests and/or as per the description provided in the original articles. A description of the individual cognitive variables that make up these 2 groups of tasks can be found in table 2. The studies were then further divided into the 2 nonoverlapping epochs. Epoch 1 was chosen to allow an examination of performances after the end of the acute recovery period and when most recovery would be expected to have occurred based on previous studies. Epoch 2 was selected to be nonoverlapping, and representative of chronic TBI. We selected a time point of 4 years postinjury as the earliest time point. Studies that met inclusion criteria ranged from a TSI of 4.5 to 10.6 years (see table 1 for studies included in each cognitive domain and epoch).

Magnitude of effect. A meta-analysis assumes that each study estimates real differences between groups. Combining several estimations thus yields a more veridical estimation of the real effect. Standardized ESs were initially computed for

each variable with adequate quantitative information (eg, mean ± SD). ESs were then averaged across studies. While the *d* statistic has been the most conventional meta-index previously used, a recent preference for correlational ES measures is notable in the literature.⁶⁶ As such, we used *r* values in our report. The *d* and *r* indices are interchangeable according to the relation $r = [d^2 / (d^2 + 4)]^{1/2}$ (assuming relatively equal sample sizes).⁴⁹ Whereas *d* is interpreted in terms of SD units (ie, mean difference/pooled SD), mean *r* values are interpreted in the same manner as typical correlation coefficients. In Cohen's⁴⁹ qualitative terms, mean *r*'s of .10, .20, and .50 can be considered small, medium, and large ESs, respectively, in behavioral-science research. The *r* values (weighted and unweighted) and CIs were calculated by first obtaining the Fisher *z*-transformed coefficients from the individual test comparisons within each study.⁶⁷

Weighted *r* values reported are corrected by sample size, thereby giving greatest weight to the studies with the most reliably estimated study ESs—those with the largest sample sizes.⁶⁸ Each mean weighted *r*² and SD was then used to

Table 2: Summary of Individual Untimed and Timed Cognitive Tests by Domain and Epoch

Untimed Tests	E 1	E 2	Timed Tests	E 1	E 2
Learning and Recall			Fluency		
AVLT Immediate Recall ⁵²	X		Controlled Oral Word Association ^{58,60}	X	
AVLT Delayed Recall ⁵²	X		Design Fluency ^{52,53,55-57,61}	X	
California Verbal Learning Test—Total ⁵³		X	Scanning		
California Verbal Learning Test—Trial 1 ⁵⁴		X	Digital cancellation ms ⁵³		X
California Verbal Learning Test—Trial 5 ⁵⁴		X	Digit cancellation hits ⁵³		X
California Verbal Learning Test Short-Delay ⁵⁴		X	Psychomotor		
Long Delay Free Recall ^{53,54}		X	Finger tapping—dominant ^{22,58,59}	X	
Prose Delayed Recall ⁵⁵	X		Grooved pegboard—dominant hand ⁵⁶		X
Related-Word Delayed Recall ⁵⁵	X		Finger tapping—nondominant ^{22,56,58,59}	X	X
Unrelated-Word Delayed Recall ⁵⁵	X		Name writing—dominant ²²	X	
WMS—Logical Memory ²²	X		Name writing—nondominant ^{22,58}	X	
WMS—Visual Reproduction ²²	X		Attention		
WMS—Logical Memory ^{22,51}	X	X	Dual Attention to Response Task ⁶²		X
WMS—Visual Reproduction ^{22,51}	X	X	PASAT (adapted) 1st Third ⁶³		X
WMS-III Word List Immediate Recall ⁵⁶		X	PASAT (adapted) 2nd Third ⁶³		X
WMS-III Word List Delayed Recall ⁵⁶		X	PASAT (adapted) 3rd Third ⁶³		X
WMS-III Word List Recognition ⁵⁶		X	Sustained Attention to Response Task—Fixed ⁶²		X
Selective Reminding Total Recall ²²	X		Sustained Attention to Response Task—Random ⁶²		X
Selective Reminding Total Delayed Recall ²²	X		Trail-Making Test Part A ^{22,52,53,58,64}	X	
Total Recall after 4-hour delay ²²	X		Word Reading/Naming		
Prospective Memory Focal Cue Hits ⁵¹		X	Stroop—color reading ²²	X	
Prospective Memory Peripheral Cue Hits ⁵¹		X	Stroop—word reading ²²	X	
Executive Function Tests			Stroop—color/word reading ^{53,65}	X	X
Raven's Progressive Matrices ⁵⁵	X		Executive		
WCST—Categories ^{53,54}		X	Trail-Making Test Part B ^{22,52,53,64}	X	
WCST—Errors ⁵²	X		Trail-Making Test Part B—A ^{51,64}	X	
WCST—Perseverations ^{53,54}		X	Trail-Making Test Part B:A Ratio ⁶⁴	X	
Category Test ^{22,55,57}	X		Trail-Making Test Part B-A/Trails A ⁶⁴	X	
Mental Efficiency					
Alphabet Span Test ⁵¹		X			
Seashore Rhythm Test ²²	X				
Visuospatial Skills					
Facial Recognition ⁵⁸	X				
Rey Figure Copy ⁵⁸	X				
Other					
Tactual Performance Test ²²	X				
WAIS—Full Scale Intelligence Quotient ^{51,53,59}		X			

Abbreviations: AVLT, Auditory Verbal Learning Test; WAIS, Wechsler Adult Intelligence Test; WCST, Wisconsin Card Sort Test; WMS, Wechsler Memory Scale.

Table 3: ES Summary Statistics for TBI Versus Control Groups on Untimed and Timed Cognitive Tasks at Epochs 1 and 2

Groups	k	n	Total Weighted <i>r</i> Score	CI _s	Total Unweighted <i>r</i> Score	Fail-Safe n	Coefficient of Robustness
Untimed cognitive tasks	12	895	-0.45	-0.36 to -0.57		34	-2.87
Overall					-0.47		
Epoch 1	5	323	-0.46	-0.32 to -0.65	-0.50	36	-1.83
Epoch 2	7	273	-0.38	-0.25 to -0.60	-0.44	70	-2.26
Timed cognitive tasks	13	1295	-0.45	-0.40 to -0.56	-0.49	88	-2.11
Overall					-0.52		
Epoch 1	7	1015	-0.46	-0.35 to -0.59	-0.48	54	-1.60
Epoch 2	6	280	-0.40	-0.32 to -0.62	-0.49	41	-1.44

compute 95% CIs for both the timed and untimed groups. Finally, the *r*² values were reconverted to *r* values.^{66,67} The 95% CI around the weighted *r* reflects the variability across studies and, if encompassing 0, indicates nonsignificant (*P*>.05) deviation of the mean ES from this null hypothesis value.

Note that, given the relatively small number of studies published in this area, the use of weighted *r* could disproportionately bias results based on a single study. Therefore, unweighted *r* values are also presented in order to provide the most comprehensive review possible.

In addition to the CIs, coefficients of robustness were calculated to compare the observed effects for robustness and homogeneity. Viewed as a “second-order effect size,”⁶⁹ the coefficients of robustness provides a common metric in order to compare average group ESs as they are standardized by their SDs.

Because of the potential for meta-analyses to be subject to publication biases—that is, the selective publication of significant results—fail-safe calculations were also conducted. A number of different methods have been proposed to deal with this issue. Consistent with our choice of the *r* measure of ES, we applied the Orwin method⁷⁰ that calculates the number of additional studies of null effect needed to reduce the average ES to a minimal size (ie, *r*=.10).^{49,71}

RESULTS

Participants

A total of 1380 participants from 16 studies were included in this meta-analysis: 694 people with moderate to severe TBI and 686 control participants. Demographic details for participants in the studies included in this analysis are summarized in table 1. Participants were similar in terms of their mean age and years of education. When the ages and educational levels were compared via *t* test, the TBI and control groups did not differ significantly (education, *t*₁₅=.55, *P*>.05; age, *t*₁₅=.76, *P*>.05), suggesting that these groups were overall well matched on these variables. Furthermore, participants in studies across both epochs, and across timed versus untimed tests, did not appear to differ in their demographic data and injury characteristics (see table 1). From among these publications, 13 studies had either similar numbers or a matched percentage of men in both TBI and control groups, 2 studies did not report the sex of participants in either group,^{63,72} 1 study reported only the sex of participants in the TBI group,⁷³ and 4 studies reported unequal numbers of men between the TBI and control groups. The overall percentage of men in the TBI group was 75.8, while overall percentage of men in the control group was 69.4. In terms of injury severity, the overall average GCS score

was 7.25, while average length of PTA was 53.23 days. Thus, participants were, overall, within the severe range of severity.

Untimed versus timed tests. Similar numbers of studies were used in each epoch for untimed and timed tests (untimed=5 studies in epoch 1, and 6 studies in epoch 2; timed=7 studies in epoch 1, and 6 studies in epoch 2).

Table 3 lists the ES differences (weighted *r*, unweighted *r*, CIs, coefficients of robustness, and fail-safe n) between patients with TBI and healthy controls for the 2 epochs organized by timed and untimed neuropsychologic tests.

The overall weighted *r* for each domain collapsed across the 2 epochs shows that patients with TBI performed worse than controls on both types of tests (table 3; untimed: weighted *r*=-.45, CI, -.36 to -.57; timed: weighted *r*=-.45, CI, -.40 to -.56). Examination of unweighted *r* yielded similar results.

For untimed tests, a moderate to large negative ES difference (weighted *r*) in both epochs (epoch 1: weighted *r*=-.46, CI, -.32 to -.65; epoch 2: weighted *r*=-.38 CI, -.25 to -.60) was observed. The negative ESs show that patients with TBI perform consistently worse than controls on untimed tests across these 2 points in the chronic TBI spectrum. Examination of unweighted *r* values yielded similar results. The overall CIs suggest that the results are reliable; the coefficient of robustness suggests the method of analysis is relatively robust to outliers and small departures from underlying assumptions.

Similarly, for timed tests, a moderate to large negative ES difference (weighted *r*) in both epochs (epoch 1: weighted *r*=-.46, CI, -.35 to -.59; epoch 2: weighted *r*=-.40; CI, -.32 to -.62) was noted. Like untimed cognitive tasks, the findings show that patients with TBI consistently performed worse than controls. Examination of unweighted *r* yielded a very similar pattern of findings from epoch 1 to 2.

DISCUSSION

To our knowledge, this is the first research synthesis that has examined untimed versus timed cognitive processing during 2 subacute periods after moderate to severe TBI. Very few longitudinal studies of recovery have examined recovery at this late postinjury phase; of these, most were plagued by significant attrition and likely sample bias. Consequently, a clear and definitive clinical picture of long-term outcome from moderate and severe TBI has remained elusive.

We observed robust residual cognitive deficits at both epochs, for both timed and untimed processing. In a meta-analytic study of subjects with moderate to severe TBI, Schretlen and Shapiro⁷⁴ noted large ESs when they explored earlier epochs than in our study (<6mo postinjury; >24mo postinjury). Our findings were compatible with these findings in that significant persisting cognitive impairments were observed during the chronic stages of recovery.

In the current study, we further characterized this picture by separately examining untimed versus timed cognitive processing across epochs, thus avoiding the potential confounding of untimed performances by impaired speed of processing. We observed moderate to large ESs at each epoch for untimed and timed tasks, indicating that significant cognitive impairments persist even when the dimension of speed of processing is parceled out from neuropsychologic tests encompassing verbal learning/recall, visuospatial learning/recall, prospective memory, executive functioning, mental efficiency, and visuospatial skills. These findings are consistent with those of a recent study³⁸ finding that deficits in divided attention, executive functions, and long-term memory were better explained by a primary deficit in working memory than a deficit in speed of processing per se at approximately 1.5 years after brain injury.

That cognitive deficits persist even in the absence of any speed of processing requirement suggests that patients with TBI, their families, and the health care professionals that work with them should be prepared to implement compensatory strategies and accommodations for a wide variety of deficits into the long term in order to facilitate functioning and improve quality of life. These efforts are of particular import given the negative impact of persistent cognitive deficits post-TBI (eg, economic toll, increased psychologic distress such as depression/suicide, psychosocial dysfunction, marital/family/social network breakdown) and may be guided by findings linking specific cognitive deficits to functional outcome (eg, Rassovsky et al²¹ found that speed of information processing but not verbal memory mediated the relationship between TBI severity and post-TBI adaptive functioning).²¹

Further, more fine-grained research is needed to characterize primary, underlying persisting deficits and possible differences across neuropathologic, demographic, or psychosocial subgroups. It is also needed in order to uncover more subtle chronic changes that may exist, such as the clinically and scientifically important possibility of postrecovery cognitive decline. Animal^{75,76} and human studies^{77,78} have suggested that the brain may atrophy after initial injury and that cognitive functioning, too, may show a decline for some people in some domains after an initial normalized period of recovery.^{8,19,20} For example, Till et al²⁰ found that approximately 1 (27%) in 4 adults with moderate to severe TBI demonstrated some degree of cognitive decline between the first year of recovery and 2 to 5 postinjury. Ng et al⁷⁹ found visible interval changes on structural magnetic resonance imaging (read by expert neuroradiologists) over the same time period, including increased gliosis, increased white matter signal intensities, and tissue loss.

Persisting cognitive impairments may also leave some people vulnerable to a downward spiral of neuroplasticity with negative consequences analogous to that proposed by Mahncke et al^{80,81} in association with aging. Turner and Green⁸² have argued that chronic TBI, with its endogenous and exogenous changes similar to those observed in normative aging (eg, cognitive impairment, loss of employment, reduced opportunities for social contact), fosters conditions for negative plasticity.

Study Limitations

It should be noted that our literature search was limited to articles published in English, and that it is possible that unpublished studies with nonsignificant findings were excluded from the current meta-analysis. It is also possible that the search terms used were not exhaustive, resulting in the omission of relevant articles. Recruitment methods of the included studies were not assessed (eg, subjects may have been enrolled because they were symptomatic or had experienced particularly good or

poor recoveries), and this too could potentially contribute to outcome heterogeneity.

The ultimate quality of a meta-analysis is guided by the quality of included primary studies. Mathias and Wheaton²⁷ describe a number of factors that must be included within TBI studies in order to allow appropriate evaluation of individual studies and integration of studies in the form of meta-analyses. Future authors are advised to include those factors cited and to examine neuropsychologic recovery course separately for timed and untimed tasks. One limitation of the primary studies—which in turn produced limitations in the current meta-analysis—is that they did not quantify the percentage of variance accounted for by speed of processing versus other mental processes. Because the tests used in the studies eligible for inclusion at epoch 1 differed from those in epoch 2, direct comparisons across the epochs should be made with caution.

Another reason comparisons across epochs must be made conservatively is that there may be differences in the samples that would influence the results. For example, clinical or demographic factors (eg, persisting symptoms, socioeconomic status, education) could carry greater influences on the probability of participating in a long-term follow-up study than an earlier study; studies conducted early postinjury are often incorporated into routine clinical care, and thus factors such as family support, socioeconomic status, and severity of injury are less likely to influence participation. In this regard, we found that years of education were slightly higher in epoch 2 than epoch 1 in the current study, suggesting that those available for or interested in participating in a neuropsychologic study many years postinjury might be better educated than those who did not participate. A mitigating factor for this concern, however, is that the disparity in education from epoch 1 to epoch 2 was the same for timed and untimed tests. Therefore, any biases as a function of TBI may have influenced the 2 test types similarly. Another mitigating factor is that severity of injury was highly similar across test type and epochs, with most studies including patients in the severe range of injury on average, and a few made up of patients in the moderate-to-severe range.

Additional factors that may be worthwhile to include in future studies and were not evaluated in our study include the presence of chronic pain symptoms, affective status, and symptom validity performance. Issues such as chronic pain and affective status are additional factors associated with TBI that could influence an individual's neuropsychologic test performance, resulting in potential decline and/or fluctuation over time. Future work incorporating these factors would enrich our current knowledge regarding TBI recovery course and possible moderators.

CONCLUSIONS

People with moderate to severe TBI exhibit wide-ranging neuropsychologic deficits in both the acute and chronic phases of recovery. Relative to healthy controls, people with moderate to severe TBI were impaired on both timed and untimed neuropsychologic tasks at 2 chronic postinjury epochs: at or shortly after recovery plateau, and much later, at 4.5 or more years postinjury. These results, using meta-analysis, converge with and provide further specificity to the relatively small number of previous longitudinal studies of cognitive deficits in chronic TBI.

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Traumatic Brain Injury in Patients With Traumatic Spinal Cord Injury: Clinical and Economic Consequences

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ABSTRACT. Bradbury CL, Wodchis WP, Mikulis DJ, Pano EG, Hitzig SL, McGillivray CF, Ahmad FN, Craven BC, Green RE. Traumatic brain injury in patients with traumatic spinal cord injury: clinical and economic consequences. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S77-84.

Objective: To evaluate the clinical and economic burden of traumatic brain injury (TBI) in people with traumatic spinal cord injury (SCI).

Design: Prospective, case-matched control study.

Setting: Inpatient spinal cord rehabilitation program.

Participants: Patients (n=10) diagnosed with traumatic SCI and concomitant TBI matched to an SCI only control group.

Interventions: Not applicable.

Main Outcome Measures: Inpatient rehabilitation length of stay, health care costs (patient care hours), clinician resource allocation, behavioral and critical incidents, FIM, Personality Assessment Inventory, and neuropsychological assessment findings.

Results: Prolonged loss of consciousness, increased rehabilitation costs, and greater demands on clinician resources (trend) were found in the SCI with TBI group relative to the SCI-only group. Neuropsychological test performance was significantly worse in the SCI with TBI group, while the FIM cognition score did not discriminate because of ceiling effects. Greater evidence of psychopathology was observed in the SCI with TBI group.

Conclusions: The presence of TBI in SCI has a range of clinical and economic consequences. This dual diagnosis has the potential to affect SCI rehabilitation negatively, as well as quality of life and reintegration in the community. Specialized care appears to be needed to improve outcomes and to minimize clinical and economic burden, but further research is required.

Key Words: Brain injuries; Rehabilitation; Spinal cord injuries.

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THE CO-OCCURRENCE OF TBI with traumatic SCI represents a comorbidity with debilitating consequences. This dual diagnosis can pose clinical challenges that are more complex than either of these traumas on its own.¹ At present, there is a paucity of specialized dual diagnosis care, although it has been suggested that specialized care is critically needed to improve rehabilitation outcomes.^{1,2} Aside from the complexity and expense, we suggest that the lack of specialized care may be a result of a dearth of information regarding the clinical and economic impact of TBI on patients with SCI. Thus, a fuller understanding of the impact of TBI on SCI may well be of significant clinical import.

In most cases of traumatic SCI and TBI, the causes of injury are the same, with motor vehicle collisions and falls accounting for approximately 70% of all TBI and traumatic SCI.^{3,4} Co-occurrence is common, with estimates of dual diagnosis ranging from approximating 25% of all traumatic SCIs to over 70%.⁵⁻¹⁴ Methodologic differences across studies likely explain this disparity.¹⁵ For example, incidence studies have differed in experimental design (eg, prospective vs retrospective),^{10,12-14} inclusion criteria,¹⁶ time postinjury,^{7,11,17} sampling techniques,¹⁶ and diagnostic criteria for TBI.^{1,15}

While even the most conservative estimates of dual diagnosis are of scientific interest and clinical concern, there is little research to date on its clinical and economic consequences. Conventional SCI rehabilitation involves the acquisition of new knowledge and skills in order to regain functional independence and facilitate recovery.¹⁸⁻²⁰ Cognitive sequelae would logically hamper or prolong this relearning.²¹ Moreover, behavioral sequelae might impede progress by causing patients to be branded as "difficult."²⁰ Rehabilitation costs should also be higher if rehabilitation takes longer and/or is less effective. Arzaga et al² speculated that the post-SCI medical and adjustment difficulties would be compounded by the presence of concurrent TBI; however, to our knowledge, only 2 studies have empirically examined this speculation. Richards et al²² conducted a prospective evaluation of the long-term consequences of TBI on SCI. Here, patients with dual diagnosis were compared with a matched SCI-only group on measures of

List of Abbreviations

GCS	Glasgow Coma Scale
LOC	loss of consciousness
LOS	length of stay
MRI	magnetic resonance imaging
PAI	Personality Assessment Inventory
PTA	posttraumatic amnesia
SCI	spinal cord injury
TBI	traumatic brain injury
WAIS-III	Wechsler Adult Intelligence Scale- Third Edition
WMS-III	Wechsler Memory Scale- Third Edition
WTAR	Wechsler Test of Adult Reading

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family, vocational, social, and personal adjustment. Diagnosis of TBI was made by consensus agreement among 3 neuropsychologists. At 2 years postinjury, patients with SCI and moderate to severe TBI had greater personal and family adjustment difficulties compared with patients with SCI only and mild TBI.

Macciocchi et al²¹ conducted a retrospective comparison of 41 patients with SCI and concurrent TBI (based on GCS, LOC, PTA, or positive neuroimaging) to a matched cohort of 41 patients with SCI only. The groups were compared on admission and discharge FIM,²³ LOS, and rehabilitation costs. No differences in LOS or costs were revealed, but the patients with SCI and TBI made fewer functional gains from pretreatment to posttreatment on the FIM. However, these findings may underestimate the true consequences of TBI because patients with normative GCS and without positive neuroimaging findings were included in the TBI-positive group. While patients were assigned based on the presence of PTA or LOC, previous research has demonstrated that the validity of PTA and LOC for people with SCI is compromised by issues such as hypoxia and substance abuse.^{24,25}

Given the limited research into the impact of TBI on SCI outcomes and the clinical evidence to suggest at least some deleterious effects, the aim of this study was to examine empirically the clinical and economic impact of TBI on patients with SCI.

We compared a group of patients with SCI and TBI to a group of patients with SCI only on 8 parameters concerning their inpatient rehabilitation. These included the number of critical and behavioral incidents, emotional/neurobehavioral sequelae of TBI on SCI, duration of inpatient stay, functional gains on the FIM, hours of therapy and hours of nursing care, and health care costs. We predicted that the dual diagnosis group would demonstrate more incidents, greater psychiatric sequelae, longer stays, smaller gains on the FIM, greater hours of therapy and nursing, and greater costs. Given that the diagnosis of TBI is often missed in acute care,²⁶ we also examined the diagnostic sensitivity of neuropsychological testing for TBI in comparison with that of the FIM cognition score. Based on the findings of Davidoff et al,²⁷ we predicted greater sensitivity to cognitive impairment of the neuropsychological tests than the FIM cognitive subscale.

Our study extended previous research in several ways. The study by Macciocchi²¹ examined differences between inpatients with dual diagnosis versus SCI only, and employed a retrospective, group-matched design. The current study was prospective and used a combination of case-matching (general level of injury) and group-matching (injury severity and demographics). A wider number of variables was studied, and assignment to group was based on strict inclusion criteria in order to minimize the risk of errors in assignment to group. For the dual diagnosis group, definitive TBI diagnosis was based in most cases on positive MRI findings and in some cases on positive computed tomography scans with corroborative neurologic findings. For the SCI only group, patients needed to demonstrate normative neuroimaging and neurologic findings.

METHODS

Participants

The study protocol was approved by the research ethics board at the Toronto Rehabilitation Institute, and the procedures of the study were in accordance with the standards of the research ethics board.

Ten patients with traumatic SCI with TBI and SCI-only controls were recruited from the Spinal Cord Rehabilitation

Program of Toronto Rehabilitation Institute, a large, urban rehabilitation hospital. Traumatic SCI was defined as an insult to the spinal cord from an external physical force resulting in varying severities of sensory and/or motor deficits as a result of impediments to conduction across the lesions.²⁸

Participants were drawn from a sample of 30 patients who had been consecutively recruited from a larger study examining the incidence of TBI in SCI. From the larger sample, all participants with confirmed TBI (the SCI with TBI group) were identified, and then a group of patients with SCI without TBI (the SCI only group) were matched to the SCI with TBI group.

Diagnosis of TBI was made on the basis of (1) MRI findings at 2 to 6 months postinjury, or computed tomography findings plus corroborative clinical evidence from acute care, and (2) collateral data indicative of a positive TBI, including any or all of the following: presence of PTA, LOC, or positive neuropsychological results. MRIs were read by a neuroradiologist. Criteria for diagnosis included increased T2 signal intensity, iron deposition, encephalomalacia, cerebral hemorrhage, and contusion or infarct consistent with traumatic injury (rather than a primary cerebrovascular event). The absence of TBI was similarly confirmed by the absence of positive neuroimaging and other injury-related findings (table 1).

The control group (SCI only) was case-matched for general level of injury (ie, cervical, thoracic, lumbar) and then group-matched on completeness of injury, sex, age, and years of education.

All participants were between the ages of 18 and 55 years, were able to provide informed consent, and had sustained the injury within the previous 2 to 6 months. Exclusion criteria were the presence of a known or suspected neurodegenerative disorder (eg, multiple sclerosis, Parkinson disease), acquired language disorder that would preclude neuropsychological testing, and a diagnosed psychotic disorder.

Outcome Measures

Critical incidents/behavioral incidents. *Behavioral incidents* were defined as aggressive, emotional outbursts toward clinical staff or others that were characterized as verbal tirades with aggressive language or violent outburst that included throwing of items or verbal threats. *Critical incidents* were defined as accidents or injuries that occurred because of patients initiating unsafe actions (usually unsupervised) such as unsafe transfers or "wheelies" resulting in falls. Both types of incidents were identified and recorded by clinicians on the inpatient program. These incidents were obtained from medical records by trained chart reviewers blind to brain-injury status of patients; only items confirmed as behavioral or critical incidents by both reviewers were included.

Psychologic measures. Mood and psychopathology were measured by the PAI.²⁹ This is a 344-item self-report instrument composed of 22 nonoverlapping full scales consisting of 4 validity scales, 11 clinical scales, 5 treatment scales, and 2 interpersonal style scales. Respondents assess the degree to which each item is true of themselves on a 4-point Likert scale ranging from false to very true. The PAI has been shown to be reliable and valid in assessing personality and psychopathology among normative and clinical populations.^{29,30}

Length of stay. Number of days from inpatient rehabilitation admission to discharge was obtained from medical records.

FIM instrument. The FIM²³ was administered on admission and discharge from inpatient SCI rehabilitation. The FIM is designed to assess the degree of independence in motor, cognitive, and global activities of daily living and is based on

Table 1: Individual Subject Demographic and Injury Variables for the SCI With TBI and the SCI Only Groups

ID	Injury Level	Severity	Injury Type	PTA	Neuroimaging of Brain	Age (y)	Years of Education	Sex
SCI with TBI group								
1	C5	Complete	Sports	Not* available	+ MRI findings	29	17	M
2	T10	Incomplete	MVC	Yes	+ MRI findings	26	14	F
3	T6	Incomplete	MVC	Yes	+ CT findings	39	8	M
4	C4	Incomplete	Fall	Yes	+ CT findings	55	16	F
5	C5	Incomplete	Fall	Yes	+ CT findings	42	8	M
6	T3	Complete	MVC	Yes	+ MRI findings	20	12	F
7	C4	Incomplete	Fall	Not available*	+ MRI findings	50	9	M
8	L4	Incomplete	Fall	No	+ MRI findings	39	16	M
9	C4	Incomplete	Blunt force	Yes	+ MRI findings	40	9	M
10	C4	Complete	MVC	Yes	+ MRI findings	19	12	M
					Mean ± SD	35.90±12.11	12.10±3.53	
SCI only group								
1	C5	Incomplete	Sports	None	- MRI findings	28	12	M
2	T11	Complete	Sports	None	- MRI findings	44	10	F
3	T12	Complete	Fall	None	- MRI findings	42	12	M
4	C4	Incomplete	Blunt force	None	- MRI findings	54	14	M
5	C5	Incomplete	Fall	None	- MRI findings	29	10	M
6	T11	Complete	MVC	None	- MRI findings	53	19	M
7	C4	Incomplete	Assault	None	- MRI findings	55	10	M
8	L1	Incomplete	Fall	None	- MRI findings	19	14	F
9	C7	Incomplete	Fall	None	- MRI findings	18	12	F
10	C5	Incomplete	Fall	Not available	- MRI findings	21	12	M
					Mean ± SD	36.30±15.00	12.50±2.71	

Abbreviations: CT, computed tomography; F, female; M, male; MVC, moving vehicle collision. *PTA was not available; however, patient had documented LOC.

a person's observed functioning. Cognitive and motor performance are scored using an ordinal scale ranging from 1 (total assistance) to 7 (complete independence) with 13 motor and 5 cognitive items. Scores from both domains can be added together to produce an overall FIM score (range, 18–126), with higher scores indicating greater functional independence.

A FIM efficiency score to calculate the efficacy of rehabilitation taking FIM change and LOS into consideration (ie, the ratio of FIM change to LOS) was computed.

Neuropsychological measures. Widely used clinical tests with confirmed validity and reliability for TBI that did not require upper extremity use were included in the neuropsychological test battery. The tests included were as follows. For estimated premorbid intelligence quotient, the WTAR³¹ was employed. For attention and speed of processing, the WAIS-III digit span forwards, Symbol Digits Modalities Test,³² and Stroop Color Word Test³³ (word reading condition, color naming condition, and color-word conditions) were used. Language and visuospatial skills were tested with the WAIS-III similarities test, the Hooper Visual Organization Test,³⁴ and the WAIS-III³⁵ matrix reasoning subtest. Verbal memory was assessed with the WMS-III³⁶ logical memory immediate recall (logical memory 1) and delayed recall (logical memory 2) and the California Verbal Learning Test-Second Edition³⁷ (total learning, immediate and delayed recall, and recognition discrimination). For visuospatial memory, the WMS-III family pictures, immediate recall (family pictures 1), and delayed recall (family pictures 2) were employed. Executive functions were measured with the Controlled Oral Word Association Test,³⁸ verbal fluency test, and the Wisconsin Card Sorting Test³⁹ (number of categories correctly sorted and percentage of perseverative errors).

Therapist/nursing hours. Clinician workload (minutes of direct care per patient) was extracted from hospital records

using a computerized extraction system designed for our hospital called "workload measurement." Hours of direct care/per patient were computed separately for nursing and for all health care therapists combined (ie, physiotherapy, occupational therapy, rehabilitation therapy, and speech language pathology).

Rehabilitation care costs. Total care costs were calculated for each patient using FIM-based rehabilitation client groups (in this case, traumatic SCI or major multiple trauma with brain or SCI) according to a rehabilitation case-costing methodology devised for the province of Ontario.⁴⁰ Here, patients were first identified by their rehabilitation group, then by the FIM motor admission score and, for patients in the mid-range of FIM scores (motor score, 17–41), also by age. LOS was also determined. Patients were assigned rehabilitation case-cost weights adjusted for LOS according to the National Rehabilitation Reporting System guidelines and Ontario-specific case-cost weights.⁴⁰ A case-cost weight for each rehabilitation group was then multiplied by the provincial average case cost (\$14,139).⁴⁰

The cost/patient divided by FIM change scores (cost a patient/FIM change score) was also calculated. The total cost an FIM change score was also computed by dividing the LOS cost by the FIM change score.

Procedures

FIM scores were collected on admission and discharge to the clinical program. Clinicians on the inpatient SCI program trained in FIM administration administered the FIM. The timing of the initial FIM relative to the time of injury differed from patient to patient because of differences in admission dates.

The neuropsychological and psychologic evaluations were administered between 2 and 6 months postinjury. Trained psychometrists (supervised by a clinical neuropsychologist) completed the neuropsychological testing and were blind to neuroimaging findings at the time of the evaluation. A master's-level

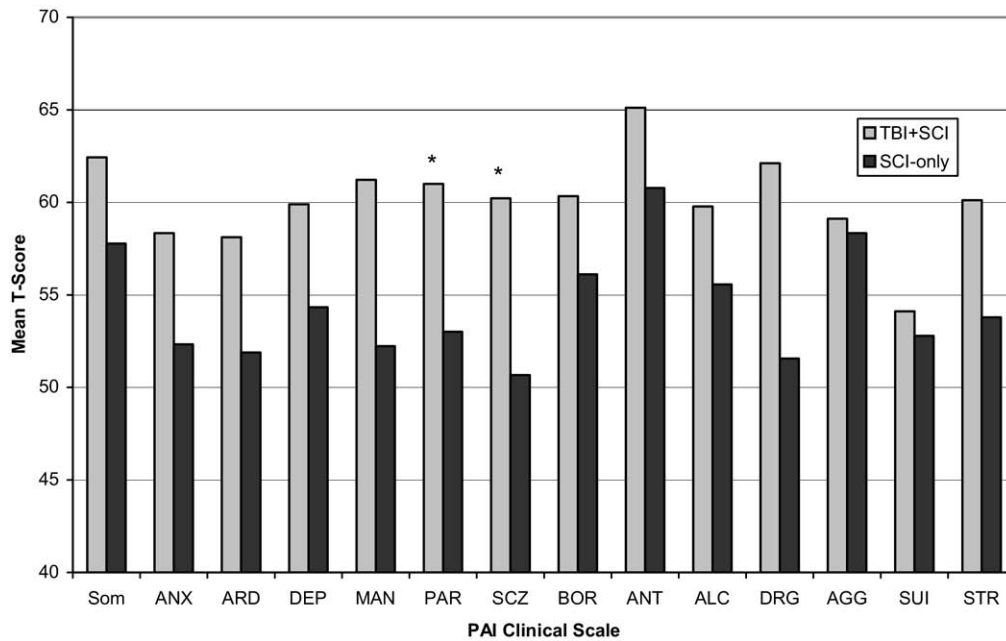


Fig 1. PAI clinical scale scores for the SCI with TBI versus SCI-only groups.

graduate student supervised by a clinical psychologist oversaw the administration of the self-report psychologic questionnaires. MRI, used to confirm presence or absence of TBI, was undertaken within 2 weeks of neuropsychological assessment. A neuroradiologist read all MRIs and determined the acquisition parameters of the scan, which were tailored to TBI (ie, dual-spin echo, fluid-attenuated inversion recovery, T2-weighted gradient echo).

Data Analyses

Descriptive statistics were calculated for demographic and injury variables to provide characterization of the 2 groups. In order to examine the hypotheses, statistical comparisons between patients with SCI only and those with SCI with TBI were completed using chi-square tests for all categorical variables and paired *t* tests for continuous variables. For all comparisons with specific, directional hypotheses, 1-tailed, unpaired *t* tests were performed.

Effect sizes (Cohen's *d*) were calculated for all comparisons. Because of the size of our clinical sample ($N=20$), the risk of type I and type II error was greater than that for a larger sample, with a risk of spurious significant findings at low effect sizes and nonsignificant findings at high effect sizes. Using null hypothesis significance testing could misrepresent the findings, and we thus employed effect sizes to interpret the data (see discussion^{41,42}). We employed a moderate cutoff of 0.4 as our index of clinical significance, which is considered high, given the low magnitude of correlations observed in well related phenomena in nature.⁴³

RESULTS

Table 1 shows the demographic and injury variables of all participants in the 2 groups individually. The groups were closely matched on all parameters with the exception of time between injury and inpatient admission. There was a difference between the groups on this parameter, with the SCI with TBI group arriving at 55.00 ± 40.81 days postinjury versus

32.90 ± 20.66 days postinjury for the SCI-only group. Although not significant on a 2-tailed unpaired *t* test ($t_{18} = -1.53$; $P = .14$), there was a large Cohen's *d* effect size of -0.68 . The admission FIM was also administered commensurately later in the SCI with TBI group. Otherwise, none of the differences between the groups approached significance, including time from injury and time to assessment.

Critical and behavioral incidents during rehabilitation.

The SCI with TBI group showed an average of 1.22 ± 1.56 behavioral incidents a person over the course of their stay compared with less than half of that, 0.44 ± 0.52 , for the SCI-only group. When corrected for LOS (which was longer in the SCI with TBI group), between-group differences approached significance ($t_{17} = 1.66$; $P = .06$), with a large Cohen's *d* effect size ($d = 0.72$).

With respect to critical incidents, the SCI with TBI group had an average of 0.44 ± 0.53 critical incidents a person, compared with 0.22 ± 0.42 incidents a person in the SCI-only control group, with a moderate effect size (Cohen's $d = 0.46$). However, when LOS was controlled for, comparable levels of critical incidents a patient per day were observed in both groups, with a negligible effect size ($d = 0.04$).

Psychologic findings. Consistent with elevated behavioral incidents, the 2 groups showed differences of greater than 10 *t* scores on most clinical subscales of the PAI, as illustrated in figure 1. These differences reached significance on the paranoia and schizophrenia subscales ($t_{16} = 1.72$, $P = .05$, Cohen's $d = 0.81$; and $t_{16} = 1.82$, $P < .05$, Cohen's $d = 0.65$, respectively). Note that the average elevation in the SCI with TBI group was not in range for clinical diagnosis of paranoia or schizophrenia. Trends toward significant between-group differences were observed on the anxiety and mania subscales, with large effect sizes ($t_{16} = 1.52$, $P = .07$, Cohen's $d = 0.71$; and $t_{16} = 1.58$, $P = .07$, Cohen's $d = 0.93$, respectively).

Neuropsychological assessment versus FIM cognitive subscale. As expected, the neuropsychological performance was poorer in the SCI with TBI group. As indicated in table 2, there

Table 2: Between Groups Neuropsychological Test Performance for SCI With TBI and SCI Only Groups

Neuropsychological Domain Test	SCI With TBI Group (n=9)	SCI Only Group (n=10)
Estimated Premorbid IQ		
WTAR [†]	98.56±17.53	105.60±13.16
Attention/speed of processing		
Digit span forwards	62.67±31.20	83.60±21.87
Symbol Digit Modalities Test	-1.11±1.27	-0.75±0.79
Stroop Word [#]	44.00±7.14	53.30±12.68*
Stroop Color Naming [#]	38.67±5.43	46.40±6.48 [†]
Stroop Color Word [#]	41.89±9.24	52.10±11.44*
Verbal Memory		
WMS-III logical memory 1 [§]	10.11±5.04	12.70±2.41
WMS-III logical memory 2 [§]	10.33±5.22	13.30±2.83
CVLT-II, short delay	-0.39±1.36	0.44±0.68
CVLT-II, long delay	-.167±1.54	0.40±0.61
CVLT-II, discriminability	-0.50±1.27	0.45±0.50*
Visual Memory		
WMS-III family pictures 1 [§]	8.44±3.71	8.70±4.14
WMS-III family pictures 2 [§]	8.00±3.97	8.90±3.64
Language/visuospatial similarities [†]	9.67±2.74	10.50±2.12
Hooper Visual Orientation Test [#]	53.56±6.86	53.10±5.69
Matrix Reasoning [§]	10.33±3.94	11.3±2.58
Executive Functions		
Digit span backwards	33.56±31.40	55.60±18.31*
Verbal Fluency (category)	-0.78±0.87	-0.07±1.03
WSCT, perseverative errors [#]	47.33±16.65	52.80±14.27

NOTE. Values are means ± SDs.

Abbreviations: CVLT, California Verbal Learning Test; WSCT, Wisconsin Card Sort Test.

* $P < .05$.

[†] $P < .01$.

[‡]standard score.

[§]scaled score.

^{||}percentile score.

^{||}z score.

[#]T score.

were no significant differences between the groups on a measure used to estimate premorbid intelligence, the WTAR. However, significant differences on 1-tailed, unpaired t tests were observed on measures of current cognitive functioning. Differences were observed on tests of attention and speed of processing: digit span backwards ($t_{17} = -1.89$, $P < .05$, Cohen's $d = -0.92$), Stroop color naming ($t_{17} = -2.80$, $P < .01$, Cohen's $d = -1.29$), and Stroop word reading ($t_{17} = -1.94$, $P < .05$, Cohen's $d = -0.90$). Verbal recognition memory also significantly differed between the groups ($t_{17} = -2.19$, $P < .05$, Cohen's $d = -0.87$). Trends toward poorer performance by the SCI with TBI group with medium to large effect sizes were observed on measures of verbal recall (logical memory, immediate recall, $t_{17} = -1.45$, $P = .08$, Cohen's $d = -0.60$; California Verbal Learning Test, short delay free recall, $t_{17} = -1.64$, $P = .06$, Cohen's $d = -1.76$; digit span forwards, $t_{17} = -1.71$, $P = .05$, Cohen's $d = -0.78$; and verbal fluency, $t_{17} = -1.60$, $P = .06$, Cohen's $d = -0.74$).

Functional outcome. Although the neuropsychological findings clearly distinguished the groups, the FIM admission cognitive subscale did not because of ceiling effects. Indeed, 10 of 10 participants in the SCI only group and 7 of 10 patients in the SCI with TBI group scored at ceiling (35 of 35).

With regard to the motor FIM subscale, the patients with SCI with TBI were tested significantly later postinjury than those in the SCI only group and were matched for severity of injury; however, their motor scores were still slightly lower, with a mean motor FIM ± SD of 24.80±13.42 in the SCI with TBI group versus a mean ± SD of 29.20±19.41 in the SCI only group. The difference was not significant ($t_{17} = -0.59$; $P = .28$), with a small Cohen's d of -0.26. However, given that the SCI with TBI group had longer recovery time, their FIM scores should logically have been higher unless the brain-injury was compromising performance on the FIM.

Length of stay. The SCI with TBI group remained in inpatient rehabilitation longer than the SCI only group, with mean LOSs ± SD of 138.3±69.71 days versus 100.30±41.41 days, respectively, with a difference that approached significance ($t_{18} = 1.48$; $P = .08$) and a medium to large effect size of Cohen's d equal to 0.66. However, the SCI with TBI group did not surpass the SCI only group on the FIM motor subscale; motor FIM discharge scores were 54.7±27.35 for the SCI with TBI group versus 62.67±23.83 for the SCI only group.

Therapy/nursing hours. Level of nursing care required revealed greatest differences, with an average ± SD of 262.34±197.56 hours of care within a 2-month period required by the SCI with TBI group compared with 185.47±107.69 hours required by the SCI only group ($t_{15} = 1.01$, $P = .16$) and a medium Cohen's d effect size of 0.48. The difference in the number of therapy hours between groups was smaller, with the SCI with TBI group requiring an average ± SD of 204.68±155.38 hours, compared with the SCI only group, which received an average ± SD of 184.05±108.74 hours ($t_{15} = -0.32$; $P = .38$; $d = 0.15$).

Economic burden. The average cost ± SD for a dual diagnosis patient to complete SCI rehabilitation was \$169,638±\$83,945, compared with \$130,773±\$90,630 for a patient with SCI only, a difference that did not reach significance ($t_{18} = -.99$; $P = .17$) but showed a medium Cohen's d effect size of 0.44. The total cost per FIM change score was also not found to differ between groups ($t_{17} = -1.18$; $P = .13$) but revealed a medium Cohen's d effect size ($d = -0.56$). Thus, these differences were of clinical significance in both cases.

DISCUSSION

Taken together, the results from the present study show a substantive, deleterious impact of comorbid TBI with SCI. First, we found that patients with SCI with TBI displayed significantly more behavioral incidents, greater psychopathology, and more severe neuropsychological impairment than patients with SCI without TBI. These findings are compatible with the previous research of Richards et al,²² who also examined psychosocial functioning (but in an outpatient population) and found poorer adjustment in patients with SCI with comorbid TBI. In the current study, increased behavioral incidents may have been associated with elevated psychopathology and neuropsychological impairment. It has previously been suggested that undiagnosed TBI with associated executive dysfunction and compromised ability to attend to and/or remember instructions leads to confusion, frustration, and tension among the patient, treating clinicians, nurses, and fellow patients.^{2,19} Anecdotal experience on our inpatient clinical program is consistent with these findings. It is unclear whether elevated psychopathology here is a consequence of brain injury or a premorbid risk factor. Ascertainment of preinjury psychopathology with the help of family members would be of interest.

As well, further research with larger sample sizes and predictive models, such as path analysis, would be helpful to understand better the interrelationships between behavioral incidents, psychopathology, and neuropsychological impairment.

A second consequence of comorbid TBI in the current study was the need for greater nursing care hours. A number of factors may have contributed to this finding. For example, given greater behavioral incidents and emotional disturbance in the SCI with TBI group, one might speculate that recorded behavioral incidents along with milder unrecorded incidents may have added to nursing hours. In addition, speed of information processing was slower in the SCI with TBI group; consequently, activities under nursing supervision (many of which are unstructured, in contrast with structured therapeutic activities) may simply have required more time. Other factors not measured in the current study may have also contributed, such as slower achievement of independence in bowel and bladder care, transfers, and self-medication. Further research is needed to examine these speculations to anticipate where added nursing hours and nursing support might be valuable to allow for the most efficient use of nursing resources.

A third difference between the groups concerned the FIM results. Despite a later arrival to inpatient rehabilitation of the SCI with TBI group, intake motor FIM scores were comparable between the SCI with TBI and SCI only groups. Moreover, despite a longer LOS, and group matching for severity of SCI injury and demographics, the SCI with TBI group did not exceed the SCI only group on FIM score by the time of discharge. These findings were compatible with those of Macciocchi et al.,²¹ who did not find differences in LOS, but did find a difference in FIM motor scores at discharge. Taken together, these results indicate that more time is needed to achieve comparable gains in independence of activities of daily living in patients with a concomitant brain injury. The findings suggest several interpretations: first, the cognitive and neurobehavioral consequences of TBI may impede SCI rehabilitation, with impairments to attention and memory—for example, diminishing the capacity for learning self-maintenance routines. A second interpretation is that the TBI itself causes motor impairments. Deficits of incoordination, motor planning, and postural control are often seen in TBI.⁴⁴ However, in our context, TBI-related motor deficits would not have been treated with interventions with demonstrated efficacy for TBI, such as forced use/constraint-induced movement.¹⁹

The findings also revealed the inadequacy of the FIM cognitive subscale to detect cognitive impairments, consistent with the findings of Davidoff et al.²⁷ Only 3 of the 10 patients in the SCI with TBI group fell below ceiling on the FIM cognitive subscale at intake. This finding has important clinical implications: The FIM is often the only screening of cognitive status that is employed on admission to inpatient spinal cord rehabilitation programs. Because the diagnosis of TBI is often missed in acute care,¹ and neuropsychological assessment is unlikely to be administered without a TBI diagnosis, there is no diagnostic safety net. One consequence of missed diagnoses is that cognitive and neurobehavioral symptoms of TBI may be misattributed, with patients labeled as “unmotivated,” “noncompliant,” or “difficult.” Perhaps more importantly, the failure to identify TBI either in acute care or inpatient rehabilitation settings would result in a failure to provide specialized services for brain injury, where available.

Last, and perhaps not surprisingly, the daily costs of inpatient spinal cord rehabilitation were greater for patients with TBI than for patients with SCI only, as were the costs/FIM change. These costs might be decreased if specialized dual diagnosis care to improve the speed and quality of learning of

self-care routines were implemented. For example, specialized care could incorporate those learning approaches that are most effective for people with explicit memory deficits, such as procedural learning^{45,46} and errorless learning.⁴⁷ For the learning of self-care routines, these approaches might prove more effective for acquisition in the short term, and more resistant to decay in the longer term.

Study Limitations

One limitation of the current study concerned matching. While patients were case-matched based on general level of injury (cervical, thoracic, lumbar), they were not case-matched for vertebral level. Overall, there were slightly higher levels of injury in the SCI with TBI group. Therefore, 1 alternative interpretation of the differences observed between the groups is that level of injury differences between the groups, rather than concomitant brain injury, played a causal role, contributing to some or all outcome variance. A close inspection of the individual data points does not support this alternative interpretation, however. When we examined each case-matched pair, there were no systematic outcome differences as a function of vertebral level. There was not a greater decrement in performance for those pairs for which the patient with SCI with TBI had a higher injury than the SCI only case-matched control versus those pairs for which the patient with SCI with TBI had a lower injury.

Another limitation concerns the patient sample. The sample size was small. Therefore, the study may have been underpowered to detect significant differences between the groups. As well, all recruitment was undertaken from a single, inpatient spinal cord treatment facility in an urban center associated with a teaching hospital. Therefore, the findings may not generalize to other types of treatment facilities or rural patient populations. The presence of pain and medication effects over time was not controlled, although we do not expect these factors to differ significantly between the groups.

As well, the presence of self-awareness deficits in TBI may have resulted in a more positive response bias on self-report questionnaires of mood and psychopathology, thereby underestimating psychopathology in the SCI with TBI group. Also, there are limitations to the validity of the PAI for patients with TBI; elevations on some subscales, including schizophrenia and somatization, may occur because of the neurologic and medical features of brain injury rather than psychopathology.

Finally, there were no differences between the groups with regard to secondary neurologic complications of the brain. However, we did not control for secondary medical complications in the study. Therefore, 1 possible explanation for differences in LOS between the groups concerns secondary medical complications. Logically, any increased risk in secondary complications caused by cognitive impairment (eg, because of poorer self-care or self-monitoring) would be likely to emerge postdischarge and would be unlikely to emerge while patients are being closely monitored during their inpatient stay. For example, patients receive daily therapy and nursing supervision, and have regular physician contact. Nonetheless, it would be valuable to control for this factor in future research.

CONCLUSIONS

The clinical and economic impact of dual diagnosis observed in this study would likely be unsurprising to clinicians working with the SCI population. In addition to the present findings and those of Macciocchi et al.,²¹ who found reduced FIM gains during rehabilitation of an SCI with TBI group, long-term

effects of dual diagnosis (on personal and family adjustment) have also been observed.²² Taken together, these findings support the need for further research on larger populations, both in the early subacute and chronic stages of injury. An understanding of the relationship, for example, between specific cognitive deficits and poor long-term outcomes could allow for prophylactic, targeted interventions. We suggest that early identification and specialized intervention could help to meet the unique and complex needs of this special population, thereby improving quality of life and reducing the negative impact on health care systems and society.

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ORIGINAL ARTICLE

Use of Diffusion-Tensor Imaging in Traumatic Spinal Cord Injury to Identify Concomitant Traumatic Brain Injury

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ABSTRACT. Wei CW, Tharmakulasingam J, Crawley A, Kideckel DM, Mikulis DJ, Bradbury C, Green RE. Use of diffusion tensor imaging in traumatic spinal cord injury to identify concomitant traumatic brain injury. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S85-91.

Objective: To characterize and differentiate cerebral white matter (WM) changes related selectively to traumatic brain injury (TBI) or spinal cord injury (SCI) in patients with SCIs in order to improve diagnostic accuracy of TBI in people with SCI.

Design: Diffusion-tensor imaging (DTI)-derived fractional anisotropy (FA) data in WM tracts were compared between a healthy control and 2 patient groups. Between-subject comparisons of FA were performed using region of interest (ROI) analysis and tract-based spatial statistics.

Setting: A large, urban inpatient SCI program.

Participants: Three groups: SCI and concomitant TBI (SCI with TBI, n=7); SCI without TBI (SCI only, n=15); and healthy control subjects (n=12).

Interventions: Not applicable.

Main Outcome Measure: FA was used as a measure of cerebral WM integrity.

Results: ROI analyses showed reduced FA in the genu and splenium of the corpus callosum and forceps minor in patients with SCI with TBI compared with both healthy controls and patients with SCI only. ROI analyses did not show evidence of FA differences in patients with SCI only compared with controls. Tract-based spatial statistics did not demonstrate between-group differences in FA.

Conclusions: DTI is a sensitive tool to detect TBI-related WM damage in patients with SCI who have suffered concomitant TBI. No WM abnormalities on DTI could be attributed to SCI alone, although this finding should be further explored in future studies. Therefore, DTI may be a valuable tool to identify TBI in the SCI population. Further research to produce normative FA values is needed to allow identification of TBI in individual patients with SCI.

Key Words: Brain injuries; Diffusion magnetic resonance imaging; Rehabilitation; Spinal cord injuries.

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THE PRESENCE OF TRAUMATIC brain injury in patients with SCI is a well documented phenomenon. This association is not surprising, given the striking similarities between the TBI and SCI populations in demographic profile as well as in injury circumstances.¹ The incidence of both TBI and SCI is higher in male subjects, with over 50% of the affected population being between the ages of 15 and 30 years.^{2,3} In addition, both types of injuries typically result from high-velocity impact such as motor vehicle collisions (50% in both cases), falls (21% in both cases), and sporting accidents.² However, the precise frequency of comorbidity of TBI with SCI has not been clearly established. In most studies using 1 or 2 indicators of neurotrauma to diagnose TBI (eg, loss of consciousness, PTA, and/or neuropsychological deficits), the prevalence of TBI in traumatic SCI was estimated to be 40% to 60%.⁴⁻¹¹ However, when structural MRI was combined with neuropsychological testing to evaluate the presence of neurotrauma, 74% of patients of SCI were found to have concomitant brain injury in 1 study.¹² Given the high frequency of the comorbidity, the ability to diagnose or rule out concomitant TBI is a major issue in the treatment and rehabilitation of patients with SCI.

A major goal of neuroradiologic investigations in brain trauma is to identify the presence of DAI, a key mechanism of neural damage after TBI.¹³ DAI results from unequal rotational or acceleration/deceleration forces that cause multifocal lesions in WM because of a shear-strain deformation.¹⁴⁻¹⁶ DAI sites of predilection include subcortical WM, corpus callosum, fornix,

List of Abbreviations

ALIC	anterior limb of the internal capsule
ANOVA	analysis of variance
DAI	diffuse axonal injury
DTI	diffusion-tensor imaging
FA	fractional anisotropy
FMRIB	functional magnetic resonance imaging of the brain
gCC	genu of the corpus callosum
GCS	Glasgow Coma Scale
MRI	magnetic resonance imaging
PLIC	posterior limb of the internal capsule
PTA	posttraumatic amnesia
ROI	region of interest
sCC	splenium of the corpus callosum
SCI	spinal cord injury
TBI	traumatic brain injury
TBSS	tract-based spatial statistics
WM	white matter

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internal capsule, and infratentorial WM.¹⁷⁻²⁰ Although conventional MRI techniques can readily visualize posttraumatic focal structural lesions, they are unable to detect microscopic WM damage in DAI. Consequently, the diagnosis of TBI is missed in some patients, particularly those with milder brain injuries.²¹

Recently, DTI has proven fruitful in detecting the loss of axonal organization in TBI.²²⁻²⁵ DTI is a novel MRI technique that can provide information about the microscopic tissue architecture. The diffusion tensor represents a model of water diffusion in biologic tissues²⁶ and describes the magnitude, direction, and orientation of the diffusion distribution. FA is an index used to characterize the local coherence of fibers²⁷ and is one of the most widely used metrics in diffusion anisotropy.²⁸ FA is a convenient measure because it is scaled from 0 (complete isotropic diffusion) to 1 (complete anisotropic diffusion). In WM, water diffusion is less restricted in the direction parallel to the fiber orientation, whereas it is highly restricted in the direction perpendicular to the fibers.²⁶ FA is highest in major WM tracts (maximum possible value, 1) while it approaches 0 in cerebrospinal fluid. For example, normative WM tracts with coherently oriented fibers typically exhibit higher FA values, whereas reduced FA usually occurs in WM disease states (although this is not always the case). Reduced FA values have been identified in DAI sites^{20,22,23,25,29-37} and are more sensitive than conventional MRI to axonal injury in a mouse model of TBI.³⁸ Early detection of DAI using diffusion-weighted MRI can not only direct acute neurologic intervention³⁹ and long-term rehabilitation but also improve outcome prediction in adult TBI.⁴⁰

Before DTI can be reliably used to assess for TBI in patients with SCI, however, several questions need to be addressed. First, does SCI without any comorbidity cause alterations in the human brain? If so, is this injury distinguishable from that caused by TBI? SCI-related brain injury must be documented so the effects of SCI alone are not confounded with the effects of brain injury. A false diagnosis of TBI could have serious clinical, ethical, and financial consequences. If injury caused by SCI can be identified and factored out when using DTI to diagnose TBI, we can greatly improve the diagnostic specificity and reduce the likelihood of a false-positive diagnosis of TBI in patients with SCI. Second, even if SCI does cause alterations to the brain, are there areas of the brain that show reduced FA secondary to TBI, but are nonetheless unaffected by the effects of traumatic SCI?

In this study, we attempted to localize WM alterations in the brain caused by traumatic SCI alone using DTI-derived FA values as a marker of axonal integrity. We also attempted to identify those regions of the brain that would reliably discriminate patients with traumatic SCI plus TBI from patients with traumatic SCI only. We therefore included 3 study groups: (1) patients with SCI and no evidence of TBI (SCI only) based on structural 3 Tesla MRI and collateral neurologic findings, (2) patients with SCI and definitive structural MRI evidence of TBI (SCI with TBI), and (3) healthy controls. We examined the data with 2 approaches. We first investigated between-group FA differences in a priori ROIs, including the ALIC and PLIC, forceps minor, and gCC and sCC. These regions were selected because previous studies have shown that DTI abnormalities in the corpus callosum and forceps are particularly sensitive markers for TBI.^{29,33} Moreover, WM tracts in the internal capsule, which conduct sensory afferents, may be a region most sensitive to traumatic SCI. In addition, we explored a novel group analysis technique, TBSS, which allows whole-brain, voxel-wise FA comparisons between groups.⁴¹⁻⁴⁴ To date, the application of TBSS has not been used to study TBI or SCI.

We conducted 3 between-group analyses of FA: SCI only versus controls, SCI with TBI versus controls, and SCI only versus SCI with TBI. We hypothesized that (1) compared with both patients with SCI only and normal controls, the SCI with TBI group would show multiple areas of FA reductions in predilection sites of DAI; and (2) in WM fiber tracts containing afferent pathways, both SCI only and SCI with TBI would have reduced FA compared with controls because of loss of afferent projections.

METHODS

Subjects

The study protocol was approved by the research ethics board at the local institution at which the study was conducted, and the procedures of the study were in accordance with the standards of the research ethics board.

Twenty-two patients (15 men, 7 women; mean age, 34.3y; range, 19-53y) with traumatic SCI were recruited from a large urban SCI program within a rehabilitation hospital, to which they were referred for subacute rehabilitation between 2006 and 2008. The demographic and clinical information of the participants in this study is summarized in [table 1](#). All patients underwent an MRI scan of the brain in the subacute period after their traumatic SCI. Each patient was assigned to 1 of 2 groups, SCI with TBI or SCI only, based on MRI findings and collateral information examinations (ie, GCS, PTA, loss of consciousness, neuropsychological assessment). For the SCI-only group, all patients had negative MRIs of the brain. Fifteen patients were assigned to the SCI-only group (13 men, 2 women; mean age, 35.7y; range, 20-54y). All collateral information available at the time of writing is included in [table 1](#), with the exception of invalid information, which was excluded. This included 2 GCS scores, invalid because of alcohol at the time of assessment, and 1 PTA score, invalid because of medications during the period of PTA. Seven patients were assigned to the SCI plus TBI group (5 men, 2 women; mean age, 31.6y; range, 20-50y). All 7 patients had positive MRI findings consistent with previous brain trauma. For this group, only collateral information with positive findings is reported in [table 1](#) (eg, depressed GCS, presence of PTA).

The healthy control group included 12 healthy volunteers (7 men, 5 women; mean age, 34.6y; range, 21-51y) who had had no known history or MRI evidence of central nervous system disease.

Exclusion criteria for all participants included any history of TBI and any history of neurologic or psychotic illness, and prior structural abnormality of the brain. All participants were proficient in English.

The patient groups were well matched on the key parameters. There were no significant differences or differences approaching significance between the 2 patient groups on age, years, or number of days between injury and MRI. There were no differences between either of the patient groups and the healthy control group on age. However, both patient groups differed significantly from the control group on years of education: the SCI-only group differed from controls at the $P < .000$ level of significance; the SCI with TBI group differed at the $P < .001$ level of significance.

Magnetic Resonance Imaging Data Acquisition

All patients and controls were scanned using a GE 3 Tesla MRI scanner^a equipped with an 8-channel head-coil (MRI devices). Subjects underwent the routine MRI protocol (including T₁-weighted spin-echo, T₂-weighted spin-echo, T₂*-weighted

Table 1: Demographic and Injury Data of Participants Included in the Study

Participants	Sex	Age at SCI	Injury Type	SCI Level/ Completeness	Structural MRI Findings	Days Between Injury and MRI	Additional Neurologic Evidence TBI+/-	Years of Education
SCI only								
1	M	28	Sports	C5/Inc	Negative	123	Neg CT	12
2	F	44	Sports	T11/Com	Negative	59	No PTA, LOC; GCS=15	10
3	M	54	Fall	C6/Com	Negative	64	No PTA; neg NP	15
4	M	44	Fall	C6/Inc	Negative	73	No PTA; neg NP	10
5	M	53	MVC	T11/Com	Negative	61	No PTA; GCS=15	19
6	M	42	Fall	T12/Com	Negative	91	No PTA, no LOC	12
7	M	21	Fall	C5/Inc	Negative	66	Neg NP	12
8	F	41	Fall	T12/Inc	Negative	59	No PTA, LOC; neg NP	16
9	M	20	MVC	C7/Inc	Negative	86	No LOC	12
10	M	31	Fall	T12/Inc	Negative	54	No LOC	12
11	M	24	MVC	C8/C5/Inc	Negative	186	No LOC, GCS=15	12
12	M	38	Fall	L1/Inc	Negative	157	No PTA, LOC	9
13	M	22	Sports	C1/Inc	Negative	102	No LOC, GCS=15	14
14	M	39	MVC	T5/Inc	Negative	74	No LOC	14
15	M	34	MVC	C4/Com	Negative	147	GCS=15	13
Mean ± SD	2F/13M	35.7±11.1	5 MVC: 10 other			93.5±41.3		12.8±2.5
SCI with TBI								
1	F	26	MVC	T11/Inc	Positive	273	GCS=11, LOS	14
2	F	20	MVC	T3/Com	Positive	134	PTA	12
3	M	50	Fall	C4/Inc	Positive	82	NA	9
4	M	39	Fall	L4/Inc	Positive	59	None	16
5	M	40	Blow/Fall	C4/Inc	Positive	64	PTA, LOC	9
6	M	19	MVC	C4/Com	Positive	185	PTA, LOC, GCS=3	12
7	M	22	MVC	T7/Com	Positive	101	PTA, LOC	12
Mean ± SD	2F/5M	31.6±12.0	4 MVC: 3 other			128.3±77.5		12.0±2.5
Controls								
Mean ± SD	5F/7M	34.6±10.2						18.1±3.1

NOTE. For SCI only, all collateral information reported except that which is invalid, as noted in text. For SCI with TBI group, only positive findings reported. The SCI only group includes patients with SCI and no evidence of TBI based on structural MRI and collateral neurologic findings. The SCI with TBI group includes patients with SCI and definitive structural MRI evidence of TBI. Abbreviations: C, cervical; Com, complete; CT, computed tomography; F, female; Inc, incomplete; LOS, loss of consciousness; L, lumbar; M, male; MVC, motor vehicle collision; NA, not applicable; Neg, negative; NP, neuropsychological assessment; T, thoracic.

gradient-echo, and fluid-attenuated inversion recovery) as well as the DTI protocol. Three sets of DTI data for each subject were acquired using a diffusion-weighted spin-echo single-shot echo-planar imaging sequence with diffusion encoding in 15 noncollinear directions. The total DTI acquisition time was approximately 9 minutes and 30 seconds. The sequence parameters were as follows: repetition time, 10,000ms; echo time, 84ms; matrix, 128 × 128; field of view, 240mm²; 5-mm thickness; 0-mm gap; *b* factor, 1000s/mm².

Evaluation of Conventional Magnetic Resonance Imaging

The conventional MRI images were qualitatively evaluated for all subjects by an experienced neuroradiologist blinded to the DTI findings and clinical ratings. This evaluation included classification of all visible lesions based on their signal characteristics. The presence or absence of DAI consistent with previous TBI was used to confirm assignment of patients with SCI to either the SCI-only or the SCI with TBI group. Healthy control subjects with incidental signal abnormalities on MRI were excluded from the study.

Diffusion-Tensor Imaging Data Processing and Tract-Based Spatial Statistics

Three sets of diffusion-weighted images were initially registered to the first reference image (*b*=0) in the first dataset

using the automatic image registration toolkit in DTI Studio, version 2.40.^b Affine transformations and the trilinear interpolation method were used. Data were then visually inspected,^b and if necessary, poor quality slices and gradient orientations were discarded to prevent biased and inaccurate estimates of FA. A mean set of DTI images was generated from the 3 DTI datasets and was then brain-extracted using a brain extraction tool,⁴¹ and FA maps were generated using the FMRIB diffusion toolbox,⁴⁵ both of which are part of the FMRIB software library suite (www.fmrib.ox.ac.uk/fsl).⁴²

Voxel-wise analysis of FA data was completed using TBSS, version 1.1 in FSL, version 4.0.^b TBSS is described in detail elsewhere.⁴³ TBSS conducted 3 between-group analyses and tested whether FA was reduced across the whole brain in SCI with TBI compared with SCI only, SCI with TBI compared with healthy controls, and SCI only compared with healthy controls. An omnibus F test was used for this purpose. In brief, TBSS analyses involved a 4-step procedure, whereby all subjects' FA images were nonlinearly aligned⁴⁶ to the 1×1×1mm MNI152 standard-space template in FSL. The mean of all aligned FA images was then created and thinned to produce a mean FA skeleton, which represents the tract centers common to the 3 groups of subjects. The skeleton was then thresholded to FA 0.20 or higher to include major WM tracts but to exclude WM tracts with great intersubject variability. Each subject's

aligned FA image was then projected onto the skeleton, and voxel-wise statistics across subjects were carried out on the skeleton-space FA data.

Group comparison of FA was performed using nonparametric inferential statistics (Monte-Carlo permutations) with threshold-free cluster enhancement.⁴⁷ Threshold-free cluster enhancement is an improvement over existing cluster-level inference methods, which required the user to specify an arbitrary cluster-forming threshold. The threshold-free cluster enhancement approach enhances areas of signal without having to rely on threshold-based clustering.

Region of Interest Analysis

ROI analyses were carried out using the same FA maps already generated for each subject from TBSS. Our study focused on ROIs in the following WM tracts: ALIC, PLIC, forceps minor, gCC, and sCC. ROIs of specific WM structures were taken from the ICBM-DTI-81 WM labels atlas included in FSL.⁴⁸ The atlas was originally created by hand-segmentation of a standard-space average of diffusion MRI tensor maps from 81 subjects (42 men, 39 women; mean age, 39y). All subjects' FA maps were nonlinearly warped onto the ICBM mean FA template using IRTK software available as part of the FMRIB software library package (www.fmrib.ox.ac.uk/fsl).^{43,b} The ROI masks were applied to each subject's FA map, and the average FA value in each ROI was computed. An example of the various ROI masks available in the ICBM-DTI-81 WM labels atlas is represented in figure 1.

Statistical Analysis

All data were analyzed using SPSS 16.0.^c Mean FA values for each group for each ROI were examined in a 1-way ANOVA. For those ANOVAs that showed statistical significance, 1-tailed, independent-samples *t* tests were implemented for comparison across groups. For each comparison, equality of variance was assessed using the Levene test. The threshold for statistical significance was set to *P* less than .05.

RESULTS

Region of Interest Analysis

One-way analysis of variance. The group mean FA value for each of the ROI is presented in table 2. Of the 5 ROIs analyzed in this study, 4 illustrated significant differences on 1-way ANOVAs: the ALIC ($F_{2,31}=4.537$; $P<.05$), forceps minor ($F_{2,31}=3.784$; $P<.05$), gCC ($F_{2,31}=3.494$; $P<.05$), and sCC ($F_{2,31}=5.186$; $P<.05$). Thus, planned comparisons were performed for these ROIs.

In the PLIC, results of the 1-way ANOVA were not significant ($F_{2,31}=0.664$; $P=.522$). Therefore, planned comparisons were not carried out.

Planned comparisons. As predicted, FA values were decreased in the predilection sites for DAI in the SCI with TBI

Table 2: Mean FA in Each ROI for All Groups

ROIs	Control	SCI Only	SCI With TBI
ALIC (bilateral)	0.495±0.124	0.508±0.133	0.474±0.133
PLIC (bilateral)	0.646±0.081	0.655±0.079	0.646±0.085
Forceps minor (bilateral)	0.447±0.108	0.446±0.108	0.400±0.106
gCC	0.582±0.139	0.580±0.148	0.540±0.147
sCC	0.636±0.168	0.634±0.170	0.593±0.171

NOTE: Means ± SDs of FA are presented for each region. The SCI-only group includes patients with SCI and no evidence of TBI based on structural MRI and collateral neurologic findings. The SCI with TBI group includes patients with SCI and definitive structural MRI evidence of TBI. ROIs in the ALIC and PLIC capsule and forceps minor combine bilateral structures.

group: for the forceps minor ROI, FA values were significantly decreased in the SCI with TBI group compared with the control group ($t_{17}=2.158$; $P<.05$) and compared with the SCI-only group ($t_{20}=2.344$; $P<.05$). FA values for the gCC were reduced in the SCI with TBI group in comparison to the healthy controls ($t_{17}=2.185$; $P<.05$) and to the SCI-only group ($t_{20}=2.334$; $P<.05$). In the sCC, too, there was a reduction in FA values in the SCI with TBI group relative to the control group ($t_{7,439}=2.192$; $P<.05$) and relative to the SCI-only group ($t_{7,499}=2.037$; $P<.05$; equal variance not assumed because of significant Levene test). There were no significant differences or differences approaching significance between the healthy controls and the SCI-only group for any of these ROIs.

Our prediction of reduced FA in the internal capsule in the patient groups was not supported. In fact, the SCI-only group showed significantly higher FA values than the SCI with TBI group ($t_{20}=2.653$; $P<.01$), suggesting that the ALIC is more vulnerable to DAI than to loss of afferent projections. The SCI-only group showed a higher mean than that of controls, a difference that did not reach statistical significance ($t_{25}=-1.673$; $P=.054$).

Tract-Based Spatial Statistics

TBSS did not reveal any cross-subject FA differences even at a liberal *P* value set to .01 uncorrected for multiple voxel comparisons.

DISCUSSION

Using DTI, we attempted to detect changes in brain WM microstructures associated with SCI using 3 groups of subjects: SCI patients with no evidence of TBI on structural MRI and neurologic examination (SCI only), SCI patients with MRI-proven brain injury (SCI with TBI), and healthy controls. We found that compared with both controls and patients with SCI only, patients with SCI with TBI had multiple WM regions with reduced FA, including the forceps minor, sCC, and gCC.

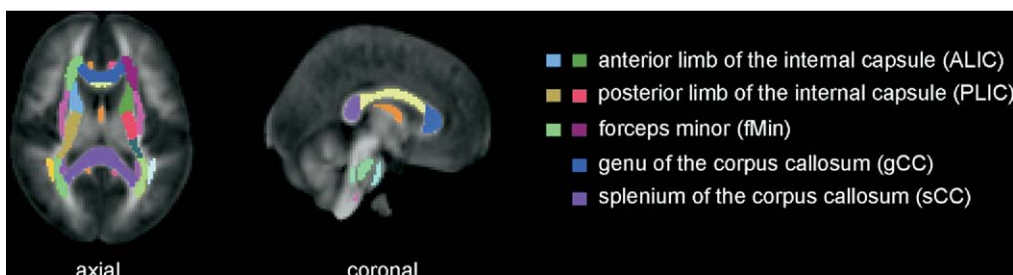


Fig 1. Various ROI masks available in ICBM-DTI-81 WM labels atlas.⁴⁸ We applied the following ROIs to each subject's FA map to derive regional mean FA values: ALIC, PLIC, forceps minor, gCC, and sCC.

In addition, patients with SCI with TBI had reduced FA in the ALIC compared with the SCI-only group, while no between-group differences were found in the PLIC. No significant regional FA differences were found between the SCI-only group and healthy controls.

In patients with SCI who have had concomitant brain injury and structural abnormalities on MRI, we expected to find FA reductions in WM tracts prone to DAI. Predilection sites of traumatic axonal injury include subcortical WM, corpus callosum, internal capsule, and infratentorial WM.¹⁷⁻²⁰ Previous studies have shown that even mild TBI could lead to significant FA reductions in the subcortical WM, including the corpus callosum, minor, and major forceps.^{29,33} In our study, patients with SCI with TBI were found to have decreased FA in the gCC, sCC, and forceps minor in the subacute period after the original trauma. However, TBI was not associated with any FA changes in the internal capsule in patients with SCI with TBI compared with controls. This is likely because abnormalities in the internal capsule are markers of more severe TBI, whereas our patients with SCI underwent different severities of brain trauma. Our results confirmed that DTI is a sensitive tool to detect microstructural WM damage associated with DAI in patients with SCI who have had concomitant brain injury. FA changes in the corpus callosum and forceps minor are sensitive markers for TBI in cross-subject comparisons; however, normative data need to be established before FA value can be used to diagnose TBI on an individual basis.

Our study did not find any WM FA changes attributable to SCI alone. SCI may cause disruption of the ascending sensory tracts to the brain. One may expect that the loss of afferent connections might lead to axonal degeneration in the higher-order neurons and thus result in reduced FA in cerebral WM tracts that conduct the sensory pathways. Major sensory afferents including the dorsal column-medial meniscus and spinothalamic pathways project to the ventral posterolateral nucleus of the thalamus, from which the thalamocortical afferents travel to the primary somatosensory cortex via the posterior limb of the internal capsule.⁴⁹ A previous study showed that patients with cervical SCI had reduced gray matter volume bilaterally in the primary somatosensory cortex.⁵⁰ However, our study did not demonstrate any between-group FA differences in the PLIC. In the ALIC, neither the SCI-only group nor the SCI with TBI group had decreased FA compared with healthy controls. In fact, the SCI-only group showed increased FA in the ALIC compared with healthy controls (trend only); this difference reached significance compared with the SCI with TBI group. This finding cannot be reasonably explained and needs to be explored in future studies. The absence of SCI-related WM changes in the chosen WM tracts as shown by our study have many causes. First, changes in cerebral WM as a result of spinal afferent denervation may develop in the chronic postinjury period, while our study included patients in the subacute period after SCI (mean time between injury and brain MRI was 93.5d). One mechanism for the cerebral WM changes in SCI is transsynaptic degeneration, a process of neuronal atrophy caused the lack of synaptic input from afferent fibers.⁵¹ Second, we placed our ROIs in the anterior and posterior limbs of the internal capsule, which contain both ascending and descending neuronal tracts. As a result, we were unable to compare FA values selectively in the ascending WM tracts, such as the thalamocortical afferents, which we expected would be most affected by SCI. Future studies should investigate cerebral WM changes in patients with chronic SCI as well as elucidate WM FA changes in afferent-specific ROIs in the internal capsule and near the sensory cortex. We should also

correlate changes in cerebral WM organization with neurologic and function outcome in patients with SCI.

We adopted TBSS as well as the ROI technique to assess between-group FA differences. TBSS is an automated technique that allows voxel-wise statistical testing of FA and has been successfully used to assess changes in neuronal WM integrity associated with various pathologic processes, including Alzheimer disease, epilepsy, and schizophrenia.⁵²⁻⁵⁴ In our study, TBSS did not find any between-group FA differences, which we detected using the ROI technique. One explanation for the negative results in TBSS is that we did not include enough subjects to achieve sufficient power for TBSS analysis, especially in the SCI with TBI group ($n=7$). In addition, the discrepancy between TBSS and ROI results may be explained by the methodology employed in TBSS, which involves creating an FA skeleton by thinning the mean of all FA images and carrying out voxel-wise statistics across subjects on the skeleton-space FA data.⁴³ As a result, this technique only considers tracts in the center of WM fiber bundles. However, it is known that 1 major mechanism of DAI is a deceleration-acceleration impact that generates enough rotational force to cause axonal shearing.⁵⁵ Maximum shearing force occurs in areas with the greatest tissue density difference—that is, at the gray-WM junction. Thus, fiber tracts in the periphery of WM tracts are more likely to be damaged in a closed-head injury and exhibit DAI-related reductions in FA. Using ROIs that incorporated both the inner and outer WM fiber tracts, we were able to detect changes in WM integrity associated with DAI in patients with SCI. These findings support the use of an ROI approach for discriminating patients with SCI with and without concomitant TBI. The current findings do not support the use of TBSS for this purpose. However, the limited power in this study may have contributed to the null findings. Further studies employing TBSS are needed to confirm our results.

Study Limitations

We present the first study that attempts to characterize and differentiate microstructural WM changes related to either brain injury or traumatic SCI in patients with SCI. We selected ROIs in WM tracts, which would best allow us to differentiate the 3 study groups. As a result, the number of ROIs included in this study was limited. Future studies can achieve a broader search for cerebral WM changes in patients with SCI by incorporating more ROIs or by using an alternative automated voxel-based technique. Another limitation of our study is that we combined bilateral brain structures into 1 ROI in the cross-subject comparisons (eg, forceps minor, ALIC, PLIC). It is possible that both TBI and SCI may cause unilateral changes in cerebral axonal organization. Finally, the sample size in the SCI with TBI group is relatively small ($n=7$). While we are presenting the preliminary data, we hope to continue to expand our data series and improve the power of the statistical analyses.

CONCLUSIONS

The present study showed that patients with SCI and concomitant brain injury had reduced FA in the corpus callosum and minor forceps, which are susceptible areas to diffuse axonal injury. SCI was not found to be associated with any changes in cerebral axonal organization. Therefore, DTI shows promise as a sensitive tool for the detection of TBI-related WM damage in patients with SCI who have had concomitant TBI. Future research that provides normative FA values in healthy control subjects would improve the use of DTI for the diagnosis of TBI in individual patients.

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