Genetic Influences on Verbal Memory Efficiency Following a Mild Traumatic Brain Injury

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Abstract

Mild traumatic brain injuries (mTBIs) are common in the U.S. veteran population, and post-concussive symptoms can impact verbal memory performance. While many veterans benefit from cognitive rehabilitation following mTBI, there are others for whom treatment does not result in significant recovery. Identifying genetic biomarkers that influence biological processes underpinning verbal memory may provide additional explanations for discrepancies in mTBI recovery. Deleterious genetic variants associated with the APOE gene, the BDNF gene, and the ANKK1 gene were studied within a veteran population to understand their impact on verbal memory after an mTBI. A sample of 257 participants (95% male, mean age = 33.2 years (*SD* = 8.3, 22-62)) participated in one of two previous studies conducted at the Minneapolis VA. Participants were genotyped and administered neurocognitive measures, including the California Verbal Learning Test-II (CVLT-II). This test measures verbal learning and memory capacity. It was hypothesized that the presence of an APOE, BDNF, or ANKK1 risk allele would contribute to poorer performance on the CVLT-II following an mTBI. These three risk alleles have been linked to memory-related deficits and may interact with neuronal repair processes that follow an mTBI. Our analysis found that APOE risk allele status was associated with the Delayed Recall CVLT-II factor, and that mTBI history predicted overall CVLT-II performance. mTBI history and APOE risk allele status did not interact in their prediction of memory function. We did not find that BDNF or ANKK1 risk allele contributes to verbal memory deficits following an mTBI in veterans. These findings do not support the hypothesis that risk alleles create additional vulnerabilities for memory deficits after an mTBI, despite APOE-ε4 and mTBI history separately predicting verbal memory deficiencies.

Keywords: traumatic brain injury, verbal memory, APOE, BDNF, ANKK1

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Traumatic brain injury (TBI) is a common cause of disability in the United States, with 2.5 million TBI-related emergency care visits yearly (Centers for Disease Control and Prevention, 2014). TBI prevalence is especially common in the U.S. service member and veteran population. It is estimated that 19% of U.S. service members who participated in Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) sustained a TBI while deployed (Tanielian & Jaycox, 2008). Based on epidemiological estimates, around 80% of these TBIs are believed to be mild (Meyer et al., 2010).

While 80-85% of mTBI patients fully recover 4 weeks post injury, the remaining minority continue to suffer from extended physical or cognitive impairments (Schwab et al., 2017). These protracted symptoms are collectively referred to as post-concussive symptoms (PCS). PCS vary in their length, composition, and severity, with some cases resolving weeks later, while other cases last months and years. A meta-analysis by Binder (1997) found that 7.4% of mTBI cases continue to experience PCS 6 months or more after injury. Typically, the acute symptoms of mTBI, such as dizziness and nausea, resolve quickly and are not considered PCS. Most PCS involve behavioral, psychological, and cognitive complaints, which tend to persist longer (Anderson et al., 2006).

The frequency and characteristics of PCS among veterans are topics of significant research. One reason for this is the heterogeneity associated with injury. An mTBI can be caused by an IED explosion, a vehicle accident, a fall, or some other physical insult. Repeated exposure to low-level blasts can also present similarly to an mTBI (Carr et al., 2015). In addition to poor surveillance efforts, it was estimated that less than half of the number of returning soldiers with probable TBI's received a formal TBI assessment prior to 2007 (Hoge et al., 2008). The passage

of the *Traumatic Brain Injury Act of 2008* intended to overhaul the surveillance and treatment of TBI and PCS in the U.S. with particular attention paid to the many returning service members (Traumatic Brain Injury Act of 2008, 2008). While this federal law directed more money and resources for TBI study in veterans, research on long-term impairments following mTBI remains inconsistent due to assessment difficulties, non-uniform diagnostic criteria, and the influences of military culture on seeking care for "invisible wounds".

Some of the most common acute and long-term post-concussive symptoms observed following a mild TBI involve cognitive impairments (McInnes et al., 2017). Learning, memory, and recall deficits have been observed in both civilians and veterans following an mTBI. A common tool to assess cognitive performance in these areas among clinical populations is the California Verbal Learning Test-II (CVLT-II; Delis et al., 2000). The CVLT-II provides information about the quantity of new information a person can learn and recall after a short delay, as well as the quality of a person's learning style.

The CVLT-II requires a participant to learn and recall words presented to them by an administrator. There are two lists of words read to them: the learning list (List A) and the interference list (List B). The first five trials involve the dictation and immediate recall of List A, followed by a single reading of List B, and then a free recall of List A. After 20 minutes, another free recall of List A is done. After the free recall, the participant must identify the 16 words of List A within a larger list of 32 words using recognition memory. The CVLT-II generates 19 variables, commonly used to calculate a single index of impairment.

Donders (2008) has shown that some of the CVLT-II's 19 variables are highly interdependent and may measure more specific verbal memory constructs. Two confirmatory factor analyses–one in a TBI sample and another in a healthy sample–have identified four

constructs that can be created when clustering some of these 19 variables together (DeJong & Donders, 2009; Donders, 2008). These four factors are Attention Span (consisting of 2 variables), Learning Efficiency (3 variables), Delayed Recall (5 variables), and Inaccurate Recall (2 variables). Each factor's scores are calculated by taking the Z-scores of all variables that compose it, multiplying each variable by its factor loading score, and then adding all standardized variable scores together.

Attention Span measures the ability to correctly recall words after a single presentation and likely maps well onto working memory. Attention Span is distinct from Learning Efficiency, which measures how well one can consolidate and recall words over several repeated exposures. Inaccurate Recall measures the number of intrusions, perseverations, or other errors that occur during recall. Finally, Delayed Recall measures the ability to freely recall words after a time delay between dictation and recall. While these four factors are not entirely independent of one another, considering each factor separately may have advantages. For example, if a patient has a normal Attention Span score but a low Learning Efficiency score, that could suggest a specific deficit in verbal consolidation. This information may help inform diagnosis and treatment decisions.

Improving mTBI treatment outcomes has been a long-time goal of the VA's Veterans Health Administration. While much progress has been made, even when accounting for similar injury profiles (e.g., blast versus impact TBI), comorbidities (e.g., PTSD, depression, physical health), and treatment regimens (e.g., cognitive rehabilitation, occupational therapy), a high level of unexplained variability still exists in mTBI outcomes in veterans (Reger et al., 2022). Inability to explain why one veteran suffers from persistent neurocognitive deficits while another does not can lead to inaccurate prognoses and unsuitable treatment recommendations. This lack of

efficiency has serious consequences. Financially, it is estimated that the cumulative costs for care across all cases of TBI in the U.S. Department of Veterans Affairs is between $591 and $910 million dollars (Tanielian & Jaycox, 2008). Since many veterans receive care from private facilities outside of the VA, this number is likely higher (Panangala & Sussman, 2020). The personal consequences are of equal concern: pursuing expensive and demanding treatments that do not yield improvement contributes to feelings of hopelessness among veterans and their families and increase the likelihood of attrition from treatment altogether.

While utilizing different diagnostic practices may explain variation, such as adopting the CVLT-II factor score method, researchers have also began studying the role that biological individual differences might play in the recovery process from mTBI. Some of these biological differences are thought to be influenced by genetic polymorphisms. Polymorphisms can be either the insertion, deletion, or replacement of nucleotides in a gene. Single nucleotide variations (SNV) are the most common type of genetic polymorphism and are the result of a G, A, C, or T nucleotide being replaced by another nucleotide. A SNV can become meaningful when it appears in a significant percentage of the population (usually >1%). This is the most common way for a SNV to be designated as a single nucleotide polymorphism (SNP), although other ways exist (International Human Genome Sequencing Consortium et al., 2001).

Certain SNPs have been identified in genome-wide association studies as influencing susceptibility to neurological diseases such as Alzheimer's (Jansen et al., 2019), multiple sclerosis (International Multiple Sclerosis Genetics Consortium, 2019), and schizophrenia (Jansen et al., 2019). Many other SNPs have been associated with the efficiency and degree of recovery that people will experience after neurological damage, including mTBI (Dardiotis et al., 2010). These SNPs are theorized to play a role in the important innate recovery mechanism

following damage to or loss of neurons (functional plasticity), defined as the ability to repair damaged neurons.

Several of these SNPs have been considered as candidate genes to be explored independently as potential mediators of the TBI recovery process and downstream cognitive performance. This paper will analyze three prominent SNPs that have been theorized to modulate neuronal repair and neural plasticity to determine their effect on verbal learning and memory post-mTBI as measured by the CVLT-II. It is hypothesized that the presence of a risk allele within any of these three SNPs will be associated with poorer overall performance on the CVLT-II. Due to high comorbidity between mTBI and PTSD in the present study's sample, data obtained from the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995) will also be used for the purpose of delineating the contributions that the two conditions have on verbal learning and memory.

APOE

The first genetic variant being considered is the ε4 allele of the apolipoprotein E gene (ApoE, protein; APOE, gene). ApoE was originally identified for its role in metabolic reactions, but it is also prevalent in the central nervous system (CNS) and has received significant attention for its role in recovery after neurotrauma (Zhou et al., 2008). The APOE gene codes for the ApoE protein, which is synthesized during times of biological stress. Apolipoproteins are broadly involved in lipid transport throughout the body. According to immunocytochemical studies within the CNS, ApoE is mainly secreted by astrocytes to transport cholesterol to neurons (Boyles et al., 1985). It is present throughout the CNS (cerebrum, cerebellum, pons, medulla, and spinal cord) in substantial quantities, suggesting that ApoE plays an important function in brain physiology. The release of cortisol, a steroid derived from cholesterol, prompts

neuroinflammation in the hippocampus (Zhang et al., 2017), a limbic structure that contributes to consolidation of information from short-term to long-term memory (Hofer et al., 1990).

ApoE has also been associated with neuronal repair (White et al., 2001) and neuroinflammation (Ebert et al., 2019), both of which play important roles in mTBI recovery (Silva Meirelles et al., 2017). Insufficient neuronal repair following head injuries has reliably predicted subsequent cognitive performance, although the effect size is reduced when accounting for pre-existing cognitive performance (Su YR et al., 2016).

The human APOE gene has three common variants (alleles), designated APOE-ε2, -ε3, and -ε4, which differ by single amino acid replacements. The functional mechanisms that these alleles influence differ. For example, APOE-ε4 has been strongly associated with the pathogenesis of neurological conditions like Alzheimer's disease in both healthy and TBI populations (Kim et al., 2009). Studies have found that people with the ε4 allele have worse memory and learning after mTBI compared to people without it (Crawford et al., 2002). However, other studies have found that ε4 has no effect compared to other variants (Chamelian, 2004). Therefore, further investigation into the role of the ε4 allele on verbal cognition after an mTBI is justified.

BDNF

The second variant being considered is one related to brain-derived neurotrophic factor (abrineurin, protein; BDNF, gene). Neurotrophic factors like BDNF are important to the development and maintenance of the nervous system. BDNF is expressed throughout the brain and is believed to play an important role in regulating synaptic connections and neuronal growth (Lu & Chow, 1999). It has been implicated in several cognitive processes relating to episodic, working, and long-term memory (Egan et al., 2003).

One of BDNF's most studied SNPs is the Val66Met polymorphism (rs6265). The Met-allele of this SNP results from guanine being substituted for adenine at position 196. While the exact mechanism of the Met-allele remains unclear, the SNP seems to result in a reduction in the expression of BDNF proteins in the brain and reduced neurocognitive functioning, especially in memory-related domains (Yamada et al., 2002). This may be due to the high prevalence of BDNF in the hippocampus (Hofer et al., 1990).

While questions remain about the Met-allele's mechanisms of action, several studies have identified differences in individuals with and without the Met-allele. Neuroimaging has consistently identified reduced hippocampal and prefrontal volumes in healthy carriers of the Met-allele compared to individuals homozygous for the Val-allele (Pezawas, 2004)

Behavioral differences have also been observed. An early study of the Met-allele was done with patients suffering from schizophrenia and found that those with the Met BDNF allele had reduced delayed recall of episodic memory (Egan et al., 2003). A more recent study by McAllister et al. (2012) compared 75 patients with mild to moderate TBI to healthy controls and found that while several BDNF SNPs correlated with cognitive speeds among both groups, among the TBI group, those with the Met-allele had compromised memory performance compared to both the controls and TBI patients without the Met-allele. These results suggest that BDNF may play a role in cognition more generally, and that the Met-allele might be linked to post-TBI cognition. However, the TBI group was tested only shortly after they sustained their injury. The present study will analyze veterans with more diverse intervals of time between injury and assessment.

ANKK1

The final SNP being considered is one from the ankyrin repeat and kinase domain containing 1 (kinase PKK2, protein; ANKK1, gene) gene, which is part of a family of enzyme-coding genes that perform essential cellular functions. ANKK1 has been found to modify dopamine receptor D_2 density (Savitz et al., 2013), although the exact mechanism it impacts is still being explored. Dopamine transmission is essential for many cognitive processes including executive functioning, processing speed, and memory (Clos et al., 2019). By extension, the availability of D_2 receptors in the hippocampus and caudate has been shown to influence memory performance (Nyberg et al., 2016). Genetic variations impacting the genes that control dopaminergic signaling could help explain some of the individual variation in memory complaints post-TBI given the importance of this mechanism in cognitive functioning.

ANKK1 contains a SNP designated as Taq1A, a C/T replacement. The A1 allele of this SNP appears to reduce dopaminergic transmission (Cerasa et al., 2009) and has been suggested as a risk factor for substance use disorder and other addictive psychopathology. It has also been studied in TBI samples. McAllister et al. (2008) found mTBI patients with the A1 allele of ANKK1 Taq1A had poorer episodic memory on the CVLT compared to both A1 absent subjects and controls. Failla et al. (2015) found that patients with the A1 allele had worse CVLT scores a month post-injury.

In summary, the three genetic markers we are considering in this study are the ε4 allele of APOE, the Met allele of BDNF, and the A1 allele of ANKK1.

Method

Sample

Participants

The present study draws on participants from two previously completed research projects done through the Minneapolis VA Medical Center; the Study of the Aftereffects of Trauma: Understanding Response in National Guard (SATURN), and its follow-up companion study Essential Features of Neural Damage in Mild Traumatic Brain Injury (DEFEND). The goal of these studies was to delineate the symptom profiles and neural functioning of U.S. veterans who sustained blast-related traumatic brain injuries (bTBI) and/or acquired post-traumatic stress disorder (PTSD) after deployment to Iraq or Afghanistan. There was a skew towards less severe injuries because participants were excluded if they had sustained a probable moderate or severe TBI. It is possible that some of those whose injuries were on the periphery between a mild and moderate TBI were excluded. Additional exclusions were the presence of a non-TBI neurological condition, psychotic disorder, DSM-IV substance abuse disorder, or risk of suicidal behavior. The inclusion criteria for the current study were as follows: 1) Status of ApoE-E4, Val66Met, and Taq1A available, 2) valid California Verbal Learning Test (CVLT) scores, 3) valid Minnesota Blast Exposure Screening Tool (MN-BEST), 4) valid Clinician Administered PTSD Scale (CAPS) data, and 5) failing < 2 effort tasks on the previously administered neuropsychological battery. Ninety-five percent of the participants were men. Participants ranged in age from 22 to 60 years with a mean and standard deviation of 32.9 $\pm$ 7.92 years, respectively.

Participants of both studies partook in largely the same series of protocols, including semi-structured clinical interviews, a battery of neuropsychological measures, several self-report

measures, an MRI scan, electroencephalography, and a blood draw or saliva collection, which was used for genotyping.

CVLT-II

The California Verbal Learning Test, 2nd edition (CVLT-II; Yi, 2011) is an hour long multifaceted neuropsychological assessment used to measure episodic verbal learning and memory. It contains recall and recognition of two lists of words over immediate and delayed trials. List A includes 16 words and requires the examinee to recall the list over five trials. List B, which is also 16 words, is administered after List A for one trial. Short-delay free recall and cued recall are administered after List B. A 20-min delay follows the short-delay recalls, followed by nonverbal testing. Long-delay recall, long-delay-cued recall, and yes/no-recognition trials of List A follow the 20-min delay. These trials are used to construct the four-factor model that measures Learning Efficiency, Attention Span, Delayed Recall, and Inaccurate Recall independently.

MN-BEST

The Minnesota Blast Exposure Screening Tool (MN-BEST; Nelson et al., 2011) is a semi-structured clinical interview used to identify the presence and assess the severity of blast- and impact-related traumatic brain injuries (bTBI). Participants are interviewed about the most significant TBI's that they have experienced in their life, as well as the number of mTBIs experienced at varying degrees of certainty (unlikely, possible, probable, or definite). The three most significant blast related TBI's are then scored based on the presence of loss of consciousness, post-traumatic amnesia, and several symptoms such as nausea, tinnitus, headache, and sensitivity to light. The three blast-related mTBI's are each given a severity score from 0-30, and the sum across the three injuries is used to calculate the TBI severity score.

CAPS

The Clinician Administered PTSD Scale (CAPS) is a 60-minute semi-structured interview used to identify the severity of symptoms commonly associated with PTSD (Weathers et al., 2018). Each symptom is rated for both intensity and frequency independently on a 5-point Likert scale. Intensity and frequency are added together to create a severity score, and total severity across all items is used as a continuous measure of PTSD symptom severity.

Procedure

Only the administration of the three pertinent instruments and DNA collection process will be discussed in detail. In both SATURN and DEFEND, voluntary informed consent was obtained before participation. Participants were administered the CVLT-II, MN-BEST, and CAPS by doctoral level clinical neuropsychologists or high-level doctoral trainees at the Minneapolis VA Medical Center. Participants received $50 for completion of the interviews, questionnaires, and cognitive testing.

Genotyping

Certified VA medical staff obtained 8 millimeters of blood from participants for the DNA specimen. Genotyping was done at the University of Minnesota's Genomics Center on the Illumina Infinium PsychArray-24 kit (Illumina, 2018).

Genotypes were determined from genome-wide association study (GWAS) results. APOE status was determined by examining the base identities at positions chr19:44908822 (rs7412; reference T (thymine), variant C (cytosine)) and chr19:44908684 (rs429358; reference T (thymine), variant C (cytosine)). Counts at these positions were converted to APOE genotypes. Having two copies of cytosine (C) at either rs7412 or rs429358 indicates the presence of the APOE-ε4 risk allele; having two copies of cytosine at both rs7412 and rs429358 indicates

homozygosity for APOE-ε4. Due to the limited number of subjects homozygous for APOE-ε4 (n=2), all participants with at least one copy of APOE-E4 were placed into the "APOE-ε4 present" group while those without were placed into an "APOE-ε4 absent" group.

Val66Met genotypes were determined by examining base identities at hg38 positions chr11:27658369 (rs6265; reference G (guanine), variant A (adenine)). The more common G allele encodes Val, while the A allele encodes Met. Following the methodology used in another study investigating the role of Val66Met on memory processes (Harrisberger et al., 2014), we combined all of those with at least one copy into an "Met present" group while those without were placed into an "Met absent" group.

Taq1A genotypes were determined from whole genome sequence samples by examining the base identified at GRCh38 positions chr11:113400106 (rs1800497; reference C, variant T). As with the previous genotypes, we combined all of those with at least one copy of the T variant into an "1A present" group while those without were placed into an "1A absent" group. This was due to low homozygosity present in our sample.

Design

Analyses were conducted using the Statistical Package for the Social Sciences (SPSS) Version 25.0.0.2 and R Version 4.1.2. Descriptive statistics were computed on the overall sample and for all allele status groups. To determine relevant covariates for the analyses, several correlation analyses were conducted; specifically, relationships between independent variables (TBI severity, APOE-ε4 group, BDNF-Met group, ANKK1-A1 group), dependent variables (four CVLT-II composite scores), and PTSD severity were all examined. Age and sex were added as data-supported covariates to the final model, while PTSD severity score was added as a

theory-driven covariate. All analyses were run with and without PTSD symptom severity score as a covariate.

The present study utilized three multivariate analyses of covariance (MANCOVAs) to test the interaction between risk allele status and blast TBI severity on CVLT-II factor scores with three covariates. The four individual CVLT-II composite factor scores served as dependent variables, with risk allele status and blast TBI group serving as the independent variables. One MANCOVA was run for each SNP. Since the blast TBI severity scale was non-normally distributed, with skewness of 1.30 (SE = 0.17) and kurtosis of 1.18 (SE = 0.10), we created three bins based on bTBI severity score: 0 (n = 110), 1-3 (n = 72), and ≥ 4 (n = 21) and treated the new "bTBI group" variable as a fixed factor.

Results

Genetic allele groupings did not significantly differ by demographics or clinical variables, with the only exception being the Taq1A A1 present group who reported more severe PTSD severity on the CAPS compared to the A1 absent group [$t(194) = -2.510$, $p = .013$] (see Table 1). PTSD severity was positively correlated with blast TBI severity ($r = .31$, $p < .01$), and negatively correlated with three of the four verbal cognitive measures: Attention Span ($r = -.18$, $p < .05$), Learning Efficiency ($r = -.20$, $p < .01$), and Delayed Recall ($r = -.29$, $p < .01$) (see figure 1).

bTBI group, allele status, and the CVLT-II verbal memory composite

APOE

Multivariate results of the MANCOVA accounting for APOE-ε4 status with age, sex, and PTSD symptom severity showed a main effect of bTBI group on verbal memory performance ($F(8, 354) = 3.04$, $p = .019$, $\eta p2 = .032$), where higher bTBI showed poorer overall verbal

memory performance than lower bTBI. There was also a significant main effect of APOE-ε4 allele status ($F(4, 168) = 3.04$, $p = .019$, $\eta p2 = .064$), such that the ε4 present group showed poorer overall verbal memory performance than the ε4 absent group. The interaction between bTBI group and APOE-ε4 status was not significant ($F(8, 356) = 1.669$, $p = .105$). Removing PTSD severity as a covariate did not significantly change the results for verbal memory composite.

Individual factors

The univariate tests showed there was a significant difference between the ε4 present and ε4 absent groups for the CVLT-II Delayed Recall factor ($p = .025$, $\eta p2 = .027$) (see Figure 2). The other three factors did not reach significance (all $p's > .470$). The univariate tests did not yield any significant differences between the bTBI groups in relation to the CVLT-II factors (all $p's > .142$).

bTBI group, BDNF-Met status, and the CVLT-II verbal memory composite

No main effect of bTBI group ($F(8, 356) = 1.513$, $p = .151$) or BDNF-Met allele status ($F(4, 177) = .598$, $p = .665$) was found on the verbal memory composite, nor was there a significant interaction between TBI group and BDNF-Met allele status ($F(8, 356) = .399$, $p = .920$). Using bTBI group as a random factor did not significantly change the results for the verbal memory composite, nor did removing PTSD severity as a covariate.

bTBI group, A1 status, and the CVLT-II verbal memory composite

No main effect of TBI group ($F(8, 354) = 1.532$, $p = .145$) or Taq1A allele status ($F(4, 176) = 1.843$, $p = .123$) was found on the verbal memory composite, nor was there a significant interaction between TBI group and Taq1A allele status ($F(8, 354) = 1.247$, $p = .270$). Using

bTBI group as a random factor did not significantly change the results for the verbal memory composite, nor did removing PTSD severity as a covariate.

Discussion

Post-concussive symptoms involving cognition are among the most frequent concerns of veterans after an mTBI. These symptoms commonly manifest as memory deficits. While most veterans return to baseline functioning several weeks after injury, the path to recovery for others is less straightforward. While many studies have investigated cognitive performance following a mild TBI, there is relatively little consensus on whether carriers of the APOE, BDNF, or ANKK1 risk alleles have higher rates of unfavorable outcomes. The approach of this study was to independently analyze the effects that three SNPs had on markers of verbal memory while considering other factors that influence recovery, such as comorbid PTSD and age.

The present analysis found evidence that APOE genotype impacts Delayed Recall ability, with the APOE-ε4 present group experiencing poorer Delayed Recall when compared to the ε4 absent group. There was also evidence suggesting that a history of at least one blast-related mTBI was associated with poorer overall verbal memory. This TBI association was not associated with any of the four CVLT-II performance factors independently but was only significant when all factors were considered together. Contrary to our hypothesis, there was no evidence of an association between the presence of an mTBI and APOE genotype, meaning the relationship between APOE genotype and CVLT-II performance did not differ according to mTBI status. When the same analyses were run on the ANKK1 and BDNF risk alleles, there were no significant findings.

The findings from this study regarding APOE genotype align with those of other recently published studies that have found the ε4 allele predisposes individuals to a range of

neurocognitive deficits, including memory impairment (Makkar et al., 2020). The deficits and risk factors associated with the ε4 variant have been one of the more reliable findings in neurological candidate gene studies (Belloy et al., 2019; Maiti et al., 2015), and its identification in this provides validation to our study design and analytical approach.

It is noteworthy that the effect of the APOE-ε4 allele on memory was limited to the Delayed Recall factor amongst the various verbal memory processes captured by the CVLT-II. Distinguishing between delayed and inaccurate recall has not always been successful on other memory tests in clinical samples (Burton et al., 2003). The fact that this analysis found Delayed Recall to be significant and inaccurate recall not to be suggests that Delayed Recall and Inaccurate Recall are distinguishable memory characteristics, which supports the four factor model of the CVLT-II proposed by DeJong & Donders (2009). It also suggests that the mechanistic pathways that contribute to these two recall abilities differ in a way that APOE directly or indirectly affects.

The fact that there was not a significant interaction effect could be due to several reasons. First, it is possible that the detrimental effects that the ε4 allele has on cognition exists before experiencing a TBI and are not influenced by the presence of TBI. It remains unknown at what point having the APOE-ε4 allele becomes a liability. If APOE plays a role in the early initial development in the brain, it may affect hippocampal functioning as early as *in utero*. It is also possible that these risks do not manifest until later in the course of neurodevelopment, such as during pruning or the myelination of axons. A longitudinal study following both APOE-ε4 present and absent children through development could shed light on whether relative differences in verbal memory as a function of APOE genotype exist early in life.

While it is possible that the present study was underpowered to detect an interaction effect, two other studies investigating the interaction between APOE and memory with similar samples have found results that coincide with ours: namely, main effects of genotype and TBI history, but no interaction effect (Chamelian, 2004; Liberman et al., 2002).

Our results also found that increased PTSD severity was associated with worse verbal memory performance on the CVLT-II: specifically, Attention Span, Learning Efficiency, and Delayed Recall. PTSD and mTBI are highly comorbid conditions in OEF/OIF veterans. The likelihood of developing PTSD after several mTBIs is far higher than in veterans without a history of mTBI (Albanese et al., 2019). If the mTBI occurred in an emotionally salient situation, such as the result of a suicide bomber or IED explosion that threatened the veteran's life, this likelihood may increase further. TBI and PTSD can present similar symptomology, and the correlations observed in our results demonstrate this.

There are many reasons why we may have not detected significant findings for the other SNPs. While the neurological effects of APOE are well known, the cognitive impact of BDNF and ANKK1 are not. Larger sample sizes may be required to detect significant effects. For ANKK1, it is possible that the positive findings of McAllister et al. (2008) are limited to the short term recovery of veterans post-mTBI, and that across longer periods of time, the discrepancy in verbal memory recovers to a comparable degree compared to A1 absent veterans. The inconsistency in findings suggest that further work is needed to isolate the effects of ANKK1 allele status on mTBI.

Additionally, recent biological investigations on the A1 allele of the Taq1A ANKK1 polymorphism have brought into question the strength of its impact on dopamine transmission. Taq1A is now believed to be located entirely within ANKK1, which is located about 10,000 base

pairs away from the DRD2 gene, which encodes the dopamine D_2 receptor. While the two genes have high linkage disequilibrium, further investigation is needed to better understand the mechanism of ANKK1 and its relation to dopaminergic functioning.

There are several implications that this work may have on both patients and clinicians dealing with mTBI. The first is that while the population being studied is veterans, the findings may be generalizable to the civilian population, especially incidents involved blast exposure. Second, even though there was not an mTBI-genotype interaction, the fact that there were main effects for both underscore the importance of a through clinical interview to yield the nature of the symptoms experienced by the patient. Finally, our results indicate that the four CVLT-II factors are informative regarding distinct aspects of learning and memory that might be disrupted following mTBI.

Some limitations of our work include the sample being relatively small for a candidate gene study, including insufficient participants homozygous for the APOE-ε4 allele to test for dose-dependent effects. Identifying the degree of dose dependence will better help identify those at greatest risk for experiencing verbal-related memory problems. A candidate gene approach also limits the number of genetic variants that can be considered, which means the true extent of the genetic influence on verbal learning and memory was not comprehensive in this work.

Future research would benefit from applying this approach in an epidemiological sample to increase the probability of being suitably powered for gene-by-environment analyses. It may also be worthwhile to test the hypothesis using a more comprehensive approach such as through a polygenic risk score approach, which has the benefit of being hypothesis-free in the sense that an *a priori* presupposition about the role that specific genes have on mTBI is not required. This approach estimates effect of many genetic variants on an individual's phenotype using a GWAS,

meaning we could assess the contributions that all three genetic variants have on verbal memory simultaneously.

The present study attempted to explain some of the variance among recovery from mTBI among U.S veterans by studying the role of three genetic variants known to impact memory. While these findings do not suggest that one's genotype determines one's outcome following an mTBI, this work may be informative in the quest to develop interventions for those who suffer long-term post-concussive symptoms.

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Table 1

Means, standard deviations, and correlations with confidence intervals

Variable	*M*	*SD*	1	2	3	4	5	6	7	8
1. Age	33.17	8.29								
2. Attention span	-0.68	1.17	.07 [-.07, .20]							
3. Learning efficiency	0.16	1.81	-.01 [-.15, .12]	.51** [.41, .60]						
4. Delayed recall	-0.73	4.00	.05 [-.08, .18]	.62** [.54, .69]	.77** [.72, .82]					
5. Inaccurate recall	0.11	1.18	.08 [-.06, .21]	-.20** [-.31, -.08]	-.35** [-.46, -.24]	-.35** [-.45, -.24]				
6. bTBI severity	1.33	1.79	-.22** [-.33, -.10]	-.00 [-.14, .13]	-.02 [-.15, .12]	-.06 [-.19, .08]	.08 [-.06, .21]			
7. iTBI severity	2.12	2.50	.02 [-.10, .14]	.06 [-.07, .20]	.07 [-.06, .21]	.12 [-.01, .25]	.02 [-.11, .16]	.00 [-.12, .13]		
8. PTSD severity	32.88	28.52	-.09 [-.21, .04]	-.18* [-.31, -.04]	-.20** [-.33, -.06]	-.29** [-.41, -.16]	.08 [-.06, .21]	.31** [.19, .42]	-.07 [-.20, .06]	
9. Months since most recent bTBI	63.57	30.21	.14 [-.03, .31]	-.10 [-.26, .07]	-.08 [-.24, .09]	-.08 [-.24, .09]	.01 [-.16, .18]	-.19* [-.35, -.02]	.04 [-.13, .21]	-.10 [-.28, .08]

Note. M and *SD* are used to represent mean and standard deviation, respectively. Values in square brackets indicate the 95% confidence interval for each correlation. The confidence interval is a plausible range of population correlations that could have caused the sample correlation. * indicates $p < .05$. ** indicates $p < .01$.

Table 2

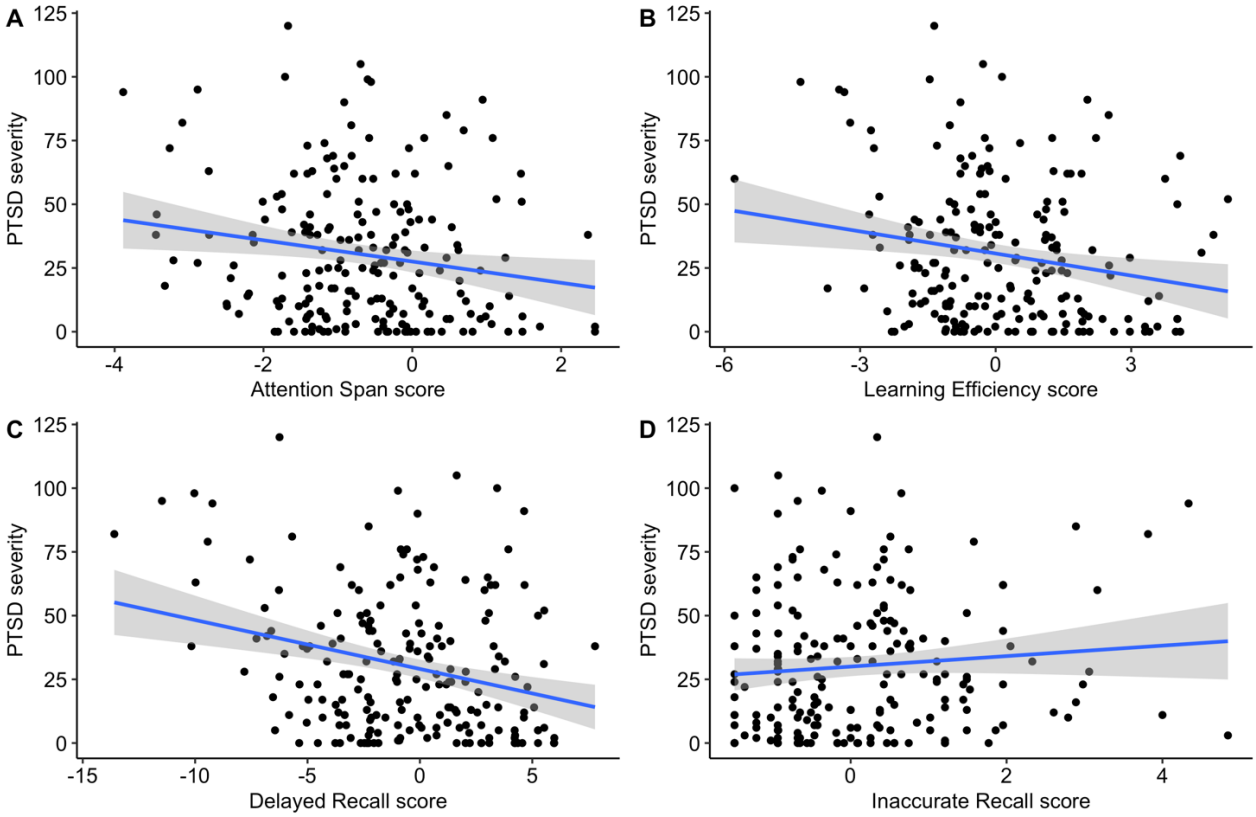
Demographic, verbal memory, TBI, and PTSD characteristics of veterans delineated by risk alleles

Measures	APOE (ε4)		ANKK1 (1A)		BDNF (Met)		
	No copy	1 or 2 copies	No copy	1 or 2 copies	No copy	1 or 2 copies	Full sample
N	165	54	142	76	139	80	257
Age	32.6 (8.2)	35.0 (8.5)	33.1 (8.5)	33.3 (8.1)	33.1 (8.3)	33.3 (8.3)	33.2 (8.3)
Sex (% female)	4.7	3.3	5.0	3.4	5.4	2.9	4.4
CLVT-II Factors							
Attention span	-0.67 (1.23)	-0.72 (1.01)	-0.71 (1.22)	-0.64 (1.13)	-0.76 (1.13)	-0.54 (1.27)	-0.68 (1.17)
Delayed recall	-0.44 (3.99)	-1.64 (4.25)	-0.90 (4.29)	-0.39 (3.69)	-0.70 (4.25)	-0.80 (3.80)	-0.73 (3.99)
Inaccurate recall	0.14 (1.21)	0.17 (1.29)	0.26 (1.33)	-0.05 (0.96)	0.23 (1.26)	0.01 (1.15)	0.11 (1.18)
Learning efficiency	0.26 (1.88)	-0.20 (1.91)	-0.03 (1.90)	0.44 (1.77)	0.12 (1.98)	0.19 (1.73)	0.16 (1.81)
TBI history							
Blast TBI score	1.32 (1.74)	1.36 (1.96)	1.25 (1.77)	1.38 (1.74)	1.31 (1.87)	1.36 (1.66)	1.33 (1.79)
Impact TBI score	2.39 (2.73)	1.87 (2.32)	2.24 (2.25)	2.29 (3.22)	2.28 (2.87)	2.23 (2.14)	2.26 (2.64)
Months since last blast TBI	65.3 (30.6)	68.4 (30.2)	68.1 (31.4)	61.3 (28.2)	67.5 (29.5)	63.3 (32.4)	65.7 (30.4)
PTSD severity (CAPS)	29.1 (25.4)	34.1 (32.1)	29.7 (26.9)	31.4 (27.7)	27.0 (25.8)	35.8 (28.7)	29.1 (25.4)

Note: This table displays the means and standard deviations across measures by allele status (copy of risk allele present or copy of risk allele not present) and in the full sample.

Figure 1

Regression of PTSD severity onto the four CLVT-II Factors



Note. Graph A shows Attention Span, graph B shows Learning Efficiency, graph C shows PTSD severity, and graph D shows Inaccurate Recall.

Figure 2

Mean Performance on the CLVT-II Factors among APOE-ε4 Allele Status

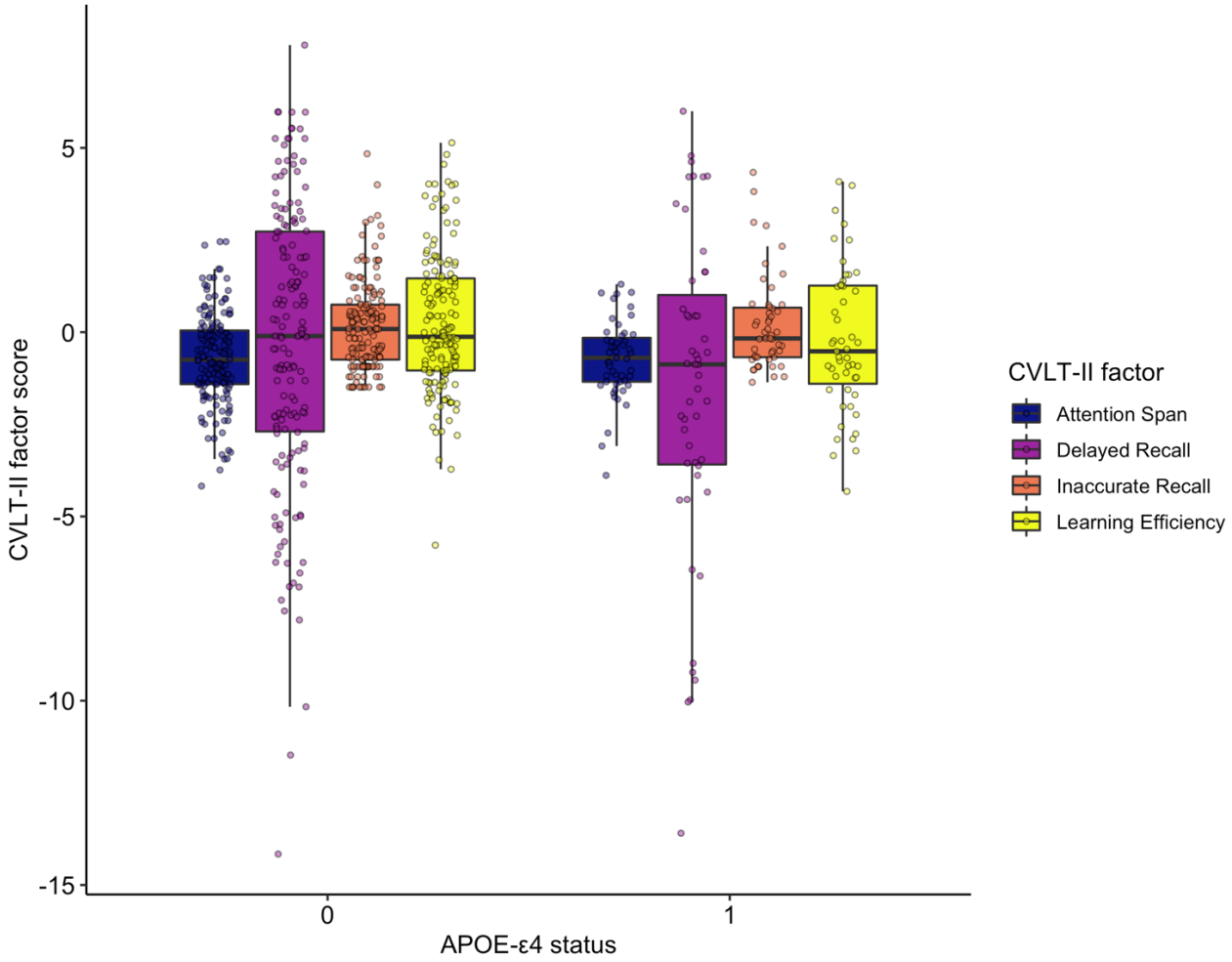


Figure 3

Mean Performance on the CLVT-II Factors by BDNF-Met Allele Status

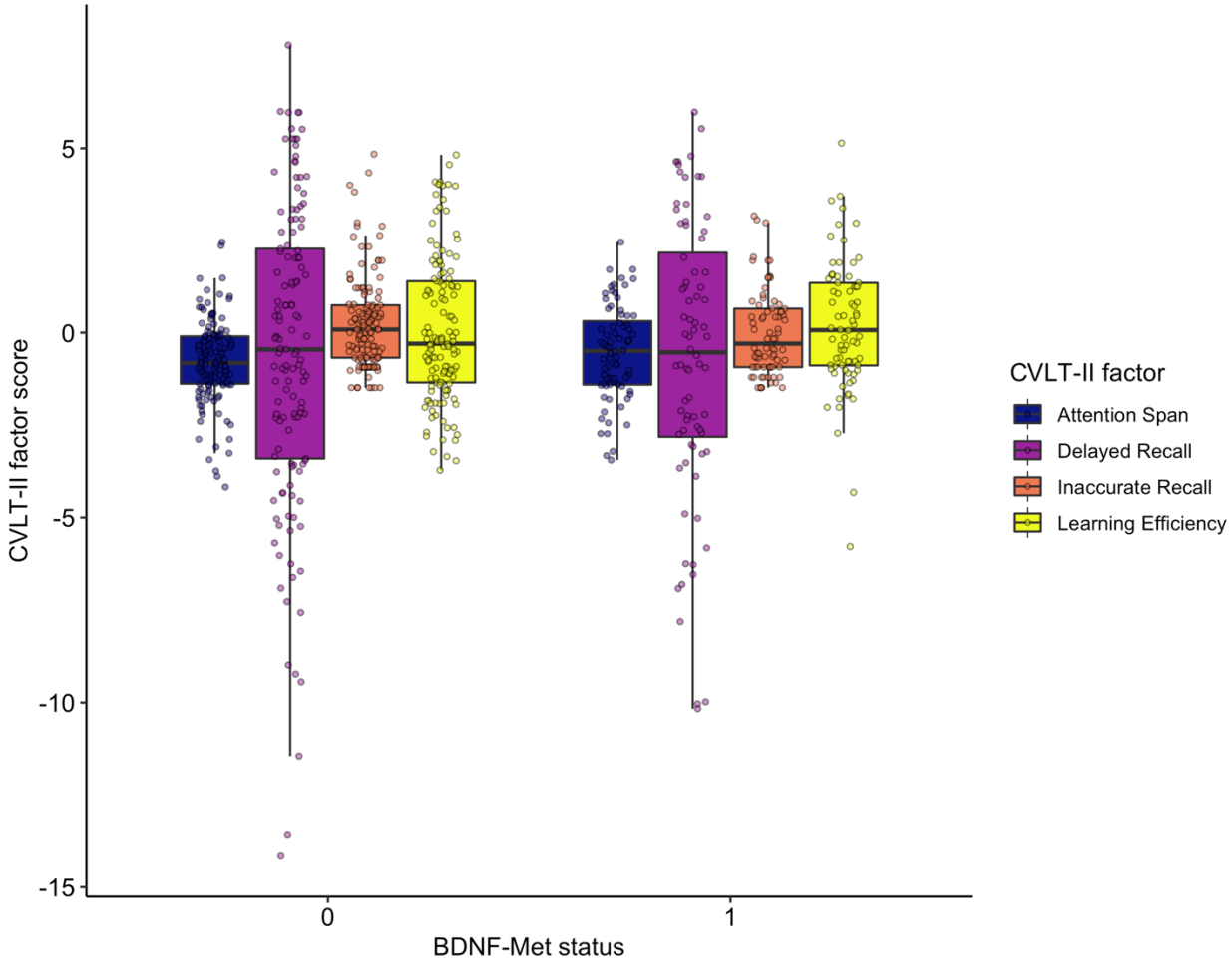


Figure 4

Mean Performance on the CLVT-II Factors by ANKK1-1A Allele Status