

# 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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**A**FTER 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.<sup>1-21</sup>

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

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,<sup>10</sup> 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

## 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

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

Variables	Main Findings							
	Positive Findings				Negative/Weak Findings			
	Demographic	Study	Design		Cognitive Tests*	Study	Design	
Pro/Ret			Size	Pro/Ret			Size	
Education	Kesler et al <sup>17</sup>	Pro	S	Battery	Chu et al <sup>10†</sup>	Ret		RAVLT
	Niemeier et al <sup>12</sup>	Ret	L	WCST	Lannoo et al <sup>5</sup>	Pro	L	Battery
	Novack et al <sup>13</sup>	Pro	L	Battery	Millis et al <sup>8</sup>	Ret	M	Battery
	Ruff et al <sup>9</sup>	Ret	S	Battery			L	
	Sherer et al <sup>16</sup>	Pro	M	Battery				
Age	Chu et al <sup>10†</sup>	Ret	L	RAVLT	Chu et al <sup>10†</sup>	Ret	L	RAVLT
	Millis et al <sup>8</sup>	Ret	L	Battery	Lannoo et al <sup>5</sup>	Pro	M	Battery
	Novack et al <sup>13</sup>	Pro	L	Battery	Lezak et al <sup>18†</sup>	Pro	S	RAVLT; DS
	Sherer et al <sup>16</sup>	Pro	M	Battery	Ruff et al <sup>9</sup>	Ret	S	Battery
	Zwaagstra et al <sup>21†</sup>	Ret	S	SOP				
Premorbid IQ					Kesler et al <sup>17</sup>	Pro	S	Battery
Injury-Related	Positive Findings				Negative/Weak Findings			
Duration of PTA	Chu et al <sup>10†</sup>	Ret	L	RAVLT	Chu et al <sup>10†</sup>	Ret	L	RAVLT
	Hellawell et al <sup>4†</sup>	Pro	M	Battery	Formisano et al <sup>19</sup>	Pro	S	Battery
	Lannoo et al <sup>5</sup>	Pro	M	Batter	Millis et al <sup>8</sup>	Ret	L	Battery
	Levin et al <sup>11</sup>	N/A	N/A	Memory	Novack et al <sup>13</sup>	Pro	L	Battery
	Mandelberg <sup>20</sup>	Pro	L	WAIS-VIQ/PIQ				
Length of coma	Dikmen et al <sup>1</sup>	Pro	M	Battery	Ruff et al <sup>9</sup>	Ret	S	Battery
	Lannoo et al <sup>5</sup>	Pro	M	Battery	Formisano et al <sup>19</sup>	Pro	S	Battery
	Levin et al <sup>7</sup>	Pro	S	Battery	Lannoo et al <sup>5</sup>	Pro	M	Battery
	Lezak et al <sup>18†</sup>	Pro	S	RAVLT; DS				
	Niemeier et al <sup>12</sup>	Ret	L	WCST				
	Ross et al <sup>14</sup>	Pro	L	Battery				
	Wong et al <sup>15</sup>	Ret	L	WAIS R-PIQ/VIQ				
GCS	Dikmen et al <sup>1</sup>	Pro	M	Battery	Lannoo et al <sup>5</sup>	Pro	M	Battery
	Levin et al <sup>6</sup>	Pro	L	Battery	Novack et al <sup>13</sup>	Pro	L	Battery
					Ruff et al <sup>9</sup>	Ret	S	Battery
Acute Care LOS					Novack et al <sup>13</sup>	Pro	L	Battery
					Formisano et al <sup>19</sup>	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 al<sup>10</sup> 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.<sup>22</sup>

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.<sup>17,23,24</sup> 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.<sup>17,25</sup>

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,<sup>19</sup> 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,<sup>26-28</sup> 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<sup>29,30</sup>) 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.<sup>31</sup>

Only a handful of cognitive recovery studies in TBI have examined recovery trajectories, and of these, few have used mixed-effects models.<sup>10,15,21,32</sup> Still fewer have examined directly the influence of reserve capacity-related variables on recovery. Chu et al<sup>10</sup> examined the impact of age on memory recovery from 1 to 5 years postinjury, using the total learning score of the RAVLT.<sup>33</sup> 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 Chu<sup>10</sup> study was that, looking over a long period, Chu<sup>10</sup> 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 al<sup>15</sup>). Zwaagstra et al<sup>21</sup> 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),<sup>31</sup> 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.<sup>33</sup> 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,<sup>29,34-41</sup> and

its recovery the most protracted.<sup>21,30,42</sup> 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 ( $\geq 17$ 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 Test<sup>43</sup>; (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)<sup>44</sup> 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).<sup>45</sup>
2. Complex speed of processing. This domain included the following: TMT-B minus TMT-A<sup>33</sup> (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)<sup>46</sup> 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—Oral<sup>47</sup> (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)<sup>48</sup>; and the Wechsler Adult Intelligence Scale, verbal abstraction test (a test requiring identification of common threads between pairs of words).<sup>49,50</sup>

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).<sup>48</sup>
5. Organized and unorganized verbal and visuospatial learning and memory. This last domain included the RAVLT<sup>33</sup> (a test of recall and recognition of an unorganized list of 15 words); the Rey Visual Design Learning Test<sup>33</sup> (a visuospatial analog to RAVLT); and the Wechsler Memory Scale—III, logical memory<sup>48</sup> (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 WTAR<sup>51</sup> or the NAART.<sup>52</sup> (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.<sup>53</sup>)

**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 al<sup>33</sup> 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 to 0 if  $T_{it}$  and equals  $T_{it} - 5$  if  $T_{it} \geq 5$ . The error term,  $\varepsilon_{it}$ , which is assumed to have a normative distribution with mean 0 and unknown variance  $\sigma^2_{\varepsilon}$ , 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  $\beta_{0i}$ ,  $\beta_{1i}$ , and  $\beta_{2i}$ :  $\beta_{0i}$  is the intercept at time  $T=0$ ,  $\beta_{1i}$  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  $\beta_{2i}$  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  $\beta_{0i}$ ,  $\beta_{1i}$ , and  $\beta_{2i}$  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,  $\delta_{0i}$ ,  $\delta_{1i}$  and  $\delta_{2i}$  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  $\delta_{1i}$  or  $\delta_{2i}$  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  $\gamma_{g0}$  are the mean population values of the corresponding  $\beta_{g0}$  for a subject whose age equals the sample average, and  $\gamma_{g1}$  is the expected difference in  $\beta_{g0}$  associated with a difference of 1 SD of age. If  $\gamma_{11}$  and  $\gamma_{12}$  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.

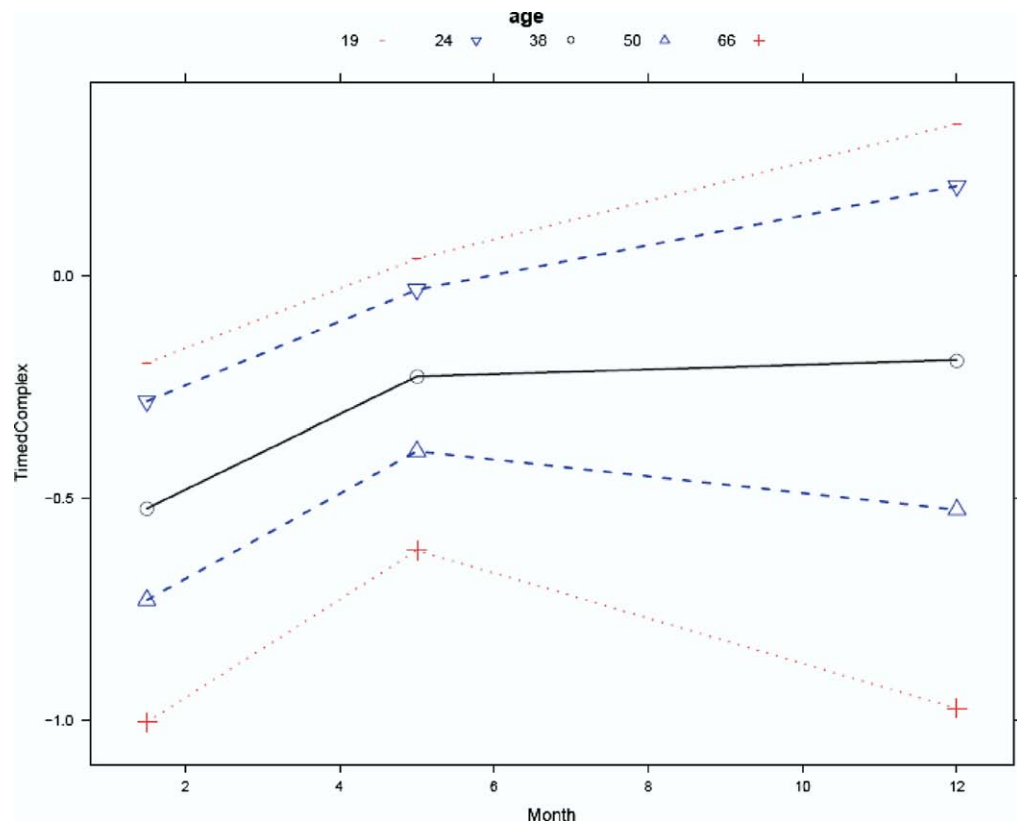
In short, mixed-effects models allow us to examine the impact of potential moderators on recovery trajectories as well as on the level of impairment (in this case, at 2 and 12mo postinjury). The purpose of these analyses is to identify which variables affect the shape of recovery trajectories. The mixed-effects 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.<sup>54</sup> 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 ( $t_{61}=-4.567, P<.001$ ).

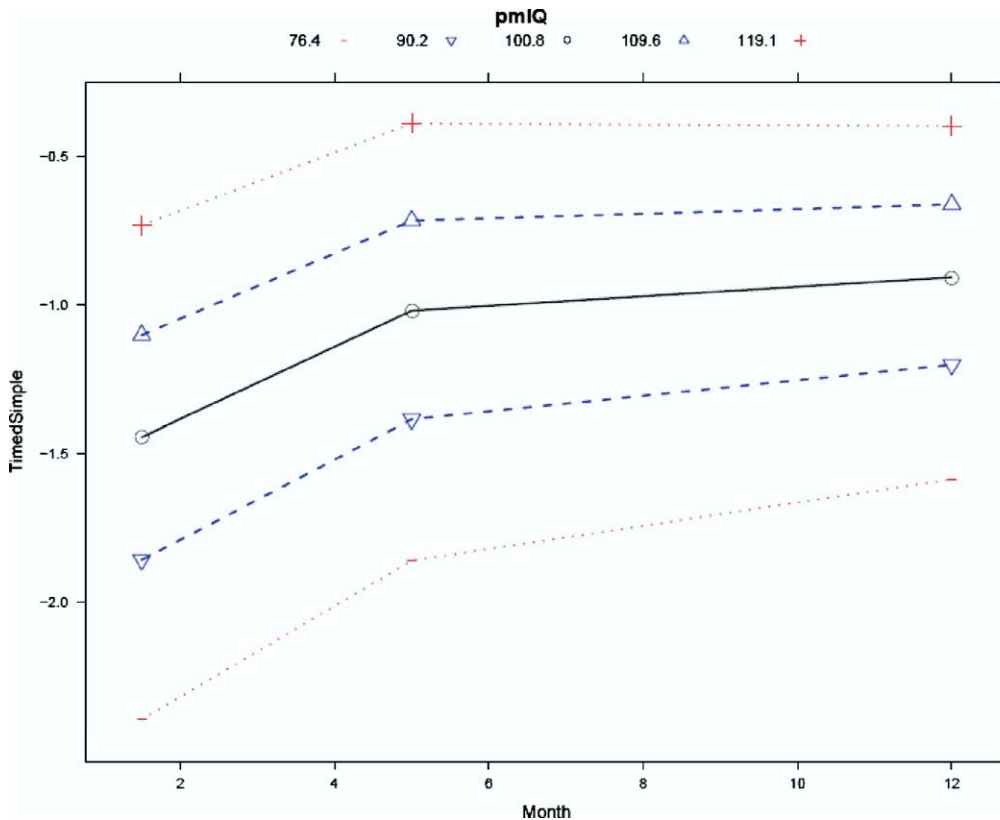
**Premorbid IQ, simple speed of processing tests.** Premorbid IQ showed a significant overall effect for simple speed of processing tests ( $F_{3,63}=11.27; P<.001$ ). It did not significantly impact recovery trajectories of the simple speed of processing tests; however, as can be seen in the parallel 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,<sup>10</sup> who, like us, found no moderating effects of age on memory recovery trajectories (1–5y postinjury), and Zwaagstra et al,<sup>21</sup> 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,<sup>10</sup> 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 al<sup>21</sup>) 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,<sup>17,25</sup> 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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