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Neuropsychological Recovery Trajectories in Moderate to Severe Traumatic Brain Injury: Influence of Patient Characteristics and Diffuse Axonal Injury – Erratum

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Abstract

Objectives—The goal of the present study was to elucidate the influence of demographic and neuropathological moderators on the longitudinal trajectory neuropsychological functions during the first year after moderate to severe traumatic brain injury (TBI). In addition to examining demographic moderators such as age and education, we included a measure of whole-brain diffuse axonal injury (DAI), and examined measures of processing speed (PS), executive function (EF), and verbal learning (VL) separately.

Methods—Forty-six adults with moderate to severe TBI were examined at 3, 6, and 12 months post-injury. Participants underwent neuropsychological evaluation and neuroimaging including diffusion tensor imaging. Using linear mixed effects modeling, we examined longitudinal trajectories and moderating factors of cognitive outcomes separately for three domains: PS, VL, and EF.

Results—VL and EF showed linear improvements, whereas PS exhibited a curvilinear trend characterized by initial improvements that plateaued or declined, depending on age. Age moderated the recovery trajectories of EF and PS. Education and DAI did not influence trajectory but were related to initial level of functioning for PS and EF in the case of DAI, and all three cognitive domains in the case of education.

Conclusions—We found disparate recovery trajectories across cognitive domains. Younger age was associated with more favorable recovery of EF and PS. These findings have both clinical and theoretical implications. Future research with a larger sample followed over a longer time period is needed to further elucidate the factors that may influence cognitive change over the acute to chronic period after TBI.

Keywords

Brain injury; Neuropsychological tests; Cognition; Executive function; Verbal learning; Diffusion tensor imaging

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Introduction

Cognitive deficits are prevalent following moderate to severe traumatic brain injury (TBI), and interfere with work, relationships, leisure, and activities of daily living. There is great heterogeneity among patients with regard to the extent and rate of cognitive recovery. Although many patients experience significant cognitive improvements over the first 2 years after injury (Schretlen & Shapiro, 2003), as many as 65% of patients report long-term problems (Whiteneck et al., 2004). Injury severity and demographic variables appear to play a role in the recovery of cognitive function after TBI (Green et al., 2008; Hellawell, Taylor, & Pentland, 1999; Lannoo, Colardyn, Jannes, & De Soete, 2001; Novack, Bush, Meythaler, & Canupp, 2001; Sherer et al., 2006). For example, younger age (Himanen et al., 2006; Senathi-Raja, Ponsford, & Schönberger, 2010) and greater educational attainment (Dawson & Chipman, 1995; Hoofien, Vakil, Gilboa, Donovick, & Barak, 2002; Kesler, Adams, Blasey, & Bigler, 2003; Ponsford, Draper, & Schönberger, 2008; Wood & Rutterford, 2006) are associated with more favorable neuropsychological outcomes.

While most studies of cognitive recovery have been cross-sectional, there have also been investigations of the trajectory of recovery from the early phases to 1–2 years post-injury. Longitudinal studies of recovery after TBI in various important cognitive domains were summarized in a systematic review by Schultz and Tate (Schultz & Tate, 2013). These authors examined only studies ($n = 20$) that included three or more assessments within 2 years (the majority were completed within 1 year of injury). Memory (new learning) showed “some recovery” across studies but typically remained impaired at the last assessment. The trajectories of attention and executive function (EF) were difficult to synthesize owing to the great variability in the specific measures used. This points to the ongoing difficulty in defining these broad domains in terms of specific cognitive operations and to the need for common metrics so that different studies may be compared (Wilde et al., 2010).

Few studies have been conducted specifically to contrast recovery trajectories in different domains of cognitive function. In one such investigation, Christensen and colleagues (Christensen et al., 2008) tested 75 patients with moderate/ severe TBI at 2, 5, and 12 months post-injury, gauging average performance against normative data, with the stated purpose of comparing multiple cognitive functions. Recovery curves tended to be asymptotic with most improvement occurring between 2 and 5 months. Between 5 and 12 months, the slopes for memory, EF, and speed of processing did not differ significantly from zero. A subsequent study of the same sample examined the influence of moderators on cognitive recovery trajectories. Younger age was associated with more favorable recovery of both simple and complex processing speed (PS). In contrast, premorbid IQ influenced the ultimate level of function, but not the shape of change. These investigators did not find support for education as a moderator of recovery trajectory or overall level of function (Green et al., 2008).

Not surprisingly, cognitive recovery following TBI is also related to the extent of brain damage. Several studies have demonstrated relationships between cognitive performance and diffusion tensor imaging (DTI) metrics, which are thought to reflect changes in white matter integrity associated with diffuse axonal injury (DAI; Farbota et al., 2012; Håberg et

al., 2015; Kraus et al., 2007; Kumar et al., 2009; Newcombe et al., 2011; Spitz, Maller, O'Sullivan, & Ponsford, 2013; Yuh et al., 2014). The extent of DAI is a promising candidate for predicting the course and outcome of cognitive recovery, as this pathophysiology is nearly ubiquitous in moderate to severe TBI, and there is evidence that it may be particularly relevant to persistent cognitive deficits (Rabinowitz & Smith, 2016). However, the influence of DAI on the trajectory of cognitive recovery has yet to be examined.

Most DTI studies use a statistical approach that relies on aggregating data at the group level and comparing means from TBI and healthy control samples. This method may provide a somewhat limited characterization of white matter changes associated with TBI, due to the substantial heterogeneity in severity and distribution of white matter injury across individuals (Ponsford et al., 2014). In response to this limitation, voxel-wise methods for summarizing whole-brain, subject-specific DTI abnormalities have been developed (Lipton et al., 2012; Mayer, Bedrick, Ling, Toulouse, & Dodd, 2014; White et al., 2009). A particularly promising approach involves quantitative comparison of individual subjects' DTI data with a normative control sample, and using a Z-transformation of DTI scalar metrics based on the voxel-wise mean and standard deviation from the normative sample (Mayer et al., 2014).

The goal of the present study was to elucidate the influence of demographic and neuropathological moderators on the longitudinal trajectory of several different neuropsychological functions during the first year after moderate to severe TBI. We took into account the heterogeneity of TBI in two ways. First, we used mixed-effects models to examine longitudinal cognitive outcomes at 3, 6, and 12 months post-injury. Mixed-effects models have the advantage of accommodating individual variation in outcome trajectories, while also allowing examination of the influence of moderators on both the level of function and the shape of change over time. Second, in addition to examining demographic moderators such as age and education, we included a measure of whole-brain DAI. We examined measures of PS, EF, and verbal learning (VL) separately, to allow the detection of disparate patterns of recovery and different moderating factors across cognitive domains.

Methods

Participants

This study was approved by the Institutional Review Board of the home institution, and all participants provided informed consent either directly or by proxy of a legally authorized representative. Forty-six (46) adults with moderate to severe TBI were examined at 3, 6, and 12 months post injury. Participants were carefully selected to create a sample with predominately diffuse TBI. Inclusion criteria were: age between 18 and 64 years and diagnosis of non-penetrating moderate or severe TBI, indicated by at least one of the following: (1) Glasgow Coma Scale (GCS) score <13 in the emergency department (ED; not due to sedation, paralysis, or intoxication), (2) documented loss of consciousness (time to follow commands; TFC) for 12 hr or greater, (3) pro-spectively documented post-traumatic amnesia (PTA) of 24 hr or greater. PTA was measured by administering serial orientation tests, at most 72 hr apart, which is a standard manner of estimating PTA duration, as the

return of continuous memory is strongly correlated to the return of orientation to time, place, person, and circumstances.

Participants were excluded from the study for: (1) history of prior TBI, central nervous system disease, seizure disorder, schizophrenia, or bipolar disorder; (2) history of serious alcohol or psychostimulant (e.g., cocaine) abuse that could have had deleterious neurologic effects, as judged by a history of medical complications related to extensive substance use (e.g., cirrhosis or peripheral neuropathy in the context of heavy drinking) or social/vocational disability from the cognitive effects of long-term substance use; (3) pregnancy; (4) inability to complete MRI scanning due to ferromagnetic implants, claustrophobia, or restlessness; (5) non-fluency in English; (6) or a level of impairment that precluded the subject's ability to complete testing and scanning at 3 months post-TBI. To ensure that the TBI was predominantly diffuse, participants were also excluded if the total estimated volume of focal intraparenchymal lesions was greater 5 cm^3 for subcortical lesions and 50 cm^3 for cortical lesions. In addition, 38 healthy volunteers comparable to TBI subjects in age, gender, and years of education were recruited. Exclusion criteria for controls were the same as above, with the addition of exclusion for any history of TBI resulting in alteration or loss of consciousness.

DTI Acquisition and Processing

Participants underwent an MRI neuroimaging protocol performed on 3 Tesla MRI scanner (Siemens Trio). The protocol included two 30-direction DTI acquisitions with two b-values (b=0s/mm^2 and b=1000 s/mm^2). Seven b0 images were spaced throughout the acquisition. DTI was acquired at a resolution of 2.2 mm^3 with an 84-ms echo time, 6500-ms repetition time, and 90° flip angle. DTI pre-processing and FA maps were acquired according to procedures described previously (Ware et al., 2017). Briefly, DTI volumes were first visually inspected for artifacts, and the two DTI acquisitions were concatenated to improve signal-to-noise ratio. The image processing tools available in FMRIB Software Library were then used for eddy current correction and removal of non-brain tissue. Then each subjects' DTI data were registered to an unbiased population-specific DTI template, and ultimately co-registered to a standard-space DTI template using the free software program, DTI-TK. Co-registered DTI data were then resampled into the standard MNI coordinate system, and subject-specific voxel-wise maps of fractional anisotropy (FA) were derived.

Individual DTI analysis was performed using the DisCo-Z method, which has previously been described in detail (Mayer et al., 2014). Briefly, subject-specific FA maps in both the control and subject groups are initially Z-transformed using the voxel-wise mean and standard deviation of the control population. Z-thresholds for the control and subject populations are then corrected to maintain identical alpha between groups, thereby eliminating bias resulting from differing degrees of freedom and non-independence of control subject responses with respect to the reference mean and standard deviation (Mayer et al., 2014; Watts, Thomas, Filippi, Nickerson, & Freeman, 2014). The magnitude of threshold adjustment, which depends only on the size of the control population, renders the probability of obtaining voxel-wise extrema from DTI scalar maps equivalent in two otherwise identical groups (Mayer et al., 2014). To focus specifically on DAI, we only

considered the lower portion of this distribution (clusters of abnormally low FA). These scores are subsequently referred to as the DAI score.

Injury Variables

Injury variables were abstracted from medical records and included mechanism of injury and GCS score on presentation to the ED. TFC was determined by the first date that the individual was able to follow simple motor commands accurately at least two times consecutively in a 24-hr period. Duration PTA, a sensitive index of the severity of neurologic injury, was calculated as the number of days between the TBI and the first of two occasions within 72 hr that the participant was fully oriented. Full orientation was defined as a score above 25 on the Orientation Log (Jackson, Novack, & Dowler, 1998), or documentation of consistent orientation for 72 hr in the acute medical record (i.e., before rehabilitation admission).

Measures of Cognitive Outcome

Demographically adjusted test scores were used whenever available. To assess speed of mental processing, we used the Processing Speed Index from the Wechsler Adult Intelligence Scale IV (WAIS-IV; Wechsler, 2014) constructed from age-corrected scores of Digit Symbol and Symbol Search sub-tests. The Rey Auditory Verbal Learning Test (RAVLT; Lezak, 2004) was administered to evaluate VL. Forms 1, 2, and 3 were administered at visits 1, 2, and 3, respectively. The age- and gender-corrected t scores of the sum of recall scores over all five learning trials were used. Five psychometric tests were included in the battery to assess different aspects of EF.

As measures of working memory with a manipulation component, the Letter-Number Sequencing subtest and the Digits Backward section of the Digit Span subtest of the Wechsler Memory Scale IV (Wechsler, 2014) were included. The Controlled Oral Word Association (COWA; Benton, Hamsher, & Sivan, 1994) test for verbal fluency was administered to measure cognitive flexibility and initiation. Letters CFL were used for visits 1 & 3, and letters PRW were used for visit 2. We used the total number of correct responses, adjusted for age and education. The Trail Making Test-Parts A and B (Reitan & Wolfson, 1985) was administered, with the Part B T-score included as a measure of mental flexibility and divided attention. The scaled score for the Color Word section of the Color Word Interference Test (CWIT) from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) provided a measure of selective attention and inhibition of habitual responding.

Statistical Analysis

We examined longitudinal trajectories of post-TBI cognitive outcomes for three cognitive domains: PS, VL, and EF. To create domain scores, all cognitive test scores were transformed to T-score units based on normative data, when available [for the WAIS-IV PSI, RAVLT trials I–V, TMT-B, D-KEFS CWIT- Color Word, WAIS IV Digit Span Backward (DSB), WAIS IV Letter Number Sequencing (LNS)]. T-scores were created using the mean and standard deviation from the control group for the COWA. The PS domain was operationalized as the T-score-transformed WAIS-IV PSI. The VL domain was

operationalized as the T-score for RAVLT immediate recall trials I–V. The EF composite was calculated as the average of the following T-score transformed scores: TMT-B, D-KEFS CWIT, COWA, DSB, and LNS.

Using the lme4 package in R, we constructed mixed-effects models to examine longitudinal patterns of cognitive performance over the first year post-TBI. Separate models were constructed for each of the three cognitive domains described above, to allow for the possibility that cognitive recovery may differ by domain (e.g., Christensen et al., 2008).

Data collection intervals were targeted for 3 months, 6 months, and 12 months post-injury, with an allowable window of 2 weeks on either side. For each model, time was modeled as subjects' precise time of data collection relative to the date of injury. Hence, the time-intervals were subject-specific, rather than uniform. Time was centered at the initial assessment (3 months post-injury) to facilitate interpretation of the between-subject variation in intercept (Fitzmaurice, Laird, & Ware, 2012, p. 197).

Models were constructed as follows. First, a random intercept model of cognitive performance over time (Model 1) was fit by maximum likelihood. Next, random slope was added and a new model (Model 2) was fit by maximum likelihood. Models 1 & 2 were compared using a likelihood ratio χ^2 test. Model 2 was selected as the base model if addition of the random slope accounted for significantly more variance in cognitive outcome, if not, Model 1 was retained as the base model. A quadratic time term ($time^2$) was added to the base model, and fit by maximum likelihood (Model 3). Model 3 and the model retained in the prior step (either Model 1 or 2) were compared using a likelihood ratio χ^2 test. Model 3 was selected if quadratic time accounted for significantly more variance in cognitive outcome, if not, the reduced model (either Model 1 or 2) was retained. A full model was then constructed by adding covariates to the model selected in the prior step—age, education, and DAI, in addition to interactions between time and each of those covariates (Model Full)—and fit using restricted maximum likelihood. An alpha of 0.05 was set as the threshold for significance. The Akaike information criterion (AIC), a measure of the relative quality of statistical models (Hurvich & Tsai, 1989), was also consulted as a test of model fit. Lower AIC values indicate better fit.

Results

Demographic and clinical characteristics are detailed in Table 1. There were no significant differences between patients and controls on any demographic variables. Sixteen GCS values were missing, primarily due to sedation/intubation in the ED. TFC data were missing for one participant. Neuropsychological test results are detailed in Table 2. At 3 months post-TBI, patients exhibited significantly poorer performance than controls on six of the eight test indices; two of these indices were impaired relative to controls at 6 months post-injury, and by 12 months post-injury, no differences between groups were significant at the $\alpha = 0.05$ level.

Ps

PS Model 1 demonstrated marked individual variation about the intercept and exhibited an AIC of 784.0. Random slope was added to the model (PS Model 2), and the correlation between random intercept and random slope was estimated as 0.31. PS Model 2 exhibited an AIC of 784.5. A likelihood ratio test revealed that PS Model 2 did not account for significantly more variance in outcome than PS Model 1 ($\chi^2 = 3.535$; $p = .171$). PS Model 3 included random intercept and fixed effects representing linear and quadratic time. This Model had an AIC value of 781.93 and accounted for more variance in outcome than PS Model 1 ($\chi^2 = 4.086$; $p = .043$). PS Model 3 was then used as the base model, to which we added the following covariates: age, education, and DAI, as well as interactions between each of those covariates and time.

The final model, displayed in Table 3, showed significant fixed effects of quadratic time, suggesting that performance improved and then plateaued; education, suggesting that higher levels of education were related to better performance; DAI, suggesting that more extensive white matter injury was related to poorer performance; and the time by age interaction. A graphical representation of the time by age interaction is depicted in Figure 1. It shows that older participants exhibited a pattern of improvement and then worsening over time, whereas younger participants showed a pattern of steep improvement, which plateaued over the course of the examination period.

Ef

EF Model 1 demonstrated marked individual variation about the intercept and had an AIC value of 709.6. Next, random slope was added to the model (EF Model 2), and the correlation between random intercept and random slope was estimated as 1.0, suggesting overparameterization of the model (Baayen, Davidson, & Bates, 2008). EF Model 2 exhibited an AIC value of 713.6, and did not account for significantly more variance in outcome than EF Model 1 ($\chi^2 = 0.011$; $p = .994$); hence, the random slope term was not included in subsequent models. EF Model 3 included random intercept and fixed effects representing linear and quadratic time. This Model had an AIC value of 711.5, and did not account for more variance in outcome than the reduced model. Hence, EF Model 1 was used as the base model, to which we added the covariates: age, education, and DAI, as well as interactions between each covariate and time.

The final model (see Table 3) showed significant fixed effects of linear time, such that performance improved over time; education, such that more years of education were associated with better performance; DAI, such that more extensive white matter injury was related to poorer performance; and a significant age by time interaction. The plot of the age by time interaction is depicted in Figure 1, and suggests that that younger participants had a steeper trajectory of improvement than older participants.[1]

[1]As a post-hoc exploratory analysis, we examined separate models for timed versus untimed tests of EF to ascertain whether speeded EF exhibited a similar longitudinal trajectory to that observed for PS (i.e. curvilinear). The final model for untimed EF (DSB and LNS), included random intercept but no random slope, with significant effects of education (t = 2.44, $p < .05$) and DAI (t =–3.49, $p < .005$). The final model for timed EF (CWIT, COWA, TMT-B) included random intercept but no random slope, with significant effects of linear time (t = 2.24, $p < .05$) and education (t = 2.01, $p < .05$). Neither model exhibited a significant effect of quadratic time, as was observed for PS.

VI

VL Model 1 demonstrated marked individual variation about the intercept and an AIC value of 820.4. Next, random slope was added to the model (VL Model 2), and the correlation between random intercept and random slope was estimated as 1.0, again, suggesting model overparameterization. VL Model 2 had an AIC value of 824.3, and it was not superior to VL Model 1 according to the likelihood ratio test ($\chi^2 = 0.113$; $p = .945$). The random slope term was not included in subsequent models. VL Model 3, including the quadratic effect of time, had an AIC value of 822.3, and was not superior to VL Model 1 per the likelihood ratio test ($\chi^2 = 0.048$; $p = .826$). Hence, VL Model 1 was used as the base model, and we added age, education, DAI, and their interactions with linear time to the full model. As shown in Table 3, the final model showed significant fixed effects of linear time, suggesting that memory performance improved over time; and education, suggesting that more years of education were associated with better memory performance. Neither age nor DAI were significant predictors of memory performance. There were no significant interactions between any of the covariates and time.

Discussion

The goal of this study was to characterize potentially disparate patterns of change and influences of moderating factors (age, education, and DAI) on longitudinal cognitive outcomes after moderate to severe TBI. We examined cognitive outcomes at 3, 6, and 12 months post-injury across three domains: PS, EF, and VL. All three cognitive domains showed significant change over time, consistent with recovery of function over the first year after moderate to severe TBI. This finding comports with previous studies in this population (Schretlen & Shapiro, 2003; Schultz & Tate, 2013).

However, we also found evidence for different trajectories in the three cognitive domains included in this study. VL and EF showed linear improvements, whereas PS exhibited a curvilinear trend characterized by initial improvements that plateaued or declined, depending on age, during the examination period. The asymptotic effects of time on PS could reflect either natural recovery patterns or ceiling effects of the instruments used to measure cognition. The first explanation is more likely than the second, given that none of instruments used in the present study have appreciable ceiling effects for patients with moderate to severe TBI.

For each of the three cognitive domains, education had a significant effect on participants' initial level of functioning, but not recovery trajectory. This finding contrasts with the results of one prior study that found education did not influence initial level of cognitive function after TBI (Green et al., 2008), but is consistent with other work demonstrating that greater educational attainment is associated with better functioning after TBI (Dawson & Chipman, 1995; Hoofien et al., 2002; Kesler et al., 2003; Ponsford et al., 2008; Wood & Rutterford, 2006). Of note, the study by Green et al. (2008) also included pre-morbid IQ, which was a significant predictor of post-TBI level of cognitive function. Pre-morbid IQ and educational attainment tend to be highly correlated, and may account for overlapping variance in cognitive performance. Furthermore, Green and colleagues used a different analytic approach, by which they removed covariates that failed to reach significance or survive

multiple comparisons from their final models. Hence, the different covariates and analytic approach in the present study may account for our disparate findings with regards to education.

Education is considered a marker of cognitive reserve capacity (Kesler et al., 2003; Stern, 2002). Stern (2002) has posited that both active and passive models of reserve may account for the heterogeneity in clinical presentation that is unrelated to neuropathological burden. A passive reserve model suggests that each individual possesses a threshold of reserve and clinical deficits manifest once the magnitude of disease or injury exceeds that threshold. Alternatively, an active reserve model suggests that the brain attempts to compensate for damage by mobilizing alternative mechanisms and brain systems (Stern, 2002). Effects of pre-injury markers of brain function, such as education and premorbid IQ, on initial level of post-injury functioning are consistent with a passive model of reserve, whereas effects on recovery *trajectory* are consistent with an active model of reserve.

The present findings are more in line with a buffering effect of education on post-injury function, suggesting that a passive reserve model may apply. However, the effects of education on post-injury cognitive performance cannot be disentangled from pre-injury effects of education on cognition in the present study. That is, the present findings cannot resolve whether education did in fact buffer the deleterious effects of brain injury, or whether higher educational attainment is simply a marker of higher baseline functioning, from which patients declined in similar measure.

The extent of DAI had robust effects on initial PS and executive functioning, but not VL. However, extent of DAI did not moderate the rate of cognitive recovery for any of the three cognitive domains examined. Although several prior studies have demonstrated a relationship between cognition and DTI measures of white-matter integrity (e.g., FA; Farbota et al., 2012; Håberg et al., 2015; Kraus et al., 2007; Kumar et al., 2009; Newcombe et al., 2011; Spitz et al., 2013; Yuh et al., 2014), to our knowledge this is the first study to evaluate the influence of white-matter integrity on *trajectory* of cognitive recovery after TBI. Our findings did not support a moderating effect of DAI on cognitive trajectory over the first post-injury year. However, it is possible that the present study was underpowered to detect subtler effects of DAI on cognitive trajectory.

Age did not have a significant effect on initial levels of VL, PS, or EF. This is most likely due to the fact that these scores were age-adjusted. However, age-adjustment does not preclude detecting a possible synergistic effect of age and brain injury on cognitive outcome that would result in poorer age-adjusted cognitive outcomes associated with older age, as observed by Green et al. (2008). Consistent with prior research, we found that age had a significant moderating effect on the trajectory of cognitive recovery for both executive functioning and PS (Green et al., 2008). In fact, as in the study by Green and colleagues (2008), age was the only significant moderator of cognitive trajectory among the covariates examined.

The present findings revealed that, in the domain of PS, younger individuals showed steep improvements followed by plateaued function over time, whereas older individuals exhibited

declines in PS after a period of initial improvement. Age also moderated the recovery trajectory of EF. Younger individuals in our sample recovered at a steeper rate as compared to older individuals. PS is among the cognitive domains that is most vulnerable to age-related cognitive decline (Salthouse, 2010). Our PS findings are consistent with results of a prior TBI study demonstrating poorer outcomes associated with older age and greater time post-injury (Senathi-Raja et al., 2010), as well as the conclusions of a systematic review suggesting that brain injury may exacerbate the deleterious cognitive effects of aging (Dikmen et al., 2009). It is not surprising to see a similar effect of age manifest in the domains of executive functioning and PS, as prior research suggests that these cognitive domains exhibit similar age-related changes (Salthouse, 2010).

The present findings have both clinical and theoretical implications. Age, education, and extent of white matter injury are non-modifiable and, thus, not amenable to post-injury intervention. However, this information provides richer detail regarding expected outcomes at different stages of recovery for an individual patient dependent on demographic and injury characteristics. Knowledge of the differential rates and trajectories of distinct cognitive outcomes might suggest sequences for targeting skills in rehabilitation. For example, our finding that PS improvements plateau by 1 year post-injury suggests that interventions to improve VL and EF, functions that can be limited by PS deficits, may be most helpful after recovery of PS has stabilized (i.e., by 1 year post-injury), whereas rehabilitation strategies that target improved speed of processing may augment recovery during the stage when natural improvements in PS are most pronounced (i.e., between 3 and 6 months). The finding of a plateau (at best) in PS highlights the need for interventions to help individuals with TBI to compensate for such deficits, as slowed processing is among the most important cognitive limitations for return to work and other complex activities (Ruff et al., 1993).

There are interesting theoretical implications of the present findings as well. For example, our results revealed associations between age and recovery trajectories for PS and EF. Of interest, this age-effect may not be due to age-related differences in white matter integrity, as associations between age and cognitive performance were significant despite controlling for whole-brain DAI. This suggests that other neurobiological mechanisms should be explored to explain the mechanisms by which older age may lead to poorer cognitive recovery after TBI. Cortical thickness, focal measures of white matter changes, or more complex models of network functioning may be promising in this regard.

Furthermore, we found that the whole-brain measure of DAI was associated with executive functioning and PS performance, but not verbal memory, suggesting that other pathological mechanisms may be more relevant to TBI-related VL deficits. Speeded processing and executive skills rely on large-scale networks distributed throughout the frontal and parietal cortex, whereas VL may be relatively more localized to medial temporal regions (Niogi et al., 2008). Hence, it is possible that more focal measures of neuropathology, such as hippocampal atrophy (Bigler et al., 1996; Palacios et al., 2013) and medial-temporal white matter integrity (Palacios et al., 2013) may be more relevant to VL.

There are limitations of this investigation that bear noting. The sample size of the current study precluded inclusion of additional covariates which may influence the trajectory of

cognitive recovery after TBI. Additionally, future studies with much larger samples would be needed to confirm the null findings reported here. The purpose of the present study was to characterize cognitive recovery trajectories within the first year post-TBI. However, our first assessment time point was at 3 months post-injury, both because of logistics related to hospitalization and because current cognitive measures suffer from floor effects early after injury. Thus, we may have missed curvilinear recovery in the earlier stages of recovery.

In addition, there is a growing appreciation that TBI is a chronic condition characterized by evolving disease processes that influence functioning for many years (Corrigan & Hammond, 2013). Hence, investigations that follow individuals beyond the first post-injury year are needed to fully appreciate trajectories of improvement and decline associated with TBI spanning the acute to chronic phase. It is possible that some participants in our TBI sample had suffered a milder TBI in the past. While no such injury resulted in persistent disability, we cannot rule out the possibility that an earlier mild injury might moderate the trajectory of recovery from the more recent and serious injury. In the present study, we measured cognition across three cognitive domains: PS, VL, and EF. These are three of the cognitive domains that have been shown to be most sensitive to TBI-related cognitive deficits (Lezak, Howieson, Bigler, & Tranel, 2012). However, other facets of cognition, such as language functioning and visuospatial reasoning, may also be relevant to cognitive changes after TBI.

Although alternate forms of tests were used when available, participants may have benefited from practice effects at 6 and 12 months post-injury; in which case, trends suggesting recovery may be overestimated and trends suggesting decline, underestimated. However, we note that many of the tests used in the current study are reasonably stable across repeated administrations in healthy individuals, with some tests (LNS and TMT-B) showing no evidence of a practice benefit (Beglinger et al., 2005). To create the domain scores, we standardized individual test scores based on the best available normative sample, published norms in most cases. This resulted in composites comprised of tests normed in different populations. Multiple normative samples introduce additional variance into standardized scores that is not attributable to the differences between the tests themselves, hence, composite scores contain more heterogeneity (error variance) than they would if norms were based on a single sample. We chose this approach, despite this limitation, because we considered it superior to the alternatives, conducting separate analyses for each individual test (which introduces the problem of multiple comparisons) or norming all tests based on our relatively small control sample.

Finally, this study is innovative in its use of a person-specific measure of whole-brain DAI burden; however, it is possible that focal white matter changes may be more relevant to specific cognitive domains (e.g., VL), and more complex measure of network function may be more relevant to active cognitive reserve processes that influence recovery trajectory.

Conclusion

Age moderated the recovery trajectories of EF and PS following TBI. Education did not influence cognitive recovery trajectory after TBI, but greater educational attainment was related to initial level of functioning for each of the three cognitive domains examined.

Similarly, whole-brain DAI burden did not influence the trajectory cognitive recovery, but did predict initial performance in the domains of PS and EF. These findings have both clinical and theoretical implications. Future research with a larger sample followed over a longer time period is needed to further elucidate the factors that may influence cognitive change over the acute to chronic period after TBI. Research incorporating complex measures of network functioning is particularly promising with regard to fully characterizing the influences of TBI-related neuropathology on dynamic cognitive outcomes following TBI.

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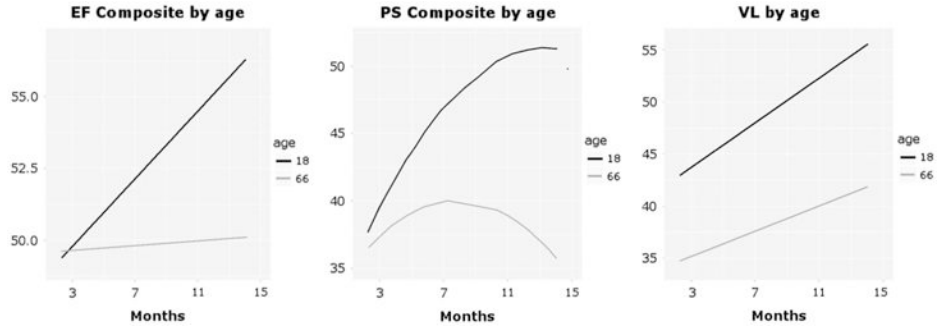

Fig. 1.

Cognitive change trajectories by age for each of the three cognitive domains. Cognitive domain scores are in T-score units. Time is depicted as time post-injury in onths. EF = executive function; PS = processing speed; VL = verbal learning.

Table 1
Demographic and clinical characteristics of the sample

	TBI (*N*=46)	Control (N= 38)	
	Mean (*SD*)	Mean (*SD*)	*p*-Value
Age[a]	35.2 (15.0)	34.51 (10.8)	.81
Education[a]	13.2 (2.4)	13.0 (2.8)	.72
Sex (% male)[b]	70%	72%	.99
Race (% Caucasian)[b]	53%	33%	.18
PTA	26.5 (21.2)	—	—
TFC	8.5 (12.1)	—	—
GCS	9.5 (4.2)	—	—
Mechanism of injury			
Vehicular	70%	—	—
Falls	20%	—	—
Intentional injury	10%	—	—

[a]Group comparison with independent sample t-test.

[b]Group comparison with Fisher's exact test.

PTA = duration of post-traumatic amnesia in days; TFC = time to follow commands in days; GCS =Glasgow Coma Scale; TBI =traumatic brain injury.

Table 2

Neuropsychological test performance

Measure	TBI 3 months *N*=46 Mean (*SD*)	TBI 6 months *N*=36 Mean (*SD*)	TBI 12 months *N*=36 Mean (*SD*)	Control *N*=38 Mean (*SD*)
RVLT—Raw Score	37.76 (12.79) ***	40.72 (13.24) *	47.25 (12.53)	47.28 (10.27)
PSI—Standard Score	81.91 (19.03) **	91.34 (20.31)	93.94 (21.87)	94.40 (20.82)
TMT Part B—T-Score	42.33 (15.30) **	46.47 (16.99)	49.75 (13.13)	51.08 (13.78)
DSB—Scaled Score	8.70 (2.42)	9.19 (2.92)	9.42 (3.30)	9.37 (2.53)
LNS—Scaled Score	8.04 (2.68)	8.47 (3.20)	8.75 (3.38)	8.59 (2.57)
COWA—Adjusted Score	22.61 (12.66) ***	33.61 (12.66) **	36.57 (11.97) †	41.19 (11.22)
CWIT Trial 3—Scaled Score	7.71 (4.29) *	8.11 (4.38) †	9.81 (3.58)	9.73 (3.86)
CWIT Trial 4—Scaled Score	6.98 (3.62) *	7.92 (4.67)	8.39 (4.38)	8.85 (3.29)

Significant differences between TBI patients and controls are indicated:

† $p<.1$,

* $p < .05$,

** $p<.01$,

*** $p < .005$

RVLT =Rey Auditory Verbal Learning Test- Trials 1-V. PSI = WAIS IV Processing Speed Index. TMT= Trail Making Test. DSB= WAIS IV Digit Span Backward. LNS=WAIS IV Letter Number Sequencing. COWA = Controlled Oral Word Association. CWIT= D-KEFS Color Word Interference Test; TBI =traumatic brain injury.

Table 3

Mixed effect model results for full models

	Processing speed			Executive functioning			Verbal learning		
Random	**Variance**	**(*SD*)**		**Variance**	**(*SD*)**		**Variance**	**(*SD*)**	
Intercept	87.470	9.352		47.685	6.905		91.470	9.564	
Months	—	—		—	—		—	—	
Fixed	Estimate	St. error	t-Value	Estimate	St. error	t-Value	Estimate	St. error	t-Value
Intercept	37.746	10.406	3.627	44.153	7.289	6.057	30.575	10.411	2.937
Months	0.697	0.685	1.018	1.402	0.528	2.654**	2.421	0.997	2.429*
Months^2	−0.113	0.043	−2.659**						
Age	−0.117	0.113	−1.036	−0.036	0.079	−0.460	−0.206	0.113	−1.828
Education	1.682	0.685	2.486*	1.189	0.474	2.506*	1.824	0.676	2.696**
DAI	−0.097	0.025	−3.961***	−0.059	0.017	−3.419***	−0.033	0.025	−1.348
Months:age	−0.025	0.007	−3.423***	−0.011	0.006	−1.982*	−0.010	0.011	−0.893
Months:Edu	0.081	0.043	1.885	−0.040	0.033	−1.207	−0.077	0.063	−1.232
Months:DAI	0.003	0.002	1.617	−0.001	0.001	−0.403	−0.001	0.002	−0.435

* $p < .05$,

** $p < .01$,

*** $p < .005$.

SD= standard deviation; DAI=diffuse axonal injury; Months:age=months by age interaction; Months:Edu=months by education interaction; Months: DAI= months by DAI interaction.