EXAMINING DEPRESSION AS A MARKER FOR DECLINE IN OLDER ADULTS WITH A HISTORY OF MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

A Thesis in

Psychology

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Abstract

Objective: To examine psychological outcomes, cognitive ability, genetic risk, and hippocampal differences in an older sample of adults with a history of traumatic brain injury (TBI) with a specific focus on the impact of depressive symptomatology. Method: In this study preregistered with the Open Science Framework, 121 participants with a history of moderate to severe or complicated mild TBI were included. All participants underwent buccal swabs for genetic testing, a comprehensive neuropsychological battery, surveys, and 46 participants underwent an MRI scan. Results: APOE e4 carrier status significantly predicted clinically significant depressive symptomatology on the Geriatric Depression Scale (GDS) with an odds ratio of 3.63 ($p = .01$), and carriers presented with a higher mean GDS score ($p = .053$). GDS was not predictive of scores on measures of executive function ($p = .71$), delayed recall ($p = .40$), or retention ($p = .68$). Although GDS score was initially associated with poorer semantic memory scores ($p = .04$), this significance dropped out in a linear model that included age and cognitive reserve. Higher GDS scores were associated with decreased hippocampal volume as a ratio of whole brain volume ($p = .04$) but were not associated with hippocampal asymmetry ($p = .84$) in models that included GDS score, time post injury, and the interaction between these two variables. Conclusions: APOE carrier status was predictive of depression in a sample of older individuals with a history of TBI a mean of 10 years post-injury. Depressive symptoms were also associated with decreased hippocampal volume but did not predict cognitive deficits in the examined domains above and beyond the effects of age and cognitive reserve. These results indicate that despite the relationship between depression and biological risks for decline, depressive symptoms in older adults with moderate to severe TBI (mSTBI) may not lead to exacerbated cognitive decline, which is better predicted by other factors (e.g., cognitive reserve).
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Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability in the United States (Peterson, Xu, Daugherty, & Breiding, 2019). In 2014, there were about 2.87 million documented emergency department visits, hospitalizations and deaths related to TBI (Peterson, Xu, Daugherty, & Breiding, 2019). Previously, it was believed that once the initial symptoms of TBI plateaued, those residual effects remained static. However, emerging research has shown that TBI at any age can lead to long-term complications (Corrigan & Hammond, 2013). Long-term cognitive decline after a traumatic brain injury event is influenced by multiple factors, such as sex and age-at-injury, and these deficits are seen globally in most cognitive domains, with the notable exception of semantic memory (Himanen et al., 2006).

Depression and Decline

Depression is the most common psychiatric symptom resulting from TBI (Seel et al., 2010). After a moderate to severe TBI (msTBI), rates of major depressive disorder (MDD) range from 26%-36%, and this can further impact post-injury outcomes (Seel et al., 2010). A prospective study from Dikmen and colleagues found that in a cohort of 283 individuals with moderate to severe TBI, 46% endorsed clinically significant depression 1 month post-injury, and 30% of this sample met for clinically significant depression 3 to 5 years out, though these symptoms generally decreased in severity with increased time post-injury (Dikmen et al., 2004). Additionally, Holsinger and colleagues found that for older veterans that had sustained a closed head-injury 50 years prior, current depression rates were 11.2% within this sample, compared to 8.5% of controls, demonstrating an increased risk for depression decades post-injury (Holsinger et al., 2002). Data from a national survey of 36,309 US adults collected from 2012 to 2013 found a 10.4% 12-month prevalence of MDD and a 20.6% lifetime prevalence in the general population (Hasin et al., 2018).
All this suggests a normalization of depression rates in the decades following the initial injury. Despite the fact that depression is a common sequela post-TBI, relatively little research has been done in terms of its cognitive impact for msTBI populations.

**Aging and Cognitive Decline**

Aging is associated with a number of health risks. Beginning in early adulthood, there is general decline in a number of cognitive domains, such as executive function and memory, and individual differences in age-related decline may be mediated by a number of different factors (Deary et al., 2009). As individuals get older, risk for depression also increases, though this is likely a direct result of health and social factors, and these rates for depression reach a peak in adults aged 80 and older (Mirowsky & Ross, 1992). Additionally, in TBI, age of injury also confers differential dementia risk (Johnson & Stewart, 2015). One study by Johnson and Stewart showed that even mild TBI occurring at age 65 and older conferred additional risk for dementia outcomes (2015). Within the scope of the present study, time post injury and age were both examined in place of age at injury to examine any potential individual interactions with depressive symptoms.

New research within the last decade shows that there is a link between TBI and dementia-onset later in life (Bittar et al., 2017; Corrigan & Hammond, 2013; Gottlieb, 2000; Kenney et al., 2018; Lucke-Wold et al., 2014; Magnoni et al., 2012; Sayed et al. 2013). Moderate TBI has been shown to double the risk for developing dementia, while severe TBI quadruples this risk (Gottlieb, 2000). While msTBI at any age is associated with increased dementia risk, mild TBI may be a more significant risk factor only for those with an older age-at-injury, especially in those 65 and older (Gardner et al., 2014). There are several interwoven mechanisms post-TBI that may set the stage for neurodegenerative processes leading to or exacerbating dementia, specifically dementia of the Alzheimer’s type (AD).
In addition to TBI, depression has also been shown to serve as a risk factor for dementia (Byers & Yaffe, 2014; Diniz et al., 2013). Green and colleagues examined over 1700 individuals that met criteria for probable AD and 175 individuals with autopsy-confirmed diagnoses of AD. Reports of depressive symptoms from surrogate sources revealed a significant association between depressive symptoms and AD (Green et al., 2003). Although this association between depression and AD is strongest when onset of depressive symptoms occurred within 1 year before onset of AD, the association still exists even for individuals for whom the onset of depressive symptomatology occurred more than 25 years prior to AD onset (Green et al., 2003). This association may in part reflect overlapping symptoms of depression and early symptoms of AD (Green et al., 2003). Apart from cognitive decline due to dementia, depression is also known to exacerbate other existing medical issues and impair cognition (Steffens et al., 2006).

**Cognitive Changes in TBI and Depression**

Both TBI and depression can lead to global cognitive deficits (Corrigan & Hammond, 2013; Himanen et al., 2006; McIntyre et al., 2013). In an older sample of veterans with a lifetime history of TBI, Kaup and colleagues found that individuals had impaired processing speed and executive function compared to healthy controls but performed similarly to controls in the domains of working memory, learning, and language (Kaup et al., 2016). The same study determined that a history of multiple mild TBIs or a single msTBI were more strongly associated with deficits than a history of a single mild TBI (Kaup et al., 2016). Further, a 30-year longitudinal study in Finland found that 30 years after a significant TBI, there was a general trend for improved semantic memory, despite overall cognitive decline, and this is a profile that directly contrasts that of AD (Himanen et al, 2006).
There is an additional relationship between the hippocampus and visual confrontation naming, which can be tested via neuropsychological tasks such as the Boston Naming Test (BNT) (Sawrie et al., 2000). Impairment on this task is common in AD (Williams, Mack, & Henderson, 1989). And although depressed patients experience psychomotor impairments, impaired free recall, and hippocampal degeneration, they are not impaired in terms of semantic memory or recognition memory (Ilsley, Moffoot, & O’Carroll, 1995; McDermott & Ebmeier, 2009; Steffens et al., 2000). Scores for recognition and delayed recall on the Hopkins Verbal Learning Test – Revised (HVLT-R), a list-learning memory task, have also been shown to reliably discriminate between depression and dementia (Lachner, Satzger, & Engel, 1994), and retrieval and retention have been shown to be unaffected by depression in the absence of anxiety (Kizilbash, Vanderploeg, & Curtiss, 2002).

Of note, clinical presentation of cognitive decline and AD is moderated by education, a concept known as cognitive reserve (Roe et al., 2007; Cosentino & Stern, 2019). Other studies have examined different variables such as premorbid IQ and occupation as proxies for cognitive reserve (Jones et al., 2011). Greater cognitive reserve has more recently been shown to moderate the effects of depressive symptoms on cognition in a healthy sample (O’Shea et al., 2015). Among those with neuropathologic diagnoses of AD post-mortem, more highly educated individuals were less likely to present with the same outward symptomatology while alive and were less likely to receive a diagnosis while alive (Roe et al., 2007; Stern, 2006). This is of particular importance when attempting to disentangle the differential chronic effects of TBI and other risk factors on subsequent cognitive outcomes in aging samples.
Genetic Risk for Depression (APOE)

APOE genotype has long been considered the most significant genetic risk factor for the development of dementia, specifically Alzheimer’s Disease (AD) (Michaelson, 2014). Estimates of e4 allelic frequency vary widely around the world, ranging as low as 5.2% in Sardinians to as high as 40.7% in certain African populations (Corbo & Scacchi, 1999). Despite a relatively low frequency globally, the e4 allele is found in as many as 48%, and these estimates also vary, ranging from an estimated 45.61% of cases in Asia to an estimated 66.95% of cases in Northern Europe (Ward et al., 2012). This risk conferred by the e4 allele increases with two e4 alleles, and those with this e4/e4 genotype were more than eight times as likely to develop AD compared to those with e2/e3 or e3/e3 genotypes (Corder et al., 1993). Additionally, e4 genotypes were also associated with a younger age of onset for AD (Corder et al., 1993), and this risk is exacerbated for patients with a history of msTBI (LoBue et al., 2017; Teasdale, Nicoll, Murray, Fiddes, 1997).

More recently, APOE genotypes have been studied as a potential risk factor for depression. The APOE e4 allele is significantly associated with depression, and depressed patients carrying the e4 allele display more severe symptomatology than non-carriers (Wang, Liu, Wang, & Bao, 2019). Older studies however, such as a study from 2000 from Mauricio and colleagues, found that APOE genotype was not associated with depression within an elderly sample (Mauricio et al., 2000; Schmand et al., 1997). Additionally, a 2004 study found that in a cohort an average 30 years post-TBI, APOE genotype predicted AD onset, but it was not predictive of psychiatric disorders in a sample examining a range of TBI severities (Koponen et al., 2004). A separate 2004 study found that APOE carrier status did not affect outcomes for mild to moderate TBI patients 6 months post-injury, including depression outcomes (Chamelian, Reis, & Feinstein, 2004). However, this is in contrast to more recent research. In a 2018 study, Merritt and colleagues found that for
veterans with a history of mild to moderate TBI, those that were e4 carriers were at higher risk for psychiatric symptoms, including depression, but e4 status did not increase symptom severity for military controls with no TBI history (Merritt et al., 2018). These contradictory results certainly merit further research, especially given that in the general population, the e4 allele has also been associated with elevated risk for depression (Feng et al., 2015). To date, there has been little research surrounding psychiatric outcomes for msTBI patients with the e4 allele, especially within geriatric samples that look at the chronic effects of msTBI.

**Hippocampal Changes**

Depression is associated with decreased hippocampal volume in addition to the cognitive deficits previously described (Steffens et al., 2000; Videbech & Ravnkilde, 2004). In addition to this, AD is also associated with decreased hippocampal volume, and in the elderly, reduced hippocampal volume can predict the onset of dementia (Wolf et al., 2001). A study by Wolf et al. found that reduced hippocampal volume and increased hippocampal asymmetry were associated with cognitive decline in questionable and mild dementia compared to healthy controls (2001). One meta-analysis that examined mild cognitive impairment (MCI) and AD across 14 studies found that on average in MCI, there was 12.9% reduction in the left hippocampus and 11.1% reduction in the right hippocampus (Shi, Liu, Zhou, & Jiang, 2009). In AD, there was an average 24.2% and 23.1% reduction in these same regions (Shi, Liu, Zhou, & Jiang, 2009). However, Barnes and colleagues show the opposite trend in hippocampal asymmetry with AD progression. Their study examined 32 cases of probable AD compared to 50 age-matched controls and found slightly greater atrophy in the right hippocampus compared to the left (Barnes, Sahill, Frost, Rossen, & Fox, 2009). Although these differences were relatively subtle, we chose to look at
hippocampal symmetry to examine any potential differences as a result of depressive symptomatology. This methodology is further elaborated on in the Methods section.

A 2007 study found that in an msTBI population evaluated at baseline and 3, 6, and 12 months post-injury, those that developed mood disorders were at higher risk for decreased hippocampal volume (Jorge, Acion, Starkstein, & Magnotta, 2007). However, there are not many studies examining these volumetric differences in msTBI patients with mood disorders, and there is a particular gap in the literature for studies examining these differences many years post-injury. The present study examined both hippocampal volume and hippocampal asymmetry in the presence of depressive symptomatology post-TBI.

**Goals and Hypotheses**

This preregistered study examined scores on cognitive assessments that are significantly impacted by cognitive decline in aging and AD. More specifically, scores on semantic memory tasks were examined, which may be reflective of a differential pattern of decline as previously described that should not be greatly impacted by TBI history or depression alone. Additionally, this study included executive function scores and scores on a non-semantic memory task to assess potentially differential patterns of cognitive decline with increasing depressive symptomatology post-TBI.

The purpose of this study was to examine patterns of cognitive decline in an older population of adults with a history of msTBI based on depressive symptomatology. This study specifically aimed to: 1) Examine the risk for depression based on APOE e4 carrier status; 2) Examine potential differential decline in three cognitive domains (executive functioning, delayed recall and retention, and semantic memory) based on depressive symptomatology, controlling for additional variables in a stepwise fashion; and 3) Examine differences in hippocampal volume and
differences in hippocampal symmetry based on depressive symptomatology, time post injury, and the interaction between these two variables. It was hypothesized that the presence of the APOE e4 allele would be related to increased depressive symptomatology as assessed by the Geriatric Depression Scale (GDS) and that the presence of the e4 allele would lead to an increased risk for clinically relevant depression. It was also hypothesized that depressive symptomatology would be associated with poorer executive functioning, delayed recall and percent retention, and semantic memory. Finally, it was hypothesized that depressive symptomatology would be associated with decreased hippocampal volume and increased hippocampal asymmetry. All hypotheses were preregistered with the Open Science Framework prior to data analysis (Link: https://osf.io/edg5w).

Materials and Methods

Participants

This study included data from an existing protocol funded by the PA-DOH including data collection at Hershey Medical Center in Hershey, PA, Moss Rehabilitation Institute in Philadelphia, and University Park, PA. Data was collected from 121 participants aged 50 and older with a history of moderate, severe, or complicated mild TBI. Classifications for TBI severity were as follows: moderate TBI was classified as a Glasgow Coma Scale (GCS) score of 9-12 and/or Post-Traumatic Amnesia (PTA) between 1-14 days, severe TBI was classified as a GCS score ≤ 8 and/or a PTA ≥ 15 days. Complicated mild TBI was classified as a GCS score of 13-15 and a PTA of 0 days with positive imaging findings indicative of trauma, such as hemorrhage. Exclusionary criteria included neurodevelopmental and psychiatric disorders such as schizophrenia, bipolar disorder, and autism. History of substance use and ADHD were not considered grounds for exclusion. Table 1 below presents demographics for the participants involved in the present study.
<table>
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<th>Characteristic</th>
<th>Complete Participant Group (N = 121)</th>
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<td>33 Male, 13 Female</td>
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<tr>
<td>Race</td>
<td>91 Caucasian, 30 African-American</td>
<td>34 Caucasian, 12 African-American</td>
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</tbody>
</table>

Table 1: Descriptive Information. The above table provides basic descriptive information for the 121 participants involved in the present study and the subset of 46 participants with MRI data.

**Procedure**

Hypotheses were preregistered at Open Science Framework (Link: [https://osf.io/edg5w](https://osf.io/edg5w)). The testing session comprised of consenting, buccal swabs for genetic data, a brief neuropsychological battery that assessed various measures of cognition that are often impaired following brain injury, including domains of attention, memory, and executive functioning. A subset of these participants underwent mock scan and then a 60-min MRI protocol that included structural scans, resting state, and task in addition to the consenting, genetics, and neuropsychological battery.
Neuropsychological Assessment

The primary measure used to assess executive function was a ratio score on Trail-Making form B to Trail-Making form A (Arbuthnott & Frank, 2000). The primary measure used to assess semantic memory was a modified Boston Naming Test (BNT) in which participants were only shown odd-numbered line drawings. The primary measure used to assess delayed recall and retention was the Hopkins Verbal Learning Test Revised Edition (HVLT-R). The Geriatric Depression Scale (GDS) was used to assess depressive symptoms and is comprised of 15 yes/no questions. A score of 5 or greater is considered indicative of depression, and this was viewed as a continuous variable for the purposes of this study, with higher scores indicating greater depressive symptomatology. Cognitive reserve was measured as a composite Z-score of education and standard scores for the Test of Premorbid Function (ToPF), which were correlated with one another ($r = .64$).

MRI Acquisition

Data were collected on one of three scanners at one of the following sites: Penn State Hershey Medical Center Department of Radiology on a Siemens 3T Prisma Fit scanner (N=8), an identical Siemens 3T Prisma Fit scanner at Moss Rehabilitation in Philadelphia (N=33), and a third identical Siemens 3T magnet at the Social, Life, and Engineering Sciences Imaging Center at University Park (N=5).

Structural Data

Anatomical structural scans were collected using an MPRAGE sequence at a spatial resolution of 1-mm x 1-mm x 1-mm voxels, with a repetition time (TR) of 2,300ms, echo time (TE) of 2.98 ms, and flip angle of 9 degrees. Slices were collected interleaved. Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis
suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/).

The “recon-all” pipeline in FreeSurfer was used to calculate hippocampal and intracranial volumes for this analysis (“FreeSurfer Analysis Pipeline Overview,” n.d.). The values for left and right hippocampus and estimated total intracranial volume were used in this analysis. Using a T1-weighted image from each subject, the processing stream performs skull stripping, volumetric labeling, intensity normalization, white matter segmentation, surface atlas registration, surface extraction, and gyral labeling (“FreeSurfer Analysis Pipeline Overview,” n.d.). This study examined the FreeSurfer default subcortical segmentation from the aseg.stats output. Each participant’s image was examined for misalignment or other gross distortions after completion of the processing stream.

*Note regarding analyses: Although the original preregistered hypotheses implied analyses that would examine GDS score alongside a number of other variables for the cognitive hypotheses within this study, depressive symptomatology became the primary predictor of interest. In light of this, GDS was examined in linear models in which it served as the only predictor, and subsequent stepwise analyses were performed to determine best fit models based on the other variables described. Additionally, HVLT-R percent retention was also examined alongside scores for delayed recall. This methodology is described in further detail in the Results section.

**Results**

* *APOE e4 and Depression*

<table>
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<th>Carriers (N=30)</th>
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<td>Age</td>
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<td>GCS Score</td>
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<td>4.25</td>
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<td>Sex</td>
<td>51 Male, 21 Female</td>
<td>24 Male, 6 Female</td>
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<tr>
<td>Race</td>
<td>55 Caucasian, 17 African-American</td>
<td>24 Caucasian, 6 African-American</td>
</tr>
</tbody>
</table>

Table 2: Demographic data for e4 carriers and noncarriers.

107 TBI participants had available and sufficient genetic data for analysis. Of these, 5 of these participants were left out of analyses due to missing or incomplete data for the Geriatric Depression Scale (GDS). Of the 102 included participants, 30 were APOE e4 carriers, and 72 were non-carriers. A two-samples independent T-test revealed a significant difference between the mean GDS scores for carriers ($M = 4.37$) and noncarriers ($M = 2.88$), $t = 1.99, p = .05$. Given concerns surrounding normality of the distribution following examination of a quantile-quantile plot, a Mann-Whitney Wilcoxon test, a nonparametric test, was chosen to examine differences in GDS score distributions between both groups. This test revealed a similar rank distribution between the two groups, $U = 831.5, p = .065$.

GDS scores were converted into a binary based on clinically significant cutoffs to determine whether or not e4 carrier status increased the likelihood of clinically relevant depression. Scores greater than or equal to 5 were considered indicative of clinically relevant depression based
on recognized cutoffs for the GDS. Within the carrier group, 14/30 participants endorsed clinical levels of depression (46.67%). Within the noncarrier group, 14/72 participants endorsed clinical levels of depression (19.44%). A logarithmic regression analysis was performed to determine the effect of genotype on depression. APOE e4 carriers were more likely to meet for clinically significant depression as assessed by the GDS by a factor of 3.63, $Z = 2.73$, $p = .006$, 95% CI [1.33, 9.29]. Overall, a model examining carrier status was significantly better at predicting clinically significant depression compared to an intercept-only model within the sample, $\chi^2 (1, N = 102) = 7.50, p = .006$.

Figure 1: Depression scores by APOE e4 Carrier Status. (A) Boxplot showing GDS score distribution by carrier status. (B) Plot showing GDS score distribution as a proportion of individual group. The horizontal line indicates the cutoff for clinically relevant depression. Scores falling above this line meet criteria for clinical levels of depression.
Cognitive Assessments

Overall, individuals with TBI showed characteristic deficits in the domains of executive function and delayed recall. When normed based on age-, race-, sex-, and education-corrected norms, participants had a mean T-score of 42.55 (± 11.49) for Trail-Making Form A and a mean T-score of 42.32 (± 11.75) for Trail-Making Form B, an average performance nearly one standard deviation below the mean for a healthy population based on Heaton Norms. When normed based on the Hopkins Verbal Learning Test-Revised Professional Manual by age-corrected normative data, participants performed at an average T-score of 33.31 (±14.24), nearly two standard deviations below the mean for a healthy population. Additionally, participants performed at a mean T-score of 39.76 (±20.44) for percent retention on the HVLT-R, determined by delayed recall divided by the highest of the final two learning trial scores, multiplied by 100. Participants performed at a mean T-score of 48.52 (±13.79) on the modified Boston Naming Test based on data provided by Lansing and colleagues (Lansing, Ivnik, Cullum, & Randolph, 1999), which is consistent with previous literature that has demonstrated intact semantic memory in patients with a history of msTBI (Himanen et al., 2006). Given that this group is impaired in the ways that would be expected in a TBI sample (Himanen et al., 2006; Lange, Iverson, Zakrzewski, Ethel-King, Franzen, 2002; Vanderploeg, Crowell, & Curtiss., 2001), raw scores were examined as Z-scores based on the sample population for each of the cognitive analyses. Both age and education (included as part of the cognitive reserve variable), which are considered for normed scores, were included in stepwise fashion to determine the overall impact of depression on scores for the cognitive assessments of interest. GDS was analyzed as a continuous variable. This was done in part because our sample did not contain enough variation in GDS to place them in groups of varying severity based on clinical cutoffs. Instead, examining depressive symptomatology as a
continuous score allowed us to take this severity into account even for those that did not meet clinical cutoffs.

Executive Function

Within the current sample, 105 participants had complete information and scores for the ToPF, education, GDS, and both Trails A and Trails B. Executive function was determined as a ratio of raw scores on Trails B/Trails A. A linear model with GDS score as a continuous variable predictor was analyzed initially. GDS score was not significantly associated with Z-scores for executive function, $t(103) = -0.07, p = .95, \eta^2 < .001$, 95% CI [-.08, .07]. Additional variables were added in stepwise fashion in the following order: time post injury, age, cognitive reserve, followed by the interaction variables: GDS*Time post injury, GDS*Age, GDS*Cognitive reserve. Time post injury and age were both centered at the mean. Stepwise analysis revealed a best fit model that included cognitive reserve and age. When the best fit model that included GDS score, cognitive reserve, and age was analyzed, only a significant effect of cognitive reserve emerged, such that for each one-unit increase in the cognitive reserve composite Z-score, the ratio of Trail B/Trail A decreased, $b = -.34, t(101) = -3.11, p = .002, \eta^2 = .09$, 95% CI [-.56, -.12]. Age was not a significant predictor of executive function in this model, $t(101) = 1.40, p = .17, \eta^2 = .02$, 95% CI [-.01, .05]. GDS score remained a non-significant predictor of executive function, $t(101) = -.38, p = .71, \eta^2 = .001$, 95% CI [-.09, .06]. Two data points were removed due to a studentized residual value greater than 3. Without these data points, the results of this analysis remained consistent. GDS remained a non-significant predictor of executive function in a model with only GDS as a predictor, and cognitive reserve remained the only significant predictor of executive function in a model that included cognitive reserve, age, and GDS score.
Delayed Recall

Within the current sample, 111 participants had complete information and scores for the ToPF, education, GDS, and the HVLT-R delayed recall. Delayed recall Z-scores were created using the raw scores of the sample. A linear model with GDS score as a continuous variable predictor was analyzed initially. GDS score was not significantly associated with Z-scores for delayed recall, $t(109) = -1.25, p = .21, \eta^2 = .01$, 95% CI [-.09, .02]. Additional variables were added in stepwise fashion in the following order: time post injury, age, cognitive reserve, followed by the interaction variables: GDS*Time post injury, GDS*Age, GDS*Cognitive reserve. Time post injury and age were both centered at the mean. Stepwise analysis revealed a best fit model that included cognitive reserve and age. When this best fit model that included GDS score,
cognitive reserve, and age was analyzed, only a significant effect of age and cognitive reserve emerged. With each standard deviation increase in the cognitive reserve composite Z-score, delayed recall Z-scores increased by .49, $t(107) = 5.00, p < .001, \eta^2 = .19, 95\% \text{ CI [.29, .68]}$. For each year increase in age, delayed recall Z-scores within the sample decreased by .03, $t(107) = -2.80, \ p = .006, \eta^2 = .07, 95\% \text{ CI [-.05, -.01]}$. Within this model, GDS score did not have a significant effect on delayed recall Z-scores, $t(107) = -.88, \ p = .38, \eta^2 = .01, 95\% \text{ CI [-.08, .03]}$.

Of these 111 participants, the percentage of retained information for delayed recall was also assessed. We examined this percentage based on the highest of the final two HVLT-R learning trial scores divided by the total delayed recall score. A linear model with GDS score as a
continuous variable predictor was analyzed initially. GDS score was not significantly associated with Z-scores for retention, $t(109) = -.49$, $p = .63$, $\eta^2 = .002$, 95% CI [-.07, .04]. Additional variables were added in stepwise fashion in the following order: time post injury, age, cognitive reserve, followed by the interaction variables: GDS*Time post injury, GDS*Age, GDS*Cognitive reserve. Time post injury and age were both centered at the mean. Stepwise analysis revealed a best fit model that included cognitive reserve and age. When this best fit model that included GDS score, cognitive reserve, and age was analyzed, none of the included variables emerged as a significant predictor. Although adding two predictors improved the overall model, neither cognitive reserve, $t(107) = 1.70$, $p = .09$, $\eta^2 = .03$, 95% CI [-.03, .40], or age $t(107) = -1.86$, $p = .07$, $\eta^2 = .03$, 95% CI [-.05, .001] significantly predicted retention scores. There was still not a significant effect of GDS on retention, $t(107) = -.41$, $p = .68$, $\eta^2 = .002$, 95% CI [-.07, .05], once both age and cognitive reserve were included as predictors.

However, one outlier was removed based on a studentized residual value greater than 3. Without this outlier, GDS remained a non-significant predictor of retention in a model that only included GDS as a predictor. After re-analyzing the linear model with GDS, age, and cognitive reserve without this data point, cognitive reserve emerged as a significant predictor of percent retention, such that each one unit increase in the cognitive reserve composite Z-score increased retention Z-score by .28, $t(106) = 2.64$, $p = .01$, $\eta^2 = .06$, 95% CI [.07, .49]. Both GDS and age remained non-significant predictors of retention in this model when this outlier was removed.
Semantic Memory

Within this TBI sample, 102 participants had complete information and scores for the ToPF, education, GDS, and the modified Boston Naming Test (BNT). BNT Z-scores were created from the raw scores of the sample. A linear model with GDS score as a continuous variable predictor was analyzed initially. GDS score was significantly associated with Z-scores on the BNT such that for each one-unit increase in GDS score, Z-scores for the BNT decreased by .27, $t(100) = -2.04, p = .04, \eta^2 = .04$, 95% CI [-.53, -.01]. Additional variables were added in stepwise fashion in the following order: time post injury, age, cognitive reserve, followed by the interaction variables: GDS*Time post injury, GDS*Age, GDS*Cognitive reserve. Time post injury and age were both
centered at the mean. Stepwise analysis revealed a best fit model that included cognitive reserve and age. When this best fit model that included GDS score, cognitive reserve, and age was analyzed, only a significant effect of age and cognitive reserve emerged. With each standard deviation increase in the cognitive reserve composite Z-score, there was a 2.20 increase in BNT Z-score, $t(98) = 5.14, p < .001, \eta^2 = .21$, $95\% \text{ CI } [1.35, 3.05]$. With each year increase in age, there was a .12 decrease in BNT Z-score, $t(98) = -2.55, p = .01, \eta^2 = .06$, $95\% \text{ CI } [-.21, -.03]$. There was not a significant effect of GDS on BNT score, $t(98) = -1.42, p = .16, \eta^2 = .02$, $95\% \text{ CI } [-.40, .07]$, once both age and cognitive reserve were included as predictors.

When two data points were removed based on a studentized residual value less than -3, a model with only GDS score as a predictor of BNT Z-scores remained significant, such that for each one unit increase in GDS score, BNT Z-scores decreased by .07, $t(98) = -2.41, p = .018, \eta^2 = .06$. However, without these data points, in a model that included age, and cognitive reserve, GDS dropped out as a significant predictor, $t(96) = -1.51, p = .13, \eta^2 = .02$, $95\% \text{ CI } [-.09, .01]$. Cognitive reserve remained a significant predictor of BNT Z-score, $b = .61, t(96) = 6.23, p < .001, \eta^2 = .29$, $95\% \text{ CI } [.42, .81]$. Age was not a significant predictor in this model, $t(96) = -1.74, p = .09, \eta^2 = .03$, $95\% \text{ CI } [-.04, .003]$ without these data points.
Hippocampal Differences

Of 46 participants with MRI data, 43 had complete GDS data. Hippocampal volume was measured as a ratio of whole brain volume and were converted to Z-scores based on the sample. Nearly one-third of participants had a hippocampal volume half a standard deviation or more below the mean, demonstrating variation in potential atrophy. In a model examining the effect of GDS score, time post injury, and the interaction between these two variables, depression emerged as a significant predictor of hippocampal volume, such that for every one point increase in GDS score, hippocampal volume Z-scores decreased by .1, $t(39) = -2.08, p = .04, \eta^2 = .10, 95\% \text{ CI } [-.19, -.003]$. There was a moderate negative correlation of -.30 between hippocampal volume and GDS score. Neither time post injury, $t(39) = .32, p = .75, \eta^2 = .003, 95\% \text{ CI } [-.06, .08]$, nor the
interaction between GDS score and time post injury, $t(39) = -.45, p = .65, \eta^2 = .005, 95\% CI [-.02, .01]$, had a significant impact on hippocampal volume. The overall model was not significant, $F(3,39) = 1.49, p = .23$. When time post injury and the interaction between time post injury and GDS score were removed from the model, GDS remained a significant predictor of volume, $t(41) = -2.11, p = .04, \eta^2 = .10$, and the overall model reached significance, $F (1, 41) = 4.46, p = .04$.

Hippocampal symmetry was measured as a ratio of left/right hippocampus. GDS score did not have a significant effect on hippocampal symmetry, $t(39) = -.21, p = .84, \eta^2 = .001, 95\% CI [-.11, .09]$. Likewise, time post injury did not have a significant effect on hippocampal symmetry, $t(39) = .24, p = .81, \eta^2 = .001, 95\% CI [-.06, .08]$. The interaction between GDS score and time

Figure 6: Hippocampal Volume by Depression.
post injury also had a non-significant effect, \( t(39) = -.83, p = .41, \eta^2 = .07, 95\% CI [-.03, .01]. \)

When one data point was removed based on a studentized residual value greater than 4, the effects of all three predictors remained non-significant.

**Discussion**

The goals of this study were to: 1) Determine the relationship between APOE genetic status and depression; 2) Determine the effects of depression on cognitive tasks; and 3) Determine the relationship between depressive symptomatology and hippocampal volume and symmetry in an older sample with a lifetime history of msTBI. First, we demonstrate that APOE e4 carrier status is associated with increased symptoms of depression in moderate and severe TBI even years post-
injury. In addition to the demographic similarities between the carrier and noncarrier groups demonstrated in Table 2, a T-test also revealed a nonsignificant difference in the cognitive reserve variable between the two groups \( (p = .38) \). Second, depressive symptomatology did not significantly predict scores on cognitive tasks measuring executive function or delayed recall and retention. Although depression was initially associated with semantic memory, this association dropped out when cognitive reserve and age were included as predictors. Of note, cognitive reserve was consistently the most significant predictor of variance for these cognitive tasks.

Finally, depressive symptomatology showed a moderate negative correlation with the ratio of hippocampal to whole brain volume even an average of nearly 10 years post injury. However, depression was not associated with hippocampal symmetry in this sample, in contrast to the some of the dementia literature examining onset of cognitive symptoms (Barnes, Scahill, Frost, Rosser, & Fox, 2009; Shi, Liu, Zhou, & Jiang, 2009; Wolf et al., 2001). In retrospect, it is perhaps unsurprising that this study did not show any differences in hippocampal symmetry given the small differences shown in the prior literature, and any differences in hippocampal volume may reflect a bilateral degeneration. For the five individuals with the lowest hippocampal volume, the average left/right hippocampal ratio Z-score was -.83 (± 1.10), nearly one standard deviation below the mean. This is particularly interesting given that this ratio data is not highly variable. Only five individuals fell one half standard deviation or more below the mean, and three of these individuals were captured in this pilot analysis based on the five lowest volumes. Based on this, it is possible that this asymmetrical atrophy does not appear until there is significant atrophy overall. Future research may examine this with a larger sample. The findings of the present study are integrated with a broader literature.
Our finding that e4 predicts depression has been shown elsewhere in the TBI literature for mild to moderate injury (Merritt et al., 2018) and extends those findings to an older civilian msTBI population. However, previous research had shown that e4 status in a TBI population an average of 30 years post-injury was only associated with dementia onset (Koponen et al., 2004). The fact that depression was not shown to impact cognition above and beyond cognitive decline demonstrates that these effects of e4 on depression may not directly relate to exacerbated decline post-TBI or more AD-like decline within the sample, despite the link between e4 and AD. The results of this study indicate that cognitive reserve demonstrably serves as a more apt marker of functioning in aging adults with a history of msTBI than depressive symptomatology. In assessing risk for decline in these populations, cognitive reserve may be one of the most critical factors to examine clinically.

Additional analyses were performed to examine the relationship between hippocampal volume and delayed recall, retention, and semantic memory. Hippocampal volume was not predictive of raw scores for the HVLT-R delayed recall \( (p = .23) \) or retention \( (p = .66) \), nor was hippocampal volume associated with raw scores for the BNT \( (p = .42) \). The existing literature on this topic is widely variable, especially for elderly populations, as demonstrated by a meta-analysis that examined 33 studies (Van Petten, 2004). Further investigation is needed to determine the cognitive and biological impacts of depression post-TBI, but the findings of this study suggest that depression with a history of msTBI in older adults may not be an indicator of further decline.

**Limitations**

There are a few limitations to this study. First, MRI data was collected on one of three scanners, which may introduce scanner-dependent differences. Future studies could replicate and extend these volumetric findings with a larger sample and fewer scanners. Further, longitudinal
studies using MRI may better demonstrate the differences in long-term hippocampal degeneration and asymmetry with more sensitivity than the present study. Second, this study had a limited number of e4 carriers and was therefore only able to examine e4 genotype as a binary of carrier vs noncarrier. Given the distribution of APOE genotypes in the population, future studies with a larger sample examining genetic differences in depression risk might look at genetic differences by specific genotype, rather than carrier status. Additionally, studies with greater diversity would have the potential to examine racial differences in genetic risk by genotype, as some studies have shown differential effects of APOE genotype by race, such as a faster rate of decline for semantic and working memory in white e4 carriers compared black carriers (Barnes et al., 2013; Morris et al., 2019). Finally, the average age of this sample was 64.31 years. Because AD risk increases over time with age, the results of this study may have been impacted by this relatively young cohort, as only about 5% of AD cases show symptoms before age 65 (Awada, 2015). However, the interaction effect between depression and age was not included in a best-fit model after stepwise analysis, and this study did include 54 individuals aged 65 and older.

**Conclusions and Future Research**

The present study found that in a cohort of older participants with a lifetime history of TBI, there was an association between APOE e4 carrier status and depression, and depression was further associated with decreased hippocampal volume. However, within the sample, depressive symptoms were not associated with diminished cognition in the domains of executive functioning, delayed recall, retention, or semantic memory when cognitive reserve and age were added as predictors. Additionally, depression was not associated with hippocampal asymmetry. These findings suggest that depression post-TBI may not be related to AD onset later in life, nor does depression exacerbate the cognitive deficits associated with chronic msTBI.
Due to the significant and persistent prevalence of depression in individuals with a history of TBI, the biological, cognitive, and social impacts of depression on patient outcomes within these populations should be further assessed. Depression serves as a risk factor for dementia and other neurodegenerative processes such as hippocampal atrophy (Byers & Yaffe, 2014; Diniz et al., 2013; Steffens et al., 2000; Videbech & Ravnikilde, 2004), and its association with APOE e4 carrier status should not be overlooked in understanding its impact on functioning even an average of a decade post-injury. This is especially relevant given the increased risk of dementia conferred by e4 status, which is further exacerbated by a history of msTBI (Michaelson, 2014; Raber, Huang, & Ashford, 2004).

Although this study did not find any cognitive impact of depression on executive function, delayed recall, retention, or semantic memory within this older TBI sample, prior studies examining the effects of depression on functioning post-TBI have largely focused on quality of life, rather than direct biological and cognitive impacts that may relate to neurodegenerative processes post-injury. Relationships exist between neuroinflammatory processes and TBI, depression, and neurodegenerative diseases (Brites & Fernandes, 2015; Byers & Yaffe, 2014). Given these relationships, as well as the relationship between depression, TBI, and APOE genetic status, depression resulting post-TBI may still be of use to examine the relationship between TBI and the onset of dementia later in life. Future studies should investigate the relationship between neuroinflammatory biomarkers post-injury and depression. It may be especially illuminating to examine this relationship longitudinally while studying the effects of these variables on cognition and long-term hippocampal degeneration, as well as any potential effects on other brain regions associated with dementia, such as the entorhinal cortex (Frisoni et al., 1999).
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