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Association Between White Matter Integrity, Injury Severity and
Variability in Neuropsychological Performance Following Traumatic Brain Injury

EMILY ELLEN CARTER
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Reviewed and approved* by the following:

Frank G. Hillary
Professor of Psychology
Thesis Supervisor
Honors Advisor

Peter Arnett
Professor of Psychology
Faculty Reader

* Electronic approvals are on file.

ABSTRACT

As people age, white matter integrity (WMI) in the central nervous system naturally declines (Bennet & Madden, 2014). Certain conditions, such as neurodegenerative disease and/or injury, can accelerate this process (Coelho et al., 2021) and there is a growing literature showing a significant relationship between increased white matter degradation and traumatic brain injury (TBI) (Kinnunen et al., 2011). Few studies have investigated how increased white matter degradation due to brain injury specifically impacts individual performance on neuropsychological assessment. Exploring this relationship is important, because it could significantly inform clinical and functional trajectories following brain injury. Therefore, the current study explored the effects of global white matter integrity on neuropsychological performance in patients with TBI compared to healthy controls. Neuropsychological functioning was measured using the Hopkins Verbal Learning Test (HVLN-R), Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Span Forward & Backward, Delis-Kaplan Executive Functioning System (DKEFS), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and the Trail Making Test A & B. White matter integrity was measured using diffuse tensor imaging (DTI) methodology. It was hypothesized that there would be a significant interaction between global white matter integrity on overall neuropsychological performance. Results indicated that there was a significant interaction between global white matter integrity, injury severity and specific neuropsychological tasks. Future studies could possibly explore how global white matter integrity impacts functional daily activities as well as other areas of cognition.

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Chapter 1: Introduction

Background

In the United States, traumatic brain injury (TBI) affects 1.5 - 2 million people each year (Thurman et al., 1999). Furthermore, it is estimated that 69 million people worldwide will suffer from a TBI each year (Dewan et al., 2018). Because of the increased awareness of TBI, clinicians and researchers alike have been able to identify key short-term and long-term effects of brain injury.

Regarding acute effects of TBI, the most common symptoms reported include headache, blurry vision, confusion, and even loss of consciousness (Heegaard and Biros, 2007). However, more prolonged symptoms, better known as persistent post-concussive disorder (PPCD), include markers such as continuous neurologic, cognitive, or behavioral complaints that are occurring past the acute phase of the injury (> 3 months).

To classify the severity of a traumatic brain injury, several methods have been developed. The most common way that brain injuries are graded is by assessing acute symptoms. It is common practice to evaluate acute symptoms rather than post-acute symptoms because acute symptoms are seen as a significant predictor of trajectory of recovery (Walker et al. 2018). It is also to avoid the possibility of other comorbid factors contributing to the complaints that are being reported. The most applicable symptoms to determine and distinguish severity include the presence and time scale of amnesia (PTA) and loss of consciousness (LOC) (Tenovuo et al., 2021).

Clinically, the most common metric to determine the severity of brain injury is the Glasgow Coma Scale (Jennett & Teasdale, 1981). The GCS is primarily used to assess post-injury neurological status by looking at verbal responsiveness, motor functioning and ocular responsiveness. Ranging from a score of 3 to 15, the GCS interprets brain injury on a mild (13-15), moderate (9-12) and severe (3-8) scale.

During and after the acute stage of brain injury, neuropsychological assessment is commonly used to identify certain cognitive domains (e.g., processing speed, new learning and retrieval, executive functioning) that may have been impacted by the injury (Soble, Critchfield, & O'Rourke, 2017). During what is called the subacute phase of injury (weeks to months), brief neuropsychological testing is common to try and aid the patients in their immediate recovery, initiate referrals, and provide psychoeducation regarding the trajectory of recovery from traumatic brain injury (Gleckman & Brill, 1994). In the post-acute phase of recovery, comprehensive neuropsychological assessment is often recommended to provide a more in-depth glimpse of possible long-term concerns post-injury (Griesbach et al., 2015). Comprehensive testing generally can be structured in a way that identifies residual cognitive deficits, but also emotional and personality attributes (Goldstein et al., 2019).

Neuroimaging

Neuroimaging has also proven to be useful in identifying the neuroanatomical implications of traumatic brain injury. During a critical care stage of traumatic brain injury, one of the most common imaging methods is computerized tomography (CT) (Jain et al., 2019). This is primarily to attempt and identify any hemorrhaging that requires immediate medical attention.

There are advanced experimental neuroimaging techniques that are becoming increasingly capable of detecting injuries on the cellular level (Mass, Stocchetti, & Bullock, 2008). Examples of these neuroimaging techniques include functional magnetic resonance imaging (fMRI) and susceptibility weighted imaging (SWI). While these methods are promising, whether they are useful in a clinical setting and in individual case conceptualization is questionable. This is due to the fact that a good majority of the time the findings are nonspecific (Douglas et al., 2018). Specifically, CT scans do not foresee possible symptoms following TBI very well. Lannsjö et al. (2012) indicate that demographic factors have been shown to be stronger indicators than CT scan results. Furthermore, in alignment with other literature, they conclude that other, more sensitive methods, are required to predict possible symptoms and long-term outcomes following TBI.

Because of the variability of traumatic brain injury, individualized treatment and intervention have been a constant point of discussion (Makarenko et al., 2016). Depending on the severity and mechanism of the injury, the trajectory of treatment can look starkly different from one patient to another. Differences can include imaging techniques used, rehabilitation approaches, neuropsychological assessments administered and whether the patient is experiencing prolonged symptoms. More recently though, researchers and clinicians have been exploring the development of a more specialized traumatic brain injury intervention that is specifically tailored towards the patient and their individual circumstances. For instance, traumatic brain injury researchers have been looking into the efficacy of using advanced neuroimaging techniques to inform how a patient will perform on specific neuropsychological assessment. This is significant because, if there is a reliable neuroimaging technique to infer and inform cognitive performance, then the interventions that follow could possibly be specialized

towards those findings (e.g., battery of tests, approach to testing, possible disability, future neurological developments, etc.).

Diffuse Tensor Imaging

Diffusion tensor imaging (DTI) could possibly be a useful neuroimaging technique to detect white matter damage following brain injury. Following non-penetrating head injuries, diffuse axonal injury (DAI) is a common occurrence. DAI microscopically stretches axons which can ultimately lead to white matter degradation in the brain. Unlike other neuroimaging methods, DTI is able to detect these alterations in white matter following brain injury. DTI is able to quantify this by detecting the direction and the amount of diffusion of water within axons. More specifically, fractional anisotropy (FA) measures the specific isotropic movement of water molecules. This allows for detection of axonal alterations in density and structure.

Using DTI, Niogi et al. (2008) examined white matter in mTBI 1 to 65 months following injury (mTBI) (N = 34). After exploring six regions of interest, they found reduced fractional anisotropy (FA) values in the corpus callosum (21%), inferior longitudinal fasciculus (21%), anterior corona radiata (41%), cingulum bundle (18%), and the uncinate fasciculus (29%). These reduced FA values were found to be correlated with impairments in memory and attention. These findings are promising, because it shows that DTI, specifically FA, may be helpful in identifying cognitive dysfunction following mTBI.

Similarly, Rutgers et al. (2008) found similar results in a study investigating both mTBI and moderate TBI. It was found that, in comparison to the mTBI patients, patients with moderate TBI showed significantly more FA reduction in the corpus callosum. The authors suggested that

a longitudinal study would provide more information regarding the reliability of using DTI to investigate injury progression and recovery.

In a study conducted by Wilde et al. (2021), they explored using DTI methods to explore plasticity following early childhood traumatic brain injury (1-8 years old). Results showed that early childhood TBI impacts white matter integrity, impacting overall developmental trajectories in some children. Furthermore, Wilde et al. (2021) urges the use of DTI techniques whenever feasible, now that a good amount of its limitations have been improved upon.

While there is quite a bit of research being conducted in this area, there are some areas left that need to be explored. For instance, more studies should explore the functionality of DTI following severe brain injury, as well as how DTI can be used among a wide array of ages following brain injury. Lastly, researchers could investigate how these methods can be implemented into the clinical setting. This would allow a broader understanding of how TBI presents on a DTI scan with a wide range of severity and ages, as well as how it can inform treatment.

Current Study

As shown, there is significant research examining the impact of traumatic brain injury on WMI. However, little research has specifically looked at the comorbid effects of global WMI, injury severity and neuropsychological performance in those have suffered from moderate to severe brain injury. This study will Specifically, exploring how TBI poses a risk for abnormal aging and being able to differentiate natural white matter loss compared to loss due to injury.

Studying a specifically aging population will be beneficial to the current study, because research has already explored DTI in younger populations.

Because of the limited research, the present study aimed to explore the impact of white matter integrity and severity of injury on neuropsychological performance in individuals with moderate to severe traumatic brain injury. Specifically, individuals older than 50 years of age and 10-years post injury were included. Furthermore, exploring the idea of utilizing the relationship between WMI, severity of injury, and neuropsychological performance to inform clinical intervention. The following hypotheses were explored:

Hypothesis 1: There will be a significant effect of TBI on overall neuropsychological functioning. Individuals aging with traumatic brain injury will have worse neuropsychological performance compared to older healthy controls.

Hypothesis 2: There will be a significant effect of white matter integrity (WMI) on overall neuropsychological functioning. Those with lower levels of WMI will have worse neuropsychological performance compared to those with higher levels of WMI.

Hypothesis 3: There will be an interaction between WMI and injury severity on overall neuropsychological functioning such that those sustaining more severe injuries and who have lower levels of WMI will perform the poorest on the neuropsychological tasks compared to the rest of the participants.

Chapter 2: Method

Design

This study was a cross-sectional study with group membership as the independent variable and WMI and neuropsychological performance as the dependent variables. Neuropsychological performance was measured using various domains including executive functioning, retention, motor speed, visuospatial reasoning, and verbal fluency. Each of the aforementioned domains were investigated using a cognitive assessment.

Participants

Data for this project was provided by a multi-site study that was funded by the Pennsylvania Department of Health (PA-DOH). Multi-site locations include data provided from Hershey Medical Center in Hershey, PA, Pennsylvania State University in State College, PA, and Moss Rehabilitation Center in Philadelphia, PA. It is important to note that the PA-DOH is supported financially through state-based funding. The material provided in this paper is solely based upon the work funded by the PA-DOH. Again, in an effort to have complete discretion, any conclusions or findings that are stated in this manuscript are those of the author and may not mirror opinions of the Pennsylvania Department of Health. Participants that were included in this specific study ranged from ages 51 – 92 years old. Exclusionary criteria include previous history of neurodevelopmental and/or psychological disorders (e.g., schizophrenia, autism, bipolar disorder, etc.). Other exclusionary criterion includes currently receiving treatment for other

injuries. In order to accurately reflect a representative sample, those with diagnosed ADHD and substance use disorder were not excluded from this study. All participants involved in the study and subsequent analyses were able to attend Hershey Medical Center, Pennsylvania State University Main Campus, or Moss Rehabilitation Center. Based off the exclusionary criteria, 56 participants were included in this study. Off those 56, 33 were in the TBI group and 23 were healthy controls (**Table 1**). **Table 1** details participant demographical information.

Procedure

Testing for this project included informed consent, a neuropsychological battery used to assess cognitive functioning after brain injury, and an hour-long MRI protocol. The MRI protocol consisted of structural, functional, and resting state scans. For the purposes of this study, we will be focusing on the sagittal T1-weighted and diffuse tensor imaging (DTI) portion of the imaging protocol.

Injury Severity

In order to measure injury severity, the Glasgow Coma Scale (GCS) was utilized. Traditionally, the GCS has been used in order to measure the degree of cognitive impairment. In order to test participants, three tasks of responsiveness are utilized. These include verbal responses, motor responses, and eye-opening abilities. By combining these tasks, an overall

score between 1 (no response, comatose) to 15 (responsive, normal levels). This measure is frequently used to measure acute TBI (Krasney-Pacini et. al., 2017).

Neuropsychological Assessment

Across all sites (Pennsylvania State University, Moss Rehabilitation Center, Hershey Medical Center) the same procedures for testing were followed. Similar to previous research, Trail Making form A and B was used in order to assess executive functioning (Arbuthnott & Frank, 2000). To assess memory, the Hopkins Verbal Learning Test – Revised (HVLT-R) and the Digit Span Forward/Backward tasks from the Weschler Adult Intelligence Scale-III (WAIS-III) was used. Furthermore, the Story Memory and Story Recall tasks from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was also utilized. To measure verbal functioning, the Verbal Fluency and Category Fluency tasks from the Delis-Kaplan Executive Functioning System (DKEFS) were administered. To examine processing speed, the Symbol Search and Coding tasks from the Weschler Adult Intelligence Scale-III (WAIS-III) were used. To measure visuospatial and constructional abilities, the Figure Copy and Figure Recall tasks from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were used.

In Trail Making form A, participants were asked to draw lines to connect a sequence of circles containing numbers in order (ex. 1-2-3-4). This test is completed when the trail is completed, or the participant has reached 150 seconds. In Trail Making form B, participants were asked to draw lines to connect circles containing both letters in numbers in alternating sequential

order (ex. 1-A-2-B). This test is completed when the trail is completed, or the participant has reached 300 seconds.

The HVLT-R requires participants to attempt to memorize a list of twelve words immediately after having the words read aloud (immediate recall) and following a twenty-minute delay (delayed recall).

The WAIS-III Digit Span consists of participants being read a series of numbers and then being asked to attempt to repeat the numbers in forward or backwards order. Digit Span Forward relies heavily on attention and memory capacity while Digit Span Backwards relies more so on working memory. For the purposes of this study, we will be utilizing both Digit Span Forward and Backward.

The DKEFS Letter Fluency task requires participants to name as many words as they can recall that start with the letter F, A, and S. For each letter, participants are allotted 60 seconds to name words that start with the given letter. Besides verbal fluency, this task can be used to examine attention, inhibition, and even long-term memory.

The DKEFS Category Fluency task requires participants to recall as many words as they can within the categories of Boys Names and Animals. For this task, participants are also allotted 60 seconds to name words in the given category.

The RBANS Story Memory task requires participants to recall a specific story that is broken up into 12 different segments over two immediate recall trials. RBANS Story Recall requires participants to recall the aforementioned story after a long delay.

The RBANS Figure Copy task requires participants to copy a 10-item figure while the copy remains on display. RBANS Figure Recall requires participants to recall and draw the figure after a long delay.

The WAIS-III Symbol Search task requires participants to search for the 2 objective symbols that are located on the left of the paper under a time limit. The WAIS-III Coding task requires participants to use a provided key (numbers associated with a unique symbol) to match with the numbers. The numbers (1-9) are presented to the participant at a random order and required to fill in the corresponding symbol with each number presented. Participants are required to do this task under a 120 second time limit.

MRI Acquisition Protocol

Neuroimaging data was collected at all three sites associated with this study (Penn State Hershey Medical Center Department of Radiology, Moss Rehabilitation Center, Social, Life, and Engineering Sciences Imaging Center at University Park.) Additionally, at all three sites neuroimaging data was collected using an identical Siemens 3 T Prisma Fit scanner and a 64 Channel head coil. The protocol included standard sequences: sagittal T1 MPRAGE and DTI. The T1 MPRAGE sequence was collected at a spatial resolution of 1.0 – mm X 1.0 mm X 1.0 mm voxels, with a reported repetition time (TR) of 2000 ms and reported echo time (TE) of 2.03 ms. The DTI scans were collected using a specific DTI sequence at a spatial resolution of 2.1- mm X 2.1-mm X 2.0-mm voxels, with a reported repetition time (TR) of 7100 ms and reported echo time (TE) of 64 ms. The Beta (b-value) was reported to be 0 s/mm². The phase encoding was in the AP direction with a PA reverse phase encoding.

Diffuse Tensor Imaging Processing and Analysis

In order to preprocess the neuroimaging data in preparation for analysis, the program MRtrix was used. The first step used to preprocess the imaging data was denoising. During image acquisition and other preprocessing steps (motion/distortion correction) can change assumed noise features. Denoising aims to reduce the impact of noise and the overall noise floor.

The second step to preprocessing was to remove Gibbs' ringing artifacts. This was done through the `mri_degibbs` function within MRtrix (Jahn, 2019). Specifically, we removed ringing artifacts based upon the resampling of the figure so that the origin of the ringing pattern is shown at its zero crossings (Kellner et al., 2015)

The final preprocessing step was to unwarp the data and remove any eddy currents. Eddy currents are defined as electrical currents produced inside conductors via the transforming magnetic field located in the conductor (Tromp, 2012). These are important to remove, because it can ultimately result in artifacts in the brain image.

Furthermore, during this step the data was checked for corrupt slices and a brain mask was made. Specifically, a white matter brain mask was made to give a reference point for setting limitations on the FA value, such that none of the values lie outside of the mask. This is to ensure that analyses only occur inside the voxels inside the brain.

For the purposes of this study, mean global fractional anisotropy (FA) was used to measure white matter integrity (WMI). To do this, the MRtrix `mrstats` function was used. Specifically, the `output field` and `mask image` options were utilized. See **Table 3** and **Table 4** for FA values.

Chapter 3: Results

Overview

One-way ANOVA analyses were utilized to examine the interaction of TBI on neuropsychological functioning. One-way ANOVA analyses were also utilized to examine the interaction of WMI on neuropsychological functioning. A linear regression model was utilized to see if WMI (IV) and injury severity (IV) significantly predicted performance on each neuropsychological assessment (DV). The following equation was used to create the linear model:

lm (FA ~ neuropsych measure + age + GCS, data = PA Health)

Analysis of Normality

A Shapiro Wilks Test of Normality was completed in order to analyze normality levels in the overall data distribution. The results demonstrated that Coding, Symbol Search, Figure Recall, Story Recall, Letter Fluency, Category Fluency, and Trail-making form B did not significantly diverge from the normal distribution ($p>0.05$) (**Table 5**).

Results demonstrated that HVLT-R Total Recall, HVLT-R Delayed Recall, HVLT-R Retention, Digit Span Forward, Digit Span Backward, Figure Copy, Story Memory, and Trail-making form A significantly diverged from a normal distribution ($p < 0.05$) (Table 5).

Hypothesis 1: Main Effects of TBI on Neuropsychological Functioning

Multiple one-way ANOVAs were performed to compare the effect of participant group on each neuropsychological assessment included in the present study.

Results showed that participant group had a significant main effect ($p < 0.05$) on, HVLT-R Total Recall, HVLT-R Delayed Recall, Coding, Digit Span Forward, Symbol Search, Story Memory, Story Recall, Letter Fluency, Category Fluency, and Trail Making Test forms A and B such that participants with TBI received significantly lower scores than the healthy controls (**Figure 2**) (**Table 2**).

Results showed that participant group did not have a significant main effect ($p > 0.05$) on HVLT-R Retention, Digit Span Backward, Figure Copy and Figure Recall, such that participants with TBI did not receive significantly lower scores than the healthy controls (**Figure 2**) (**Table 2**).

Therefore, the null hypothesis that TBI does not have an impact on certain neuropsychological functions was rejected with these findings. See **Table 2** for results .

Hypothesis 2: Main Effects of WMI on Neuropsychological Functioning

Multiple one-way ANOVAs were performed to compare the effect of WMI (calculated via FA values) on each neuropsychological assessment included in the present study.

Results showed that WMI had a significant main effect ($p < 0.05$) on HVLT-R Total Recall, HVLT-R Delayed Recall, Coding, Symbol Search, Figure Recall, Story Memory, Story Recall, Letter Fluency, Category Fluency, and Trail Making forms A and B, such that participants with TBI received lower scores than the healthy controls (**Table 6**).

Results showed that WMI did not have a significant main effect ($p > 0.05$) on HVLT-R Retention, Digit Span Forward, Digit Span Backward, and Figure Copy, such that participants with lower levels of WMI did not receive significantly lower scores than the healthy controls. (**Table 6**).

Therefore, the null hypothesis that WMI does not have an impact on certain neuropsychological functions was rejected with these findings. See **Table 6** for results.

Hypothesis 3: Interactional Effects between WMI and Injury Severity on overall Neuropsychological Functioning

Mean FA ($M = 0.19969033$; $M = 0.18071275$) values were significantly less in those with moderate-severe TBI compared to mild TBI ($M = 0.20078353$). **Table 4** presents the mean values and SD in each group. Furthermore, mean FA values were significantly less in those with TBI ($M = 0.19809082$) compared to healthy controls ($M = 0.21129822$). **Table 3** presents the mean values and SD in each group.

Multiple linear regression was used to test if WMI and injury severity significantly predicted performance on each neuropsychological assessment included in the present study, while controlling for age reported at time of testing. This model is illustrated in **Figure 1**.

Some participants in this study did not have GCS data at the onset of this study. Due to this, 17 participants in the TBI group were excluded from the linear regression model.

Results showed that the overall model between HVLTR Total Recall, HVLTR Retention, Coding, Digit Span Forward, Digit Span Backward, Figure Copy, Figure Recall, Story Memory, Letter Fluency, Category Fluency, Trail Making form B scores and GCS total scores was nonsignificant ($p > 0.05$). See **Table 7** for results.

Results showed that the overall model between HVLTR Delayed Recall scores, Symbol Search, Story Recall, Trail Making form A and GCS total scores were significant ($p < 0.05$). See **Table 7** for results.

Chapter 4: Discussion

The purpose of this study was to glean a better understanding of how white matter integrity impacts neuropsychological performance in those who have suffered from traumatic brain injury. Specifically, the study focused on the relationship between global white matter integrity and neuropsychological performance in older adults who have suffered from moderate, and severe traumatic brain injury. More broadly though, the study also aimed at exploring how advanced neuroimaging techniques can be used to predict neuropsychological performance and inform clinical intervention.

Hypothesis 1: Main Effects of TBI on Neuropsychological Functioning

A primary finding in this study was that TBI has a significant impact on certain neuropsychological tasks, specifically, the tasks that measure executive functioning, memory, and processing speed. This was seen through the significant main effect of participant group on the HVLТ-R Total Recall, HVLТ-R Delayed Recall, Coding, Digit Span Forward, Symbol Search, Story Memory, Story Recall, Letter Fluency, Category Fluency, and Trail Making Test forms A and B. While each of these tests examine a different neuropsychological domain (e.g., executive functioning, processing speed, memory, etc.), these findings show that the presence of traumatic brain injury (ranging from mild to severe) was associated with deficits in certain neuropsychological tasks compared to healthy controls. With that being said, participant group

did not significantly affect HVLT-R Retention, Digit Span Backward, Figure Copy, or Figure Recall. These findings are supported by previous research that shows that the heterogeneous nature of brain injury causes differences in how deficits are presented on neuropsychological assessment. For instance, depending on the mechanism of injury, a participant may show deficits in one area but present completely normal in another.

Be that as it may, these specific results are important because it helps glean a better understanding of how brain injury impacts certain neuropsychological functions. Furthermore, it also contributes to generalizability and replication efforts relating to brain injury in the state of Pennsylvania.

Hypothesis 2: Main Effects of WMI on Neuropsychological Functioning

Another primary finding of this study was that WMI has a significant impact on certain neuropsychological tasks. Similar to Hypothesis 1, the tasks that measure executive functioning, memory, and processing speed were most affected. This was shown through the significant main effect of WMI on the HVLT-R Total Recall, HVLT-R Delayed Recall, Coding, Symbol Search, Figure Recall, Story Memory, Story Recall, Letter Fluency, Category Fluency, and Trail Making Test forms A and B. These findings are also important because they support the current literature that indicates how WMI can be used to infer performance on assessment and predict cognitive decline (REF).

One significant confound that is discussed in the limitations section, and may have impacted the significance levels, is age. White matter degradation is a natural process that

increases as we age. However, it is important to differentiate between natural degradation and clinical levels of degradation due to injury, neurodegenerative disease, etc.

Even with this limitation, these findings are important because they show how white matter degradation can manifest itself onto specific neuropsychological assessments. Moreover, our findings show how this specific phenomenon applies to those who have suffered from brain injury in the state of Pennsylvania.

Hypothesis 3: Interactional Effects between WMI and Injury Severity on overall Neuropsychological Functioning

Results of this study also showed a significant interaction between WMI, injury severity, and neuropsychological functioning on HVLT-R Delay, Symbol Search, Story Recall, and Trail Making Test form A. These findings show that varying levels of WMI and injury severity can cause patients to perform worse on specific neuropsychological assessments, specifically, tasks that measure memory, processing speed, and attention. Even though there is limited research regarding this specific interaction, these findings do support current literature regarding the effect of WMI and injury severity on neuropsychological functioning (Kraus et al., 2007).

While there surely needs to be more research regarding this specific interaction, these results are promising in showing the implications of using a combination of advanced neuroimaging techniques, acute measures of injury severity, and comprehensive neuropsychological assessment.

Limitations

A potential factor that could threaten the validity of the results could be age. As individuals age, white matter degradation is a natural process. Furthermore, natural aging has also been shown to result in poorer cognitive functioning. For the purposes of this study, it required us to ponder whether the relationships being explored were due to the results of brain injury or due to natural aging processes. To try and combat this, age was controlled for in the linear regression model.

As mentioned before, three different sites were utilized to collect data. This creates risk for scanner dependent differences and protocol in between scans.

Furthermore, a longitudinal study model using fMRI and multiple testing sessions may provide more generalizable results and long-term insight regarding WMI, injury severity and neuropsychological performance.

Finally, after the Shapiro Wilks test of normality, it was found that the HVLT-R Total Recall, HVLT-R Delayed Recall, HVLT-R Retention, Digit Span Forward, Digit Span Backward, Figure Copy, Story Memory, and Trail-making form A significantly diverged from the normal distribution (**Table 5**). This creates an issue with overall generalizability. With that being said, this also encourages further study in more diverse patient populations.

Importance and Future Applications

Even with the mentioned limitations, this study explored an important topic that could be used for future exploration on how advanced neuroimaging techniques can be used to

inform/predict performance on specific neuropsychological tasks and other clinically relevant interventions.

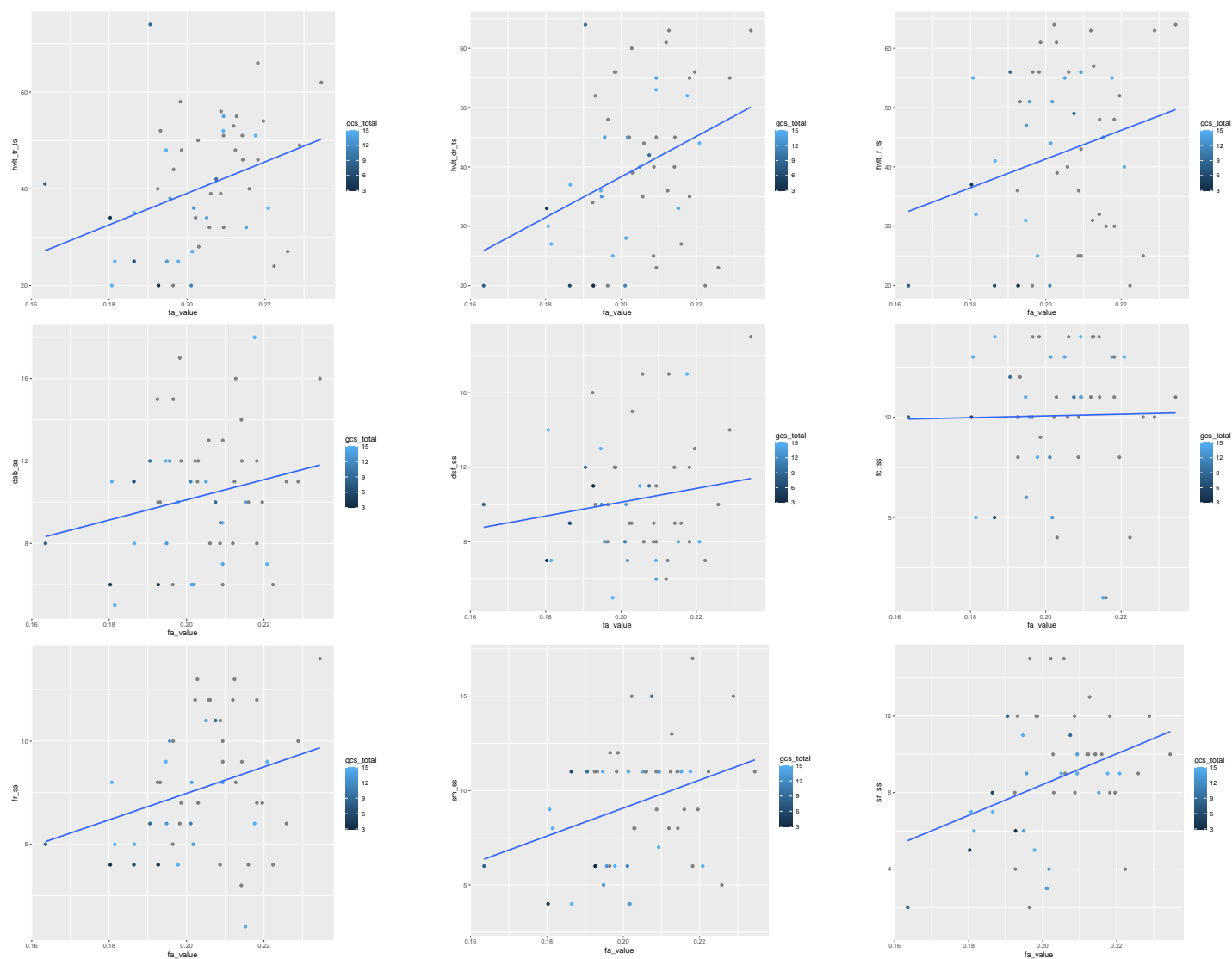
White matter integrity is a critical indicator of cognition. While white matter degradation is a natural process, it also an important indicator of increased rates of cognitive decline following brain injury. By understanding the implications of white matter degradation following brain injury,

With the increased capabilities of neuroimaging techniques, it has been debated whether it is useful in a clinical setting. Specifically in DTI, this is due to the fact that findings are generally non-specific and make it difficult to decide whether the degradation is due to injury, another illness, or even just simply aging. However, by even just having a baseline understanding of patients WMI it still may be useful to help glean a better understanding of present cognitive functioning.

By exploring these combinations of techniques, it may help clinicians to individualize treatment, recommendations, and overall trajectories. Therefore, the present study and future research may be able to create individualized plans for care, decrease prolonged symptoms of brain injury, and assist patients in returning to activities of daily living (ADL).

Figure 1.

Interaction between global WMI, Injury Severity and overall neuropsychological performance



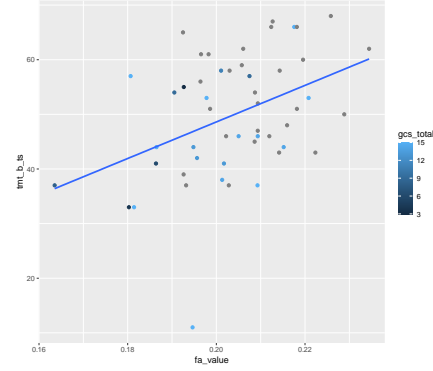
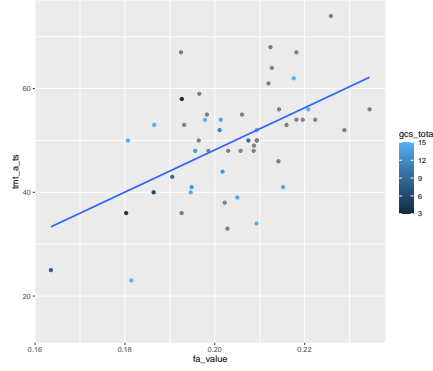
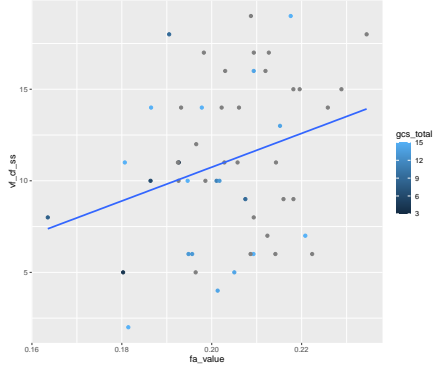
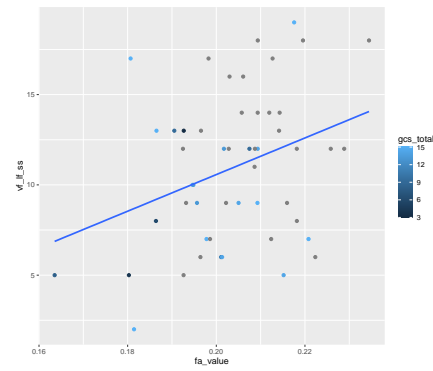
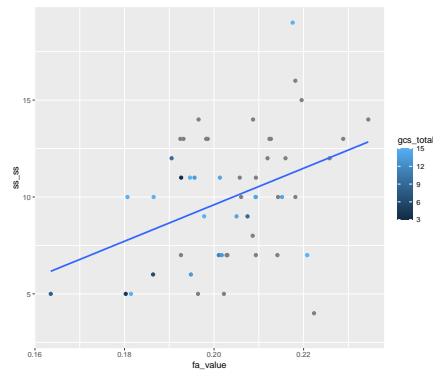
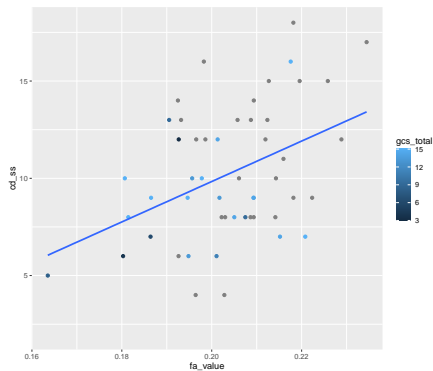
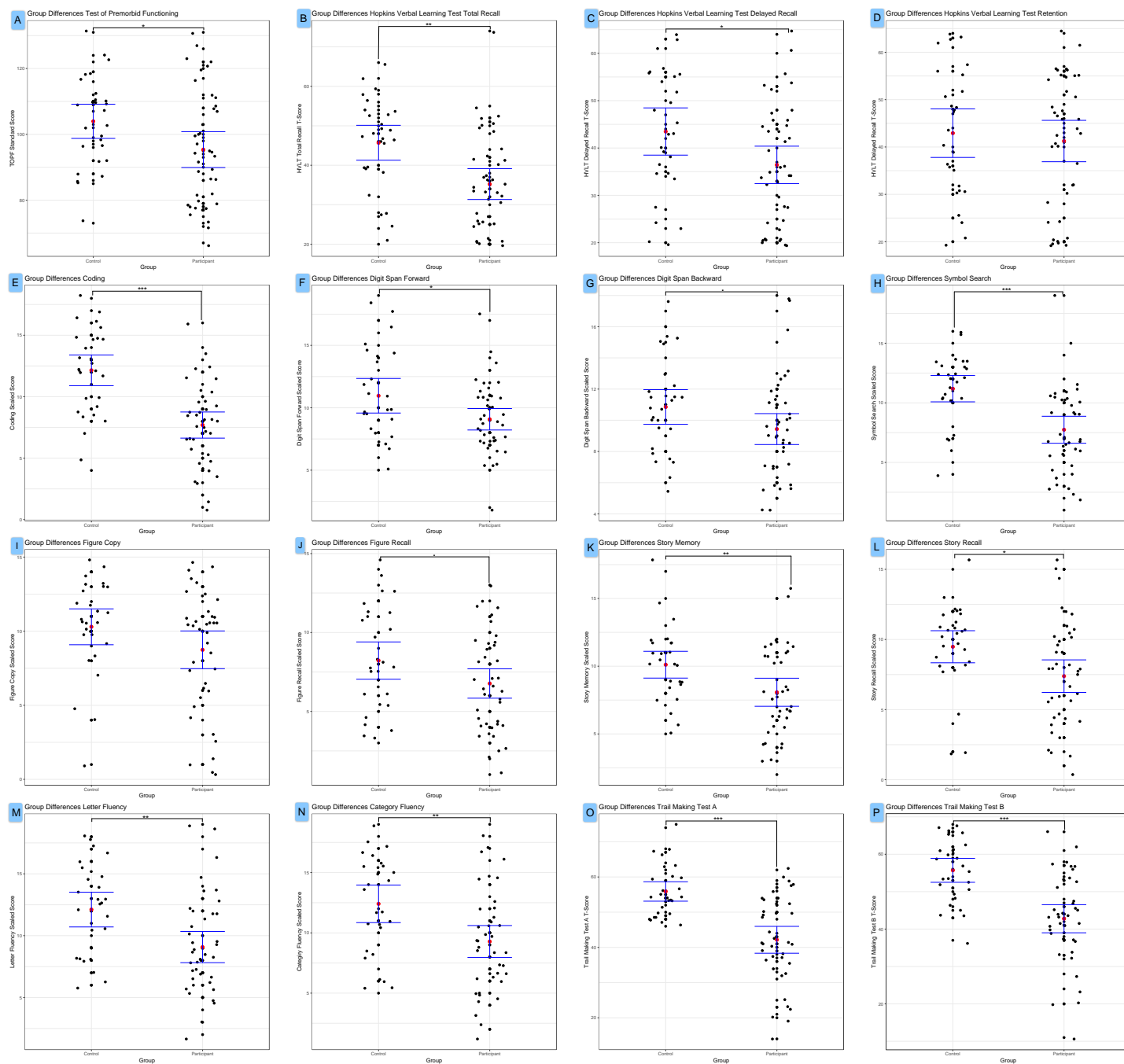


Figure 2. Differences Between Groups on Neuropsychological Measures



Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Some of these are rather small and challenging to appreciate, let's discuss.

Table 1.
Participant Demographics

Characteristic	Control (N = 23)		Participant (N = 33)	
	M	SD	M	SD
Education	15.85	2.76	13.74	2.88
Age	63.26	6.99	62.77	7.47
Sex	12 Male, 11 Female		29 Male, 4 Female	
Time Post Injury (years)	NA	NA	9.23	5.24
PTA (days)	NA	NA	20	17.65
TOPF Standard Score	103.96	13.78	95.36	17.39

Table 2.
One-way ANOVA Test Results: Healthy Controls Versus Participants Performance on Neuropsychological Assessment

Task	Control		Participant		F	Sig.
	M	SD	M	SD		
HVLT-R Total Recall	45.70	11.71	35.23	12.44	11.86	**
HVLT-R Delayed Recall	43.48	13.21	36.44	12.58	4.803	*
HVLT-R Retention	42.93	13.59	41.26	13.92	0.234	.
Coding	12.15	3.31	7.69	3.39	28.09	**

Digit Span Forward	10.96	3.67	9.08	2.74	5.713	*
Digit Span Backward	10.85	2.94	9.44	3.16	3.384	.
Symbol Search	11.19	2.92	7.74	3.60	16.9	***
Figure Copy	10.30	3.21	8.74	4.06	2.757	.
Figure Recall	8.22	3.13	6.77	2.96	3.669	.
Story Memory	10.11	2.62	8.08	3.30	7.12	**
Story Recall	9.48	3.03	7.38	3.70	5.908	*
Letter Fluency Category	12.11	3.72	9.08	4.01	9.677	**
Fluency	12.41	4.13	9.29	4.22	8.886	**
Trail-making form A	55.89	7.31	42.15	12.17	27.46	***
Trail-making form B	55.70	8.47	42.77	11.97	23.36	***

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Table 3.

Mean Values, Standard Deviations, and Confidence Intervals of the CSF Volume and FA in Controls versus Participants

Variable	Control		Participant	
	Mean	SD	Mean	SD
FA (dimensionless)	0.2113	0.0112	0.1981	0.0112

Table 4.

Mean Values, Standard Deviations, and Confidence Intervals of FA in Mild, Moderate, and Severe TBI

Variable	Mild		Moderate		Severe	
	Mean	SD	Mean	SD	Mean	SD
FA (dimensionless)	0.2008	0.01238	0.1997	0.0086	0.1807	0.0125

Table 5.*Shapiro Wilks Test of Normality*

Test	P-value
HVLT-R Total Recall	0.04314*
HVLT-R Delayed Recall	0.006935*
HVLT-R Retention	0.002003*
Coding	0.461
Digit Span Forward	0.0207*
Digit Span Backward	0.01277*
Symbol Search	0.2261
Figure Copy	0.000001455*
Figure Recall	0.1142
Story Memory	0.00362*
Story Recall	0.04204
Letter Fluency	0.08471
Category Fluency	0.08743
Trail-making form A	0.04595*
Trail-making form B	0.05206

*p<0.05

Table 6.*One-way ANOVA Test Results: Impact of Differentiating WMI Levels on Participant Performance on Neuropsychological Assessment*

Test	P-value	F-value
HVLT-R Total Recall	0.016*	6.232

HVLT-R Delayed Recall	0.0135*	6.566
HVLT-R Retention	0.104	2.742
Coding	0.00242	10.24
Digit Span Forward	0.269	1.251
Digit Span Backward	0.131	2.362
Symbol Search	0.0047*	8.777
Figure Copy	0.902	0.015
Figure Recall	0.041*	4.407
Story Memory	0.0184*	5.952
Story Recall	0.0142	6.465
Letter Fluency	0.0168*	6.133
Category Fluency	0.0413*	4.39
Trail-making form A	0.00000505*	19.75
Trail-making form B	0.00294	9.801

*p<0.05

Table 7. Overall Linear Regression Model Results

Test	ΔR^2	F-value	p-value
HVLT-R Total Recall	0.1636	2.369	0.1046
HVLT-R Delayed Recall	0.3437	4.666	0.01395*
HVLT-R Retention	0.2063	2.819	0.06832
Coding	0.1537	2.271	0.115
Digit Span Forward	0.08595	1.658	0.2115
Digit Span Backward	0.1264	2.013	0.1482
Symbol Search	0.2358	3.159	0.05003*
Figure Copy	0.08586	1.657	0.2116
Figure Recall	0.1219	1.972	0.1543
Story Memory	0.1802	2.538	0.08897
Story Recall	0.3055	4.079	0.02251*
Letter Fluency	0.116	1.919	0.1627
Category Fluency	0.1227	1.979	0.1532
Trail-making form A	0.3266	4.395	0.01734*
Trail-making form B	0.2105	2.866	0.06542

*p<0.05

Appendix A

Due to the risk of copyright infringement and continued use of these assessments in research and clinical settings, digital copies of the neuropsychological assessments could not be provided. Below you will find a list of the assessments that were utilized in this specific study and their publishing companies.

Table 8.

List of Neuropsychological Assessments and Associated Publishing Companies

Neuropsychological Assessment	Publishing Company
Boston Naming Test (BNT)	Pro-ed Inc.
Delis-Kaplan Executive Function System (DKEFS)	Pearson Publishing
Hopkins Verbal Learning Test- Revised (HVLTR)	PAR Publishing
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	Pearson Publishing
Trail Making Test A & B	
WAIS-IV Digit Span Forward & Backward	Pearson Publishing

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Emily Ellen Carter

EDUCATIONAL HISTORY

B.S. (anticipated): Psychology, Pennsylvania State University, May 2023
H.S. Diploma: Briar Woods High School, Ashburn, VA, June 2019

HONORS AND AWARDS

Spring 2023	Costello Family Scholarship in Psychology , Penn State University, Department of Psychology
Spring 2023	Graham Open Doors Honors Scholarship Recipient , Penn State University, Schreyer Honors College
Fall 2022 – Spring 2023	Penn State Academic Grant Recipient , Penn State University
Fall 2022	Poole Family Honors Scholarship Recipient , Penn State University, Schreyer Honors College
Spring 2022	Whitney Family Open Doors Honors Scholarship Recipient , Penn State University, Schreyer Honors College
Fall 2021 - Present	Schreyer Honors Scholar , Penn State University
Fall 2021 - Spring 2022	Liberal Arts Enrichment Fund Recipient , Penn State University, College of Liberal Arts
Fall 2019 - Present	Schwartz Trustee Scholarship Recipient , Penn State University, College of Liberal Arts
Fall 2019 - Present	Federal Pell Grant Recipient , Penn State University
Fall 2019 - Present	Dean's List , Penn State University

RESEARCH EXPERIENCE

The Pennsylvania State University Relationships and Stress Research Laboratory

Research Assistant/Lab Manager, Fall 2020 - Present

Principle Investigator: Amy D. Marshall, Ph.D.

- Examine the mechanisms and factors that influence the occurrence of psychological and physical violence in intimate partnerships
- Analyze behavioral data from individuals who have survived intimate partner violence (IPV) and healthy control participants
- Responsible for undergraduate research assistants
- Attend laboratory meetings

The Pennsylvania State University Brain Injury and Neuroplasticity Laboratory

Research Assistant, Spring 2021 - Present

Principle Investigator: Frank G. Hillary, Ph.D.

- Investigate structural, functional, and cognitive changes over the course of recovery following traumatic brain injury using neuroimaging techniques and neuropsychological testing
- Collect and analyze behavioral, genetic, and brain imaging data from individuals with traumatic brain injury and healthy control participants
- Administer and score comprehensive neuropsychological assessments to victims of domestic violence with and without resulting head trauma
- Collect and analyze behavioral data, information from structured and semi-structured interviews, and brain imaging data from individuals who have experienced domestic violence with and without brain injury
- Assist in development of research ideas, projects, and manuscripts
- Collaborate with fellow researchers
- Attend laboratory meetings

The University of Florida Department of Clinical Health and Psychology

Research Assistant, Fall 2022 - Present

Principal Investigator: Russell Bauer, Ph.D., ABPP

- Register patients into the National Neuropsychological Network (NNN)
- Enter patient neuropsychological data into the National Neuropsychological Network (NNN) using both the Q-Interactive and SAILOR/SHiP programs.
- Attend laboratory meetings

The University of Florida Department of Clinical Health and Psychology

Research Assistant, May 2022 - Present

Principal Investigators: Aliyah Snyder, Ph.D. Jessica Bove, M.S.,

- Investigating the various biological, behavioral and psychological impacts of persistent post-concussion symptoms in youth

The University of Florida Department of Clinical Health and Psychology

Research Assistant, May 2022 - August 2022

Principal Investigators: Catherine Tocci, M.S., William M. Perlstein, Ph.D.

- Studied the efficacy of computerized attention training in survivors of TBI

The University of Florida Department of Clinical Health and Psychology

Research Volunteer, Summers 2021, 2022

Principal Investigators: Russell Bauer, Ph.D., ABPP

- Entered patient neuropsychological data into the National Neuropsychological Network (NNN) using both the Q-Interactive and SAILOR/SHiP programs

The University of Florida Summer Undergraduate Research Fellowship (SURF) Program

Fellowship Student, May 2021 - August 2021

Principal Investigators: Dr. Lisa Scott, Ph.D., Dr. Lori Knackstedt, Ph.D., Dr. Andreas Keil, Ph.D.

- Dr. Lisa Scott
 - Studied the development of facial recognition in infants through the use of EEG analysis and other perceptual, cognitive, or social factors
- Dr. Lori Knackstedt
 - Investigated the effects of polysubstance use on the GLT-1 protein in the rodent brain by using microscopy and other cell analysis methods
- Dr. Andreas Keil
 - Examined oscillatory brain activity and behavior through EEG imaging methods

PUBLICATIONS

Mesa, J., **Carter, E.**, Padovan-Hernandez Y., Knackstedt, L. (accepted). *Alcohol consumption modulates Prelimbic cortex responding to cocaine in sequential cocaine and alcohol polysubstance use.*

MANUSCRIPTS IN PREPARATION

Carter, E., Hillary, F.G. (in prep). *Association Between White Matter Integrity and Intraindividual Variability in Neuropsychological Assessment Performance Following Traumatic Brain Injury.*

Snyder, A., **Carter, E. E.**, Bove, J., Choe, M., Giza, C., Babikian, T., Asarnow, R. (in prep). *The Influence of Baseline Psychophysiological Stress Responses, Mood and Coping Style on Neuropsychological Performance in Youth with Persistent Post Concussive Symptoms.*

- Intend to submit to Clinical Journal of Sports Medicine, Frontiers of Neurology, Brain Injury, or Archives of Clinical Neuropsychology

CONFERENCE PRESENTATIONS

Carter, E. E., Bove, J., Snyder, A., Choe, M., Giza, C., Babikian, T., Asarnow, R. (2023, February). *The Impact of Pain Catastrophizing on Neuropsychological Performance in Youth with Persistent Post Concussive Symptoms.* Poster presented at the 51st Meeting of the International Neuropsychological Society. February 2023, San Diego, California.

Cwiek, A., **Carter, E. E.**, Vervoordt, S. M., & Hillary, F. G. (2023, February). *Quality or quantity? Predicting quality of life in a chronic brain injury population with objective participation and subjective interpretation.* Poster presented at the 51st annual meeting of the International Neuropsychological Society. February 2023, San Diego, California.

Carter, E. E., Mesa J., Padovan-Hernandez Y., Knackstedt L., (2022, April). *Distinct Activity in Reward Neurocircuitry in a Rodent Model of Cocaine-Alcohol Polysubstance Use.* Pennsylvania State University Psi Chi Annual Conference, State College, PA.

Carter, E. E., Zhang Z., Marshall, A. D., (2021, April). *Does the numbers of People College Students Live with Affect their Experience of COVID Related Stress?* Pennsylvania State University Psi Chi Annual Conference, State College, PA.

Meyer, J., **Carter, E. E.**, Hillary, F. G., (2021, April). *Serotonin's Role in the Development of Spirituality.* Pennsylvania State University Psi Chi Annual Conference, State College, PA.

CLINICAL EXPERIENCE

Research Examiner

Penn State University, Brain Injury and Neuroplasticity Lab, University Park, PA

Supervisor: Frank Hillary, Ph.D.

- Administer and score comprehensive neuropsychological assessments to older adults with moderate-severe TBI and victims of domestic violence
- Assessments are part of research protocol associated with laboratory study that includes neuroimaging portion

Student Examiner

University of Florida, Norman Fixel Center for Neurological Diseases, Gainesville, FL

Supervisor: Aliyah Snyder, Ph.D.

- Clinical observation for the duration of summer 2022
 - Brain Injury Rehabilitation and Assessment Interdisciplinary Clinic
 - Holistic Intervention for Brain Health and Recovery Clinic (HI-BHaR)

Student Examiner

University of Florida, Norman Fixel Center for Neurological Diseases, Gainesville, FL

Supervisor: Russell Bauer, Ph.D., ABPP

- Clinical observation for the duration of summer 2021
 - Brain Injury Rehabilitation and Assessment Interdisciplinary Clinic

TEACHING EXPERIENCE**Study Abroad Teaching Assistant/Trip Coordinator (Spring 2023)**

Supervisor: Cathleen Hunt, Ph.D., Alicia Drais-Parillo, Ph.D.

PSYCH 212: Developmental Psychology, PSYCH 256: Multicultural Psychology

Location: Rome, Italy

- Assisted supervisors in coordinating educational experiences abroad
- Created assignments based on trip objectives
- Communicated trip goals and guidelines to students
- Mentored fellow students regarding the trip
- Held weekly meetings leading up to the trip

Head Undergraduate Teaching Assistant (Spring 2022 - Present)

Supervisor: Cathleen Hunt, Ph.D.

PSYCH 212: Developmental Psychology

- Created questions for lecture-based quizzes
- Attended weekly teacher's assistant meetings
- Aided students inquiring about class expectations and course content
- Mentored fellow undergraduate students
- Held weekly office hours

Undergraduate Teaching Assistant (Fall 2021)

Supervisor: Dustin Elliott, Ph.D.

PSYCH 100: Introduction to Psychology

- Created questions for exams throughout the semester
- Administered review sessions for students
- Held weekly office hours

GUEST LECTURES

Carter, E. | *Concussion in Youth: Symptoms, Testing, and Intervention.* The Pennsylvania State University; Spring 2023

Carter, E. | *Diffuse Axonal Injury and Its Impacts Through Childhood, Adolescence, and Adulthood.* Department of Psychology. The Pennsylvania State University; Fall 2022

Carter, E. | *Psychiatric Comorbidities Following Traumatic Brain Injury in Adults.* Department of Psychology. The Pennsylvania State University; Fall 2022

Carter, E. | *Efficacy and Ecological Validity of Neuropsychological/Neurophysiological Tests of Traumatic Brain Injury.* Department of Psychology. The Pennsylvania State University; Fall 2022

Carter, E. | *Sports and Its Impacts on Developmental Trajectories in Youth.* Department of Psychology. The Pennsylvania State University; Spring 2022

Carter, E. | *Traumatic Brain Injury, Concussion, and Sport-Related Head Injuries.* Department of Psychology. The Pennsylvania State University; Spring 2022

Carter, E. | *The Basics of Schizophrenia.* Department of Psychology. The Pennsylvania State University; Fall 2021

SELECTED PANELS

February 2023 Panelist, “Successfully Preparing Yourself for Postgraduate Endeavors in Psychology” (Student Events Committee), Pennsylvania State University (State College, PA)

SPECIALIZED GRADUATE COURSEWORK

- **Psychology 511** - Specialization in Cognitive and Affective Neuroscience (Spring 2022)
- **Psychology 554** - Clinical Assessment (Fall 2022)
- **Psychology 556** - Clinical Neuropsychology (Spring 2023)

PROFESSIONAL DEVELOPMENT

Mental Health First Aid Training, Pennsylvania State University;
 PA Mandated Reporter Training, Pennsylvania State University;
 SLEIC 3T MRI Safety and Technology Training, Pennsylvania State University;
 HIPAA and Privacy - General Awareness, University of Florida

PROFESSIONAL ACTIVITIES

July 2021-Present KnowNeuropsychology Webinar Series

PROFESSIONAL MEMBERSHIPS

Spring 2022 - Present Psi Chi, The International Honors Society in Psychology,
Distinguished Member

SERVICE AND LEADERSHIP

Spring 2022 - Present Psi Chi, The International Honors Society in Psychology, Penn State University, *Secretary*

Spring 2022 Introduction to Statistics, Penn State University, *Student Tutor*

Spring 2022 Psi Chi Annual Research Conference, Penn State University,
Student Judge

Fall 2021 - Present	Christian Student Fellowship, Penn State University, <i>Secretary</i>
Fall 2021 - Present	Department of Psychology, Penn State University, <i>Exam Proctor</i>
Summer 2021	Summer Undergraduate Research Fellowship, University of Florida, <i>Student Speaker</i>

CAMPUS ACTIVITIES

Spring 2021 - Present	Daily Collegian News Reporter, Penn State University
Spring 2021 - Present	Christian Student Fellowship, Penn State University
Fall 2019 - Present	Club Gymnastics Team, Penn State University

SKILLS

Computer: Proficient in R Studio, SPSS, MATLAB, Qualtrics, and RedCap
Brain Imaging: fMRIPrep, BIDS, MRtrix3

REFERENCES

Available upon request

Appendix

Tests Administered

- Boston Naming Test
- California Verbal Learning Test, Third Edition
- Clinician-Administered PTSD Scale for DSM-5
- Clock Drawing Test
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Delis Kaplan Executive Function System
 - Trail Making Test, Conditions 1-5
 - Color-Word Interference
 - Verbal Fluency
- Grooved Pegboard Test

- Judgment of Line Orientation Test
- Mindfulness Awareness of Attention Scale-Lapses Only
- NIH Toolbox
- Ohio State Traumatic Brain Injury Identification Method (OSU TBI-ID)
- The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- Rey Complex Figure Test
- Stroop Color-Word Test
- Test of Memory Malinger
- Trail Making Test A and B
- Wechsler Adult Intelligence Scale IV
- Wechsler Memory Scale IV

Tests Trained

- Beck Depression Inventory (BDI)
- Beck Anxiety Inventory (BAI)
- Brain Injury Screening Questionnaire (BISQ)
- Controlled Oral Word Association Test (COWAT)
- Glasgow Coma Scale (GCS)
- Geriatric Depression Scale (GDS)
- Mini Mental State Examination (MMSE)
- Montreal Cognitive Assessment (MoCA)