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# Influence of Demographic, Clinical, and Neuroimaging Variables on Neuropsychological Recovery Trajectories After Moderate-to-Severe Traumatic Brain Injury

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# INFLUENCE OF DEMOGRAPHIC, CLINICAL, AND NEUROIMAGING VARIABLES ON NEUROPSYCHOLOGICAL RECOVERY TRAJECTORIES AFTER MODERATE-TO-SEVERE TRAUMATIC BRAIN INJURY

by

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This manuscript has been read and accepted for the Graduate Faculty in Cognitive Neuroscience in satisfaction of the thesis requirement for the degree of Master of Science.

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# ABSTRACT

Influence of Demographic, Clinical, and Neuroimaging Variables on Neuropsychological Recovery Trajectories After Moderate-to-Severe Traumatic Brain Injury

by

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Traumatic brain injury (TBI) is prevalent in people of all ages and all walks of life. Cognitive deficits are common after TBI and the recovery patterns are known to be variable across individuals. The current study investigates diffuse axonal injury (DAI), cerebral blood flow (CBF), and focal lesions, in addition to post-traumatic amnesia (PTA), as possible predictors of cognitive trajectory in moderate-to-severe TBI patients. Cognitive trajectory was evaluated with a battery of neuropsychological tests that were combined into three domains: processing speed, verbal learning, and executive function. Patients (N=44) were tested three times at 3, 6, and 12 months post-injury. A linear mixed effects model was used for analyses to account for individual differences in longitudinal changes. Results displayed significant fixed effects of DAI, CBF, PTA, age, and education. However, age was the only moderator of neuropsychological recovery trajectory. Future studies would benefit from a larger sample size and including additional assessment time points including more acute phase and longer-term follow-up evaluations in later years post-injury.

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# 1. Introduction

## 1.1. Traumatic brain injury: Definition, prevalence, and severity measures

Traumatic brain injury (TBI) is a serious health issue that may cause disability or even death (Huang, 2013; Langlois et al., 2006). It can be defined as a change in the function of the brain or neuropathology as created by an outside factor (Menon et al., 2010). TBI affects people of all ages worldwide; most cases occur in people 75 years of age and older, while the second most common occurring in the age group of 0-4 years (Taylor et al., 2017). There is also a peak of incidents occurring in those aged 15 to 24, but overall occurring more frequently in males (Bruns & Hauser, 2003; Ponsford et al., 2013; Taylor et al., 2017). The causes of such an injury are vast. The most common cause of TBI in the older adult population is falls; however, this is also a common cause for those aged 0-4. Motor vehicle accidents are the most common for people in the 15-24 age group, but other common cases in general include: assaults, combat, or objects hitting the head (Taylor et al., 2017). With such an array of causes, the severity and pathology of the injury also varies.

TBI is classified as mild, moderate, and/or severe. The Glasgow Coma Scale (GCS) is a widely used behavioral scale that measures severity based on the score the individual receives (Lueckel et al., 2019; Ponsford et al., 2013). The score ranges from 3-15 with lower scores indicating a more severe injury. However, just because two different patients have the same GCS score, it does not mean that their ability to function is the same (Signoretti et al., 2010). Post traumatic amnesia (PTA) is another widely used measure of severity. PTA refers to the time after one reaches consciousness, but still remains confused and unable to form new memories, also known as anterograde amnesia (Ponsford et al., 2013). PTA and GCS are often used together and have both been suggested to help predict patient outcome (Ponsford et al., 2013).

### 1.2. Post-traumatic cognitive deficits and heterogeneity of recovery

There is a plethora of symptoms that can result from moderate-to-severe TBI and all vary from person to person; however, most patients will experience some form of cognitive, behavioral, or emotional change (Menon et al., 2010; Tiersky et al., 2005; Ponsford et al., 2013). Initial cognitive changes that may result from TBI include issues with attention and problems with information processing speed (Ponsford et al., 2013). Later, more severe consequences may be observed, such as Alzheimer's disease (Masel & DeWitt, 2010).

A study by Till et al. (2008) demonstrates that heterogeneity of recovery trajectory that can be seen on an individual basis but may be missed when studying group means. Till et al. (2008) researched the post-injury cognitive decline after TBI patients. The study used 12 different neuropsychological tests at 12 months post-injury, as a baseline, and then between 2 and 5 years after injury with 33 individuals who had sustained a moderate-to-severe TBI. Analyses looked at individual recovery rather than group means in order to better depict the heterogeneity of recovery. The group means did not display the post-cognitive decline that has previously been seen, but some of the individual scores did display this trend. Using a previously established method of determining what participants should be categorized as a "decliner," 9 out of the 33 were categorized as such. Decline was seen most in the memory tests and the oral fluency test used. Those who were classified as non-"decliners" were seen to have received more therapy within the 5 months post injury, whereas the "decliners" showed higher incidence of previous alcohol abuse or dependency. Interestingly, post-recovery decline did not show a correlation with severity or length of PTA, even though these have been correlated to initial recovery (Till et al., 2008).

### 1.3. Potential moderators of recovery trajectory

### *1.3.1. Demographic factors*

While some effects of TBI may be more permanent, other aspects are believed to recover with time. Green et al. (2008) points out many moderating factors that contribute to cognitive recovery, which include age, education, and premorbid IQ. Interestingly, age appears to have a moderating effect on processing speed, such that younger patients have better outcomes than those who are older (Green et al., 2008; Rabinowitz et al., 2018). The current study, modeled after Rabinowitz et al. (2018), will focus on three domains of cognitive recovery, which include processing speed (PS), verbal learning (VL), and executive function (EF), while considering the role age and education play.

### *1.3.2. Injury severity*

Longer durations of PTA are related to increased severity and poorer outcomes on cognitive tests. The cognitive measures included in the study by Hart et al. (2016) were the Extended Glasgow Outcome Scale (GOS-E) to measure functional recovery, the California Verbal Learning Test-II (CVLT-II) to evaluate memory functioning, and the Controlled Oral Word Association Test (COWAT) to measure verbal fluency (Hart et al., 2016). Although all patients' GCS scores were between 13-15, suggesting mild head injury, only a quarter of the patients experienced PTA less than 1 day. There were 47% who experienced PTA 1-7 days and 28% who met the greater-than-7-days category. Patients with PTA greater than 7 days showed significantly worse cognitive outcome scores on all measures at 30 days, 90 days, and 180 days post injury than those with PTA lasting 1 to 7 days and those with PTA lasting less than 1 day. There was also a difference between the group with PTA lasting 1 to 7 days and those in the less than 1 day group on GOS-E and CVLT-II, with those in the shorter PTA group having a better outcome (Hart et al., 2016). The results from Hart et al. (2016) show that PTA duration can be

correlated with the cognitive outcome expected in patients after a TBI.

### *1.3.3. Conventional imaging*

Imaging measures for TBI include computed tomography (CT) scans and magnetic resonance imaging (MRI). Typically, CT is used in the initial stages of assessment due to its imaging being able to detect focal injuries and the amount of time it takes to run the scan is comparatively short (Andriessen, Jacobs, & Vos, 2010; Ponsford et al., 2013). CT is believed to provide enough information to detect any major pathology; however, arguably MRI would be a better option to have a clearer understanding of the injury (Hughes et al., 2004). MRI is often used at later points in assessment because it provides more detailed imaging, such as detecting non-hemorrhagic contusions and oedema and also takes longer to perform (Andriessen et al., 2010; Ponsford et al., 2013). These methods are more recently acknowledged as possible indicators of severity; however, there is interest in finding out if other measures can tell us more about the influence of the pathology of the injury on the patient's recovery process (Hughes et al., 2004).

Hughes et al. (2004) found a weak correlation between abnormalities detected by MRI, which were defined as hemorrhage or local mass effect, and abnormal cognitive function, specifically in attention. In general, there also appeared to be a trend between abnormalities detected by MRI and poor results on attention and executive function testing (Hughes et al., 2004). Lee et al. (2008) also discussed the benefit of MRI over CT with mild TBI patients. The patients were given both a CT and MRI and neuroradiologists, without knowledge of the study, were asked to assess the images. In general, this study showed the MRI is able to better detect intraparenchymal lesions, subdural hematomas, hemorrhagic traumatic axonal injuries, non-hemorrhagic traumatic axonal injuries, and cerebral contusions than CT (Lee et al., 2008).

However, the patients' CTs did show more traumatic subarachnoid hemorrhages and epidural hematomas than MRI. This is believed to be a result from the CTs being taken before the MRIs and subarachnoid hemorrhages fixing themselves relatively fast (Lee et al., 2008). Overall, MRIs were more sensitive to detecting injuries in the patients' brains. However, there is a possibility that other mechanisms, such as diffuse axonal injury (DAI), cerebral blood flow (CBF), and lesion volume, can tell us more about the influence of the pathology of the injury on the patients' recovery processes (Hughes et al., 2004).

### *1.3.4. Diffuse axonal injury*

DAI is characterized by white matter changes that typically result from acceleration/deceleration injuries (Ponsford et al., 2013; Rabinowitz et al., 2018). Measures of DAI include DTI, which is a metric of MRI that is able to pick up on even the smallest tissue changes (Alexander et al., 2007). It is a form of MRI which measures the changes in the brain tissue through the diffusion of water molecules; the more space between membrane layers suggests more diffusivity, whereas less space suggests less diffusivity (Alexander et al., 2007). If there is damage to a given part of the brain, more space to the damaged area would be apparent in this measure. Because it is a form of MRI, the imaging has a higher resolution than a CT and can provide more detail, even during the recovery process (Alexander et al., 2007).

In several studies, DTI has served as a useful measure for DAI. Results from a study by Niogi et al. (2008) indicated that DTI picked up on DAI that was not detectable on MRI and that delayed reaction time was correlated with injuries seen on DTI, but reaction time was not correlated with the injuries seen in MRI. Niogi et al. (2008) compared standard MRI to DTI, which is believed to detect white matter damage or DAI, with the hypothesis that DTI would account for reaction time delay on cognitive tasks. Reaction time was calculated using the

patients' mean response time across multiple conditions on the Attention Network Task, which measures executive attention (Niogi et al., 2008).

Similar to this study was the one performed by Kraus et al. (2007), which examined the amount of white matter damage in chronic TBI patients across severity levels as well as the relationship between white matter damage and cognition. Results showed the highest rates of reduced white matter integrity occurred in those with moderate-to-severe TBI. Although moderate-to-severe patients had significantly higher rates, mild TBI patients still remained showing significantly more white matter injuries than the control group (Kraus et al., 2007). Additionally, Kraus et al. (2007) found those in the moderate-to-severe TBI group being significantly more impaired on executive, attention, and memory tests from the other two groups, whereas those in the mild TBI group only trended toward being more impaired than the control group in executive and attention functions.

Rabinowitz et al. (2018) looked at the influence of demographic, as well as neuropathological moderators, on longitudinal neuropsychological recovery trajectory up to one year after TBI. DTI was suggested as a possible moderator of the recovery trajectory of the three main cognitive domains focused on by Rabinowitz et al. (2018)—PS, EF, and VL. Rabinowitz et al. (2018) found age functioned as a moderator for the relationship between time and PS (Rabinowitz et al., 2018) indicating that younger patients showed faster recovery trajectory compared to older patients. Additionally, education was a significant predictor of PS, such that more years of education is correlated with better PS outcome (Rabinowitz et al., 2018). Results for EF found significant fixed effects suggesting linear improvement over time (Rabinowitz et al., 2018). As with PS, more years of education indicated better performances and there was a significant age by time interaction, where being younger led to a better recovery trajectory

(Rabinowitz et al., 2018). DAI was also a significant predictor of EF, meaning more extensive white matter damage was associated with poorer EF performance (Rabinowitz et al., 2018). The VL model showed significant fixed effects of linear time, which suggested memory performance improved over time and more years of education was associated with better memory performance (Rabinowitz et al., 2018). Unlike EF, age and DAI were not significant for VL (Rabinowitz et al., 2018).

#### *1.3.5. Cerebral blood flow*

A few studies have demonstrated that measures of CBF are related to cognitive recovery in TBI. Ischemia or hypoperfusion, which is a lack of blood flow to the brain, is common after TBI (Rostami et al., 2014). Blood carries important nutrients like oxygen and glucose that allow the brain to function and as a result, a lack in blood leads to the death and decay of brain tissue and henceforth improper functioning. CBF has been shown to be an acute marker of neurological outcome and death that can be determined as early as 12 hours after injury (Kaloostian et al., 2012). A decrease in CBF in certain areas may be a sign of decreased neural activity or a loss in neuronal volume (Kim et al., 2010).

CBF is measured by arterial spin labeling (ASL) MRI. ASL magnetically labels arterial blood water using radiofrequency pulses (Wolf & Detre, 2007). It works by first labeling the arterial blood that then moves into the image field, an area which a control image has already been captured. Next, the image capturing of the labeled blood is taken. Finally, in order to understand the true amount of CBF, the labeled blood image is subtracted from the control image, producing the final image as a product (Petcharunpaisan et al., 2010; Wolf & Detre, 2007). ASL is a noninvasive way to measure CBF and can be used quantitatively (Deibler et al., 2008).

Kim et al. (2010) found that TBI patients displayed hypoperfusion as compared to the healthy controls, reporting a significant group difference in both grey matter and white matter CBF levels. The TBI group was then split into focal and diffuse lesion subgroups to compare CBF values between the two. The frontal regions of those in the focal lesions group showed lower CBF values than the diffuse lesion group; these areas of difference occurred in the areas of focal structural lesions (Kim et al., 2010). While this outlines the relationship between CBF and TBI, the relationship between CBF and cognitive recovery is not well understood yet. However, it was recently reported that CBF can predict the rate of cognitive recovery (Ware et al., 2020). Cognitive decline has been studied using ASL CBF for neurodegenerative diseases, which further addresses a relationship between cognitive impairments and this imaging mechanism (Xekardaki et al., 2015). ASL was able to distinguish a difference from participants in the stable cognitive function group from those in the decreased cognitive function group as well as those who were categorized as having mild cognitive impairment (Xekardaki et al., 2015). It was markedly evident through the decrease in blood flow seen in the decreased cognitive function group.

#### *1.3.6. Focal lesion*

TBI neuropathology can be roughly classified into two categories—i.e., focal and diffuse. DAI and focal lesion volume have been shown to be useful separate metrics in understanding regional volumetric changes and their relationship to injury severity, with more changes suggesting a more severe injury (Levine et al., 2008). Spikman and van der Naalt (2010) also believed presence of large focal lesions to suggest a more serious injury. Additionally, they found patients belonging to the focal frontal lesion group to perform poorer on EF measures than TBI patients without focal frontal lesions and healthy controls (Spikman & van der Naalt, 2010).

While focal lesions may be able to help predict severity of injury, according to literature, it is unclear if they can predict cognitive trajectory. Levine et al. (2013) found that grey matter volume covaried with patient behavior and that the presence of focal lesions modified the relationship; however, even in patients without focal lesions the relationship remained significant. That being said, it can be suggested that there is a clear relationship between DAI and the behavioral outcome of patients after TBI, but the relationship with focal lesion may not be significant on its own.

The results of a study by Skandsen et al. (2010) suggest that focal lesions and DAI may be more intertwined than suspected initially, with focal lesions maybe not indicating recovery as clearly as DAI. Skandsen et al. (2010) examined DAI in patients with moderate and severe TBI. The main interest of the study was to examine the type and amount of DAI in these patients, as well as be able to relate these findings to patient outcome 1 year later (Skandsen et al., 2010). Analyses revealed that 50% of patients displayed both DAI and some other form of lesion (contusion or hematoma) and only 22% showed 'pure DAI' (Skandsen et al., 2010). As this relates to outcome, patients who had some form of DAI had GCS scores that correlated with outcome, whereas patients without DAI showed no correlation of GCS to outcome scores (Skandsen et al., 2010). In another study with mild TBI patients, it was found that in 28% at least one lesion was present (van der Horn et al., 2018). Although it may be partially due to the small sample size, the number of lesions and of complaints regarding cognitive or affective issues had no significant correlation (van der Horn et al., 2018).

### 1.4. The current study

The current study aims to examine whether the imaging modalities described above can serve as moderating factors of longitudinal trajectories of neuropsychological recovery during

the first year after moderate-to-severe TBI. To our knowledge, there was no previous attempt in moderate-to-severe TBI literature to investigate the influence of the three different imaging modalities (i.e., DTI, CBF, and focal lesion volume) as well as prospectively measured PTA on recovery trajectory within a single study. For example, a recent study by Rabinowitz and colleagues (2018) included only DTI.

We hypothesize that DAI and CBF will be correlated with cognitive outcome, such that more severe DAI and hypoperfusion will indicate poorer outcome. In addition, it is predicted that these imaging variables will moderate the relationship between cognitive outcome and time post-injury. However, based on previous literature, it is unclear if focal lesion volume, independent of DAI, has an effect on cognitive function. It is hypothesized that focal lesion volume will not predict cognitive outcome. Among demographic factors, education is expected to be a predictor of outcome, with fewer years of education suggesting poorer outcome. We also predict that age will have a moderating effect on cognitive recovery trajectory—that is, the relationship between time and cognitive outcome. Identifying predictors and moderators of the recovery trajectory of individual patients' cognitive function will eventually facilitate development of more effective treatment plans for TBI survivors.

## 2. Methods

### 2.1. Participants

The neuroimaging and neuropsychological data used in the current study were collected as part of a larger longitudinal multimodal neuroimaging study investigating neural correlates of functional recovery after TBI. The initial data analysis was published recently (Choi et al., 2019; Rabinowitz et al., 2018; Ware et al., 2020). The local institutional review board approved the study. All participants provided informed consent. Inclusion criteria for participants included age

between 18 and 64, and a diagnosis of non-penetrating moderate or severe TBI. This diagnosis was determined by either a Glasgow Coma Scale (GCS) score of $< 13$ in the emergency department, documented loss of consciousness for 12 hours or more, or prospectively documented post-traumatic amnesia (PTA) of 24 hours or greater. Exclusion criteria included having a history of a prior TBI, a central nervous system disease, seizure disorder, schizophrenia, or bipolar disorder. Participants were excluded for alcohol or psychostimulants abuse that may affect the individual neurologically. This was determined by having health complications from abuse, or the resulting social and vocational disability from the cognitive effects long term substance abuse has on an individual. Further exclusion criteria included pregnancy, inability to complete MRI scanning, not being fluent in English, or impairment that prevented the individual from completing testing and scanning at 3 months post injury.

Demographic variables included were age, education, sex, and race. The injury variables that were included were mechanism of injury and GCS upon arrival at the emergency department. The Orientation Log (Jackson, Novack, Dowler, 1998) was used to help determine the length of PTA. If the patient did not have an Orientation Log score, then it was based off of documentation stating the patient had consistent orientation during a 72-hour period. The date at which the patient was considered fully oriented, a score of 25 or more on the Orientation Log, at least twice within a 72-hour period from the time injury first occurred was the calculation used to determine PTA.

### 2.2. Cognitive outcome measures

Measures for the cognitive domains include the Processing Speed Index from the Wechsler Adult Intelligence Scale IV (WAIS-IV; Wechsler, 2014), which assess speed of mental processing, this was constructed from age-corrected scores of Digit Symbol and Symbol Search

subtests. The age and gender corrected *t* scores of the sum of recall scores over all five learning trials were used for the Rey Auditory Verbal Learning Test (RAVLT; Lezak, 2004), which measures episodic memory. For this test, forms 1, 2, and 3 were administered at the 3-, 6-, and 12-month visits in order to evaluate VL.

A battery of 5 different psychometric tests was used to assess aspects of EF. The Letter-Number Sequencing subtest and the Digits Backward section of the Digit Span subtest of the Wechsler Memory Scale IV (Wechsler, 2014) were used to test working memory with a manipulation component. The Controlled Oral Word Association (COWA; Benton, Hamsher, & Sivan, 1994) test (letters CFL were used for the 3- and 12-month visits while letters PRW were used for the 6 month visit) was administered for verbal fluency to assess cognitive flexibility and initiation. The Trail Making Test-Parts A and B (Reitan & Wolfson, 1985) were also administered with the Part B T-score being included as a measure of mental flexibility and divided attention. Finally, the Color Word Interference Test (CWIT) from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) was used for selective attention and inhibition of habitual responding. Time-intervals were subject-specific; specifically, data was collected at roughly 3 months ± 2 weeks, 6 months ± 2 weeks, and 12 months ± 2 weeks post injury. The models allowed for subject-specific time points to be used, but initially the time points were centered around the first assessment at 3 months (Rabinowitz et al., 2018).

### 2.3. DTI acquisition

A 3 Tesla MRI scanner (Siemens Trio) was used to perform the scanning. The MRI neuroimaging protocol used two 30-direction DTI acquisitions with two b-values ($b = 0$ s/mm$^2$ and $b = 1000$s/mm$^2$) as well as seven b0 images that were spread throughout the acquisition. DTI images were acquired at a resolution of 2.2mm$^3$ with an 84-ms echo time, 6500-ms repetition

time, and a 90° flip angle. The detailed methods of DTI pre-processing and constructions of fractional anisotropy (FA) maps were published in our previous study (Ware et al., 2017). Briefly, the collected images were visually examined for artifacts, then the two images were combined in order to improve image quality. Next, corrections to DTI volume accounting for eddy current distortions and non-brain tissue were made using the FMRIB Software Library (FSL) processing tools. After, DTI-TK, a tensor-based registration procedure that combines affine and diffeomorphic registration steps that is believed to be superior to other methods, was used to register each subject's DTI data to an unbiased population-specific DTI template and then co-registered to a standard-space DTI template (IIT-256). Then these data were resampled into a coordinate system by the Montreal Neurological Institute (MNI), which provided the subject-specific voxel-wise maps of FA (Ware et al., 2017).

A subject-specific approach developed by Mayer et al. (2014) was used to quantify the extent of DAI in each subject. Specifically, the distribution corrected *z*-score (DisCo-Z) was used to better statistically align the control groups to the patients when it came to the two groups having the same chance of extreme values. The subject-specific voxel-wise FA maps were then taken and *z*-transformed with the voxel-wise mean and standard deviation of the control population; after which, extreme voxels are identified as group specific, adjusted *z*-thresholds (Mayer et al., 2014). The scale of threshold adjustment tells the likelihood of seeing voxel-wise extrema from DTI scalar maps in two groups that are otherwise identical (Mayer et al., 2017). Thus, the DAI score is composed of clusters of extremely low FA, which made up the bottom portion of the distribution.

**2.4. CBF and focal lesion data acquisition**

The MRI was taken on the same 3 Tesla MRI scanner (Siemens Trio; Siemens, Erlangen, Germany) mentioned above. The scan had a high-resolution $T_1$ magnetization prepared rapid gradient echo sequence captured at 1-mm isotropic resolution using an echo time (TE) of 3.08ms, repetition time (TR) of 1620ms, inversion time of 950ms, flip angle of 15 degrees, and matrix of 256 x 192. ASL imaging was performed using a pseudo-continuous labeling technique 9 cm below the center of the imaging volume. Labeling duration and post-labeling delay had a time of 1.5 s. Images were acquired using a two-dimensional echo planar sequence with these parameters: TR 4 s, TE 18 ms, field of view 220 mm, matrix 64 x 64, and voxel size 3.4 x 3.4 x 7.2 $mm^3$. Eighteen slices were obtained with a distance factor of 20%. They were taken consecutively in the order of inferior to superior. In order to perform signal averaging, 45 label-control pairs were gathered.

Using the longitudinal processing pipeline of the Advanced Normalization Tool (ANTs), a population-specific anatomical template was made from 40 study participants' structural images. All structural scans from the subjects underwent brain extraction, six-tissue segmentation, and non-linear transformation to the group template using the ANTs structural processing pipeline. In order to improve the accuracy when co-registering the brains with focal lesions, the macrostructural encephalomalacic lesions were segmented by a trained observer.

ASL data were processed through SPM12, the ASL toolbox, and in-house MATLAB scripts. Details of the analysis pipeline were described in the lab's previous paper (Ware et al., 2020). First, a CBF time series was gathered by pair-wise control label subtraction after motion correcting the raw echo planar imaging label-control time series. For CBF estimation was obtained by dividing the corresponding control image and application of the recommended model. Through data cleaning, a denoised mean CBF map was created; final CBF maps were

visually inspected by qualified individuals for quality. Finally, using Gaussian kernel of 6 mm full width at half maximum, the data for standard and structural space CBF was smoothed; down-sampling to 2 mm isotropic resolution to reduce the number of comparisons in the following whole-brain, voxel-wise testing occurred for standard space CBF maps.

### 2.5. Statistical analysis

Data analyses were performed using the lme4 package in R. Multilevel modeling was used because it allows for longitudinal data to be used within the framework of an individual rather than the data for all individuals having to be fixed (Christensen et al., 2008). All of the cognitive test scores were transformed to T-score units before running the linear mixed effects models. Model 1 was a random intercept model that was fit by maximum likelihood. Model 2 was like model one, but added random slope fit by maximum likelihood. If Model 2, with the addition of the random slope, accounted for more variance in the cognitive outcome, then it was used as the base model. If not, then Model 1 was used. Model 3 added a quadratic time term of time^2 to the base model and was fit by maximum likelihood. Model 3 was used if the addition of the quadratic time term accounted for significantly more variance in the cognitive outcome than Models 1 or 2, if not, the Base Model was used.

## 3. Results

No significant difference in demographic variables between the patients (N = 44) and controls (N = 35) was found, corroborating the results from our previous paper that used a larger sample (Rabinowitz et al., 2018). Demographic variables were age, education, sex, and race. Clinical values included were length of post-traumatic amnesia in days, time to follow commands in days, Glasgow Coma Scale, and mechanism of injury. For PS, the current study has used Model 1. Although Model 2 was slightly significant compared to Model 1 ($X^2 = 6.333$;

$p = 0.042$), there were convergence warnings when used with the Full Model, which suggested overparameterization. Model 3 was not used as it did not have a significantly better fit than Model 1 ($X^2 = 3.159$; $p = 0.076$), as seen by the level of variance the Model accounts for according to the AIC values (Model 1 AIC = 780.1, Model 2 AIC = 777.8, Model 3 AIC = 779.0). Covariates of age, education, and time were added to the Model and so were interactions between the covariates and time.

EF used the Model 1 version of the Full Model as the AIC (Model 1 AIC = 716.2, Model 2 AIC = 720.2, Model 3 AIC = 717.6) suggested better fit and there was no significant difference in the amount of variance accounted for when comparing Model 1 to Model 2 ($X^2 = 0$; $P = 1$) and Model 1 to Model 3 ($X^2 = 0.557$; $P = 0.455$). This model added the same covariates of age, education, and time to the model as well as interactions between the covariates and time. VL also used Model 1 as the Base Model to add the covariates of age, education, time, and the interactions (Model 1 AIC = 885.4, Model 2 AIC = 889.3, Model 3 AIC = 887.4) as there was no significant difference of variance in outcome between Models 1 and 2 ($X^2 = 0.102$; $P = 0.950$) or Models 1 and 3 ($X^2 = 0$; $P = 0.998$).

### 3.1. DAI

Model 1 was used as the base model for all the full models that followed. The results indicated significant fixed effects of months, education, and DAI on EF. Months and education showed significant fixed effects on VL. DAI and education showed significant fixed effects on PS, as well as a significant interaction between months and age, with age moderating the relationship between time of scan and PS score. Spearman's correlation was conducted to observe the strength of the relationship between PTA and DAI; results indicate that there is a moderately strong, positive relationship (rho = 0.678, $p = 2.2e^{-16}$). Additional correlations were

run between DAI and the other imaging modalities. DAI had a weak, negative correlation with CBF in grey ($r$ = -0.329, $p$ = 0.0004) and white matter ($r$ = -0.311, $p$ = 0.0009) as well as a weak, positive correlation with focal lesion volume ($r$ = 0.292, $p$ = 0.002).

### 3.2. CBF

Using the base Model 1, this full model replaced DAI with grey matter CBF values. In regard to PS, education was a significant predictor ($p$ = 0.0102). Additionally, as seen in Table 1, age was a significant moderator of the relationship between months and PS ($p$ = 0.0103). The EF Full Model had significant predictors of months ($p$ = 0.0270) and education ($p$ = 0.0204), but no significant moderators. For the VL Full Model, education was the only significant predictor ($p$ = 0.0078) and there were no moderating variables.

CBF values were also calculated using white matter, and Model 1 as the base for the Full Model. For PS, education remained a significant predictor ($p$ = 0.0085) and age continued to be a modifier of the relationship between months and PS ($p$ = 0.0129). The Full Model for EF using white matter showed months ($p$ = 0.0485), white matter ($p$ = 0.0361), and education ($p$ = 0.0115) as all being significant predictors but had no modifiers. The VL Model continued to only have the result of education being a significant predictor ($p$ = 0.0049).

### 3.3. Focal lesion volume

Model 1 was again adjusted to include focal lesion volume instead of CBF. The results, as seen in Table 4, for PS continued to show that education was still a significant predictor ($p$ = 0.0121) and age still moderated the relationship between PS and months ($p$ = 0.0044). The Model looking at EF showed months ($p$ = 0.0039) and education ($p$ = 0.0118) being significant predictors. The moderating relationship of age for months and EF neared significance ($p$ =

0.0597). VL had significant predictors of months ($p$ = 0.0091) and education ($p$ = 0.0039), but no moderating variables.

### 3.4. Post traumatic amnesia

The model was adjusted once more to assess the influence of PTA on neuropsychological variables. Results regarding PS showed that age ($p$ = 0.0426), PTA ($p$ = 0.0001), and education ($p$ = 0.0373) all served as significant predictors. Additionally, age served as a moderator of the relationship between months and PS ($p$ = 0.0039). Significant predictors for EF were months ($p$ = 0.0135), PTA ($p$ = 0.0003), and education ($p$ = 0.0489). VL only showed months ($p$ = 0.0135) and education ($p$ = 0.0074) being significant predictors. Neither EF nor VL had significant moderators.

Additionally, correlations between PTA and the neuroimaging variables were explored. There was a moderately strong, positive correlation between DAI and PTA ($r$ = 0.6783, $p$ = $2.2e^{-16}$). CBF values, both grey ($r$ = -0.3367, $p$ = 0.0002) and white matter ($r$ = -.3407, $p$ = 0.0002), indicated weak, negative correlations with PTA. Focal lesion volume was the only neuroimaging variable that had no significant correlation (see Table 3.).

## 4. Discussion

Using linear mixed effects models, the current study intended to examine multiple neuroimaging variables including CBF, DAI, and focal lesion volume in terms of their ability to predict the recovery trajectory of patients with moderate-to-severe TBI. White matter CBF and DAI were the only imaging modalities that had significant effects on some of the neuropsychological scores. Specifically, DAI, as previously shown by Rabinowitz et al. (2018), was related to poorer outcomes in EF and PS. Lower white matter CBF also was related to poorer outcomes, but only in EF. In all PS results, age moderated the recovery trajectory—that

is, the relationship between time and PS. PTA, as well as all neuroimaging variables examined in the current study, did not moderate the recovery trajectory. All EF results showed significant effects of time, indicating time being a consistent predictor of EF outcome. Time was also a predictor for VL in the DAI Full Model as well as the lesion volume Full Model, but not in either CBF Full Model. Time was also not a predictor of PS outcome in any of the Full Models. Longer durations of PTA predicted poorer outcomes in PS and EF, but not VL. Additionally, for PTA, age was a moderator of PS. DAI, CBF, focal lesion volume, and PTA analyses all showed more years of education predicted better outcome for PS, EF, and VL.

These findings suggest that DAI or white matter CBF would be more reliable measures for predicting cognitive recovery of patients in moderate or severe TBI. DAI and CBF values were also found to correlate with PTA duration. Focal lesion volume displayed no correlation with PTA and had no significant effect on neuropsychological measures. As suggested in previous literature, it seems likely that diffuse axonal injury is a better predictor of recovery (Skandsen et al., 2010; van der Horn et al., 2018). Our finding that only age moderated the recovery trajectory emphasizes the importance of patients' characteristics in predicting the course of cognitive recovery. However, we cannot rule out the possibility that our sample size might have been too small for detecting a moderating effect of neuroimaging variables.

The current framework and timeline of testing occurred in the first-year post injury due to previous literature's indication that recovery takes place in the first year. Christensen et al. (2008) explored cognitive recovery after TBI in the first-year post-injury. They found the most recovery to take place within the first 5 months, with only manual motor, visuospatial domains, and visual memory continuing to improve from the 5 to 12 month range. These results, where it is suggested that recovery occurs in the first year after injury, are also seen in Rabinowitz et al.

(2018). The current study suggests that among the neuroimaging variables, DAI or CBF may have the best chance of predicting cognitive recovery, which further indicates that these methods should be used in the acute phase when assessing patients with TBI. Additionally, clinicians should take extra care to consider elderly patients as well as those with fewer years of education as these patients were seen to have poorer outcomes.

Future studies should continue following up with imaging and testing over the course of years following the injury as some research suggests that even one moderate or severe TBI can have lasting effects on an individual (Corrigan & Hammond, 2013). This would further benefit the search to find the imaging method best for predicting outcome and would have huge clinical implications. The variability seen in injuries leads to the substantial variability in severity, which makes it even harder for therapies to be effectively developed and matched to patients' needs (Kaloostian et al., 2012). Hammond and Malec (2016) suggested that due to the wide range of health issues that often occur after a TBI, the best approach is to treat TBIs as if they are a type of chronic disease. Masel and DeWitt (2010) suggest a wide variety of health problems that are more likely to occur in an individual with a history of TBI than someone in the general population. These health problems go beyond the cognitive dysfunction or psychiatric disorders that one may assume and include cardiovascular disease, metabolic dysfunction, neurodegenerative diseases, and neuroendocrine disorders (Masel & DeWitt, 2010). This also emphasizes the necessity to treat TBI as a chronic condition because it correlates with individuals having increased predispositions as well as increased mortality rates than healthy counterparts. This entails the patient having frequent follow-up visits with doctors to ensure the treatment plan is fit according to the individual needs of that patient.

This concept is furthered by the aforementioned study by Till et al. (2008). While initial

recovery and then stagnation may be displayed in the first year, what happens after is just as important. The Till et al. (2008) study is based on prior research done by Millis et al. (2001), which addressed the concept that not all recovery is linear after the first year. Till et al. (2008) suggested that there are a few different explanations to why post recovery decline may be seen. The first one they propose is that one area of the brain may be more affected than another or that a particular tissue, like white matter, being more affected has something to do with the observed deterioration (Till et al., 2008). The current study acknowledged the exploration of this by addressing DAI and its effect on recovery. However, this concept also ties in closely with the emphasis that neuroimaging studies should continue to follow the patients' recovery over many years. Although it appears that after the initial improvement followed by stagnation seen in the first year of recovery would remain as a new level of cognitive function for the individual, the study by Till et al. (2008) suggests change could still occur in the following years as a result of injury.

The second hypothesis Till et al. (2008) suggested is that post recovery decline could be explained by injury severity. This possibility ties in well with the current study's results showing PTA's relationship to outcomes seen in PS and EF and PTA correlating with DAI and CBF. A future study exploring the connection between neuroimaging variables, severity, and cognitive outcome would greatly benefit from a longer timeline.

Finally, the third possible explanation explored was that decline had to do with demographic variables (Till et al., 2008). This theory holds a lot of weight based on the findings that the non-"decliners" had more therapy within the first five months than the "decliners" as well as more of the non-"decliners" having access to third-party insurance (Till et al., 2008). Additional factors, which are seen in the current study, as well as previous literature, include age

and education. These demographic factors play a significant part in the outcome seen and should be included in all future studies. This study could have benefitted from information regarding therapy and access to therapy.

More research should also be done to determine what treatment protocols should be for individuals being released from the hospital with a diagnosis of TBI. Due to the heterogeneous nature of TBI, it can make this process challenging, but one equation that may help was presented by Cioe et al. (2016) was: outcome = injury + expertise + intensity + duration + timing + follow-up. In this scenario, expertise refers to those providing treatment and their knowledge and ability to cater to the needs of patients, intensity refers to treatment intensity with more intense being desired, duration refers to the length of time a patient receives care, timing refers to access to care in the first year being most beneficial, and follow-up refers to the periodic check-in on patients (Cioe et al., 2016). This shows how broad the variables are that factor into outcome, as a general concept. While it might initially sound logical to assume that by limiting what type of outcome one wishes to research, such as cognitive, it should also be considered that there are many other aspects that deserve attention, such as psychological and social outcomes. These outcomes are all related and ultimately have a large effect on the quality of life a person has after the injury.

TBI continues to be a health condition that affects a large portion of the population. This injury is so variable that it can range from mild to death. Having an imaging technique that can inform professionals from the time of injury the expected recovery of a given patient is essential. Both DTI and ASL CBF appear to be the most promising methods for addressing TBI and the future cognitive recovery of the patient. It is clear that looking at focal lesions alone is not enough to understand the true nature of the injury's recovery trajectory. However, PTA

continues to be a valid indicator of TBI severity. There are limited studies comparing imaging modalities for TBI and few are longer than 1 year. It would be in the best interest of future research to continue following up with patients past the 1-year mark with both imaging and neuropsychological tests to see if there is an effect in decliners that can be seen physically as well as neuropsychologically.

**Table 1. DAI full model mixed effect model results**

| | Processing speed | | | Executive function | | | Verbal learning | | |
|---|---|---|---|---|---|---|---|---|---|
| Random | Intercept | Residual | | Intercept | Residual | | Intercept | Residual | |
| (SD) | 9.907 | 3.629 | | 7.249 | 2.896 | | 12.843 | 7.339 | |
| Fixed | Estimate | Std. Error | T-Value | Estimate | Std. Error | T-Value | Estimate | Std. Error | T-Value |
| Intercept | 36.437 | 10.381 | 3.509*** | 38.955 | 7.639 | 5.099*** | 0.982 | 14.016 | 0.070 |
| Months | 0.378 | 0.678 | 0.558 | 1.497 | 0.540 | 2.768** | 3.561 | 1.364 | 2.609* |
| Age | -0.121 | 0.112 | -1.077 | -0.035 | 0.082 | -0.423 | 0.104 | 0.151 | 0.687 |
| DAI | -0.095 | 0.024 | -3.894*** | -0.062 | 0.018 | -3.471** | -0.034 | 0.033 | -1.057 |
| Edu | 1.681 | 0.675 | 2.486* | 1.147 | 0.497 | 2.308* | 2.553 | 0.910 | 2.803** |
| Age:Months | -0.024 | 0.007 | -3.301** | -0.010 | 0.005 | -1.802 | -0.013 | 0.014 | -0.920 |
| Months:DAI | 0.002 | 0.001 | 1.558 | -0.000 | 0.001 | -0.205 | -0.001 | 0.003 | -0.509 |
| Months:Edu | 0.070 | 0.042 | 1.668 | -0.050 | 0.033 | -1.476 | -0.128 | 0.085 | -1.499 |

Signif. codes: 0.001 '***' 0.01 '**' 0.05 '*'
DAI= diffuse axonal injury; Edu = education

**Table 2. Grey matter CBF full model mixed effect model results**

| | Processing speed | | | Executive function | | | Verbal learning | | |
|---|---|---|---|---|---|---|---|---|---|
| Random | Intercept | Residual | | Intercept | Residual | | Intercept | Residual | |
| (SD) | 11.761 | 3.689 | | 8.123 | 2.892 | | 12.883 | 7.283 | |
| Fixed | Estimate | Std. Error | T-Value | Estimate | Std. Error | T-Value | Estimate | Std. Error | T-Value |
| Intercept | 17.680 | 13.585 | 1.301 | 20.427 | 9.439 | 2.163* | -14.919 | 15.538 | -0.960 |
| Months | 0.924 | 0.706 | 1.308 | 1.252 | 0.553 | 2.263* | 2.453 | 1.39 | 1.764 |
| Age | -0.240 | 0.138 | -1.735 | -0.066 | 0.096 | -0.689 | 0.128 | 0.158 | 0.809 |
| GM | 0.093 | 0.207 | 0.450 | 0.221 | 0.143 | 1.538 | 0.267 | 0.237 | 1.125 |
| Edu | 2.149 | 0.797 | 2.697* | 1.337 | 0.553 | 2.415* | 2.553 | 0.911 | 2.799 * |
| Age:Months | -0.021 | 0.008 | -2.644* | -0.009 | 0.006 | -1.477 | -0.008 | 0.015 | -0.564 |
| Months:GM | -0.001 | 0.011 | -0.095 | 0.004 | 0.008 | 0.524 | 0.020 | 0.021 | 0.959 |
| Months:Edu | 0.050 | 0.043 | 1.184 | -0.050 | 0.033 | -1.532 | -0.135 | 0.083 | -1.622 |

Signif. codes: 0.001 '***' 0.01 '**' 0.05 '*'
GM (CBF value) = grey matter; Edu = education

**Table 3. White matter CBF full model mixed effect model results**

| | Processing speed | | | Executive function | | | Verbal learning | | |
|---|---|---|---|---|---|---|---|---|---|
| Random | Intercept | Residual | | Intercept | Residual | | Intercept | Residual | |
| (SD) | 11.625 | 3.681 | | 7.902 | 2.883 | | 12.615 | 7.266 | |
| Fixed | Estimate | Std. Error | T-Value | Estimate | Std. Error | T-Value | Estimate | Std. Error | T-Value |
| Intercept | 12.244 | 14.020 | 0.873 | 16.086 | 9.593 | 1.676 | -21.095 | 15.906 | -1.326 |
| Months | 0.679 | 0.728 | 0.933 | 1.146 | 0.569 | 2.011* | 2.279 | 1.433 | 1.590 |
| Age | -0.218 | 0.132 | -1.645 | -0.060 | 0.090 | -0.664 | 0.141 | 0.151 | 0.931 |
| WM | 0.246 | 0.235 | 1.045 | 0.344 | 0.160 | 2.140* | 0.442 | 0.267 | 1.655 |
| Edu | 2.138 | 0.772 | 2.767** | 1.400 | 0.528 | 2.649* | 2.616 | 0.877 | 2.982** |
| Age:Months | -0.019 | 0.008 | -2.558* | -0.009 | 0.006 | -1.519 | -0.010 | 0.015 | -0.665 |
| Months:WM | 0.007 | 0.013 | 0.495 | 0.008 | 0.010 | 0.802 | 0.028 | 0.026 | 1.085 |
| Months:Edu | 0.043 | 0.042 | 1.058 | -0.051 | 0.032 | -1.6 | -0.132 | 0.081 | -1.623 |

Signif. codes: 0.001 '***' 0.01 '**' 0.05 '*'
WM (CBF value)= white matter; Edu = education

**Table 4. Lesion volume full model mixed effect model results**

| | Processing speed | | | Executive function | | | Verbal learning | | |
|---|---|---|---|---|---|---|---|---|---|
| Random | Intercept | Residual | | Intercept | Residual | | Intercept | Residual | |
| (SD) | 11.330 | 3.674 | | 8.360 | 2.897 | | 12.949 | 7.375 | |
| Fixed | Estimate | Std. Error | T-Value | Estimate | Std. Error | T-Value | Estimate | Std. Error | T-Value |
| Intercept | 20.804 | 10.855 | 1.916 | 28.508 | 8.035 | 3.548*** | -5.191 | 12.946 | -0.400 |
| Months | 0.856 | 0.593 | 1.442 | 1.399 | 0.468 | 2.988** | 3.195 | 1.188 | 2.689** |
| Age | -0.228 | 0.123 | -1.856 | -0.121 | 0.090 | -1.340 | 0.054 | 0.146 | 0.369 |
| LV | 0.404 | 0.228 | 1.765 | 0.069 | 0.169 | 0.413 | 0.006 | 0.272 | 0.025 |
| Edu | 2.001 | 0.760 | 2.630* | 1.488 | 0.562 | 2.643* | 2.785 | 0.906 | 3.072** |
| Age:Months | -0.021 | 0.007 | -2.952** | -0.010 | 0.005 | -1.916 | -0.015 | 0.014 | -1.078 |
| Months:LV | -0.009 | 0.012 | -0.751 | -0.003 | 0.009 | -0.391 | 0.010 | 0.024 | 0.416 |
| Months:Edu | 0.055 | 0.040 | 1.349 | -0.042 | 0.032 | -1.334 | -0.115 | 0.081 | -1.416 |

Signif. codes: 0.001 '***' 0.01 '**' 0.05 '*'
LV= lesion volume; Edu = education

**Table 5. PTA full model mixed effect model results**

| | Processing speed | | | Executive function | | | Verbal learning | | |
|---|---|---|---|---|---|---|---|---|---|
| Random | Intercept | Residual | | Intercept | Residual | | Intercept | Residual | |
| (SD) | 9.441 | 3.667 | | 6.967 | 2.899 | | 12.988 | 7.327 | |
| Fixed | Estimate | Std. Error | T-Value | Estimate | Std. Error | T-Value | Estimate | Std. Error | T-Value |
| Intercept | 39.268 | 10.003 | 3.925*** | 40.544 | 7.417 | 5.466*** | -1.945 | 14.246 | -0.136 |
| Months | 0.549 | 0.704 | 0.779 | 1.414 | 0.556 | 2.539* | 3.752 | 1.402 | 2.676** |
| Age | -0.212 | 0.102 | -2.068* | -0.093 | 0.075 | -1.227 | 0.062 | 0.145 | 0.428 |
| PTA | -0.333 | 0.073 | -4.510*** | -0.218 | 0.054 | -3.981*** | -0.055 | 0.105 | -0.525 |
| Edu | 1.416 | 0.656 | 2.156* | 0.989 | 0.486 | 2.032* | 2.639 | 0.934 | 2.824** |
| Age:Months | -0.021 | 0.007 | -2.993** | -0.010 | 0.005 | -1.931 | -0.015 | 0.014 | -1.069 |
| Months:PTA | 0.004 | 0.005 | 0.863 | 0.000 | 0.004 | 0.019 | -0.008 | 0.010 | -0.756 |
| Months:Edu | 0.066 | 0.044 | 1.497 | -0.045 | 0.035 | -1.293 | -0.139 | 0.088 | -1.574 |

Signif. codes: 0.001 '***' 0.01 '**' 0.05 '*'
PTA= post traumatic amnesia; Edu = education

**Table 6. Correlations between PTA and neuroimaging variables**

| Spearman's rho PTA Correlations | Rho | P-value |
|---|---|---|
| **DAI** | 0.6783206 | $2.2e^{-16}$ *** |
| **CBF grey matter** | -0.3367179 | 0.0002833 *** |
| **CBF white matter** | -0.3407109 | 0.000237 *** |
| **Lesion voxels$^3$** | 0.09398044 | 0.3243 |

* $p < .05$, ** $p < .01$, *** $p < .005$.
PTA = post traumatic amnesia; DAI = diffuse axonal injury; CBF = cerebral blood flow

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