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Authors

Merritt, Victoria C
Clark, Alexandra L
Evangelista, Nicole D
et al.

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Dissociation of BDNF Val66Met Polymorphism on Neurocognitive Functioning in Military Veterans With and Without a History of Remote Mild Traumatic Brain Injury

Victoria C. Merritt[1,2], **Alexandra L. Clark**[1,2], **Nicole D. Evangelista**[3], **Scott F. Sorg**[1,2], **Dawn M. Schiehser**[1,2,4], **Lisa Delano-Wood**[1,4,2]

[1]VA San Diego Healthcare System (VASDHS)

[2]University of California San Diego (UCSD), School of Medicine, Department of Psychiatry

[3]Center for Cognitive Aging and Memory, Department of Clinical and Health Psychology, McKnight Brain Institute, College of Public Health and Health Professions, University of Florida

[4]Center of Excellence for Stress and Mental Health, VASDHS

Abstract

Objective: Since neurocognitive functioning following mild traumatic brain injury (mTBI) may be influenced by genetic factors that mediate synaptic survival and repair, we examined the influence of a common brain-derived neurotrophic factor (BDNF) polymorphism (Val66Met) on cognition using a well-defined sample of military Veterans with and without a history of mTBI.

Method: Participants included 138 Veterans (mTBI=75; military controls [MCs]=63) who underwent neuropsychological testing, including completion of self-report measures assessing psychiatric distress, and BDNF genotyping. The mTBI group was tested roughly 66.7 months following their most recent mTBI. Veterans were divided into two groups—Met+ (Met/Met and Met/Val; n=49) and Met- (Val/Val; n=89) and compared on domain-specific cognitive composite scores representing memory, executive functioning, and visuospatial speed.

Results: ANCOVAs adjusting for psychiatric distress, sex, years of education, and ethnicity/race revealed a significant group (mTBI vs. MC) by BDNF genotype (Met+ vs. Met-) interaction for the memory (p=.024; η_p^2=.039) and executive functioning (p=.010; η_p^2=.050) composites, such that Met+ mTBI Veterans demonstrated better performance than Met- mTBI Veterans on the cognitive measures, whereas Met+ MCs demonstrated worse performance relative to Met- MCs on the cognitive measures. No significant interaction was observed for the visuospatial speed composite (p=.938; η_p^2<.001).

Conclusions: These findings offer preliminary evidence to suggest that the Met allele may be protective in the context of remote mTBI. Findings need to be replicated using larger samples, and

Address correspondence to: Lisa Delano-Wood, Ph.D., VA San Diego Healthcare System (151B), 3350 La Jolla Village Drive, San Diego, CA 92161, Phone: (858) 552-8585 ×2667, ldelano@ucsd.edu.

Declaration of Interest Statement

The authors have no conflict of interests to report.

future studies are necessary to elucidate the precise mechanisms and neural underpinnings of this interaction.

Keywords

brain-derived neurotrophic factor; cognition; mild traumatic brain injury; neuropsychological assessment; military Veterans

Introduction

Understanding the acute and chronic effects of traumatic brain injury (TBI) is of paramount importance to the Department of Defense and the Department of Veterans Affairs healthcare systems. Notably, almost 400,000 medically diagnosed TBIs were sustained by military service members between 2000–2018, of which approximately 80% were classified as mild[1]. Although designated as “mild,” a wide range of clinically meaningful symptoms often develop acutely post-injury, including but not limited to problems with thinking and cognition[2]. Likewise, objective cognitive deficits as measured by neuropsychological testing are also apparent acutely following mild TBI (mTBI)[3–5]. Despite the expectation of symptom resolution and cognitive recovery within a few weeks to months after mTBI[4,6,7], negative sequelae can persist for many years[8–10]. Unfortunately, these persisting symptoms and concomitant deficits are often associated with a number of adverse outcomes, including problems with community reintegration following military separation as well as reduced psychosocial functioning and poor quality of life[11–13].

A number of theories have been proposed to account for the heterogeneous clinical outcomes experienced by patients with mTBI[14]. Demographic factors such as age, biological sex, and lifetime number of mTBIs have been evaluated as possible variables contributing to the widespread outcomes observed post-injury[15–17]. Pre-morbid factors such as cognitive or intellectual functioning and psychological or psychosocial well-being have also been examined as predictors of clinical outcome[18–20]. Furthermore, injury-specific factors such as mechanism of injury (blast versus blunt force), degree of combat exposure, and presence and duration of loss of consciousness (LOC) and/or posttraumatic amnesia (PTA) have been examined as potential contributors to recovery and outcome following mTBI[21–23]. Yet, despite these numerous pursuits, the prognostic factors identified above typically explain only a small portion of the variability, suggesting that other factors are involved in determining outcome. This has raised questions regarding the extent to which biological factors such as genetic predisposition impact recovery. However, at present, our understanding of the influence of genetic factors on clinical outcome following mTBI remains unclear and incomplete.

To date, the apolipoprotein E (APOE) gene has been the most extensively studied gene within the context of TBI[24–26]. For example, several studies have shown that head injury history interacts with APOE-ε4 genotype to contribute to poorer neuropsychological function[27] as well as accelerated age-related cognitive decline post-TBI and elevated risk for neurodegenerative disorders such as Alzheimer’s disease[28–31]. More recently, brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, has also received some

attention due to its association with central nervous system development and maintenance[32–35]. Specifically, BDNF is understood to be involved in neuronal growth and differentiation as well synaptic plasticity and connectivity[36–39]. Highly expressed within the cerebral cortex, especially in hippocampal and prefrontal regions, BDNF has been implicated in both neurocognitive functioning and the pathophysiology of complex neuropsychiatric (bipolar disorder, schizophrenia, posttraumatic stress disorder, etc.) and neurodegenerative (Alzheimer's disease, Parkinson's disease, etc.) disorders[32,35,40–42].

The *BDNF* gene has several known single nucleotide polymorphisms (SNPs)—one of which is rs6265, also referred to as the "Val66Met" BDNF polymorphism[43]. This particular SNP involves substitution of the amino acid valine ("Val", or Val*G) for methionine ("Met", or Met*A) at codon 66, resulting in the following three genotypes: Val/Val, Met/Val, or Met/Met. Importantly, the Val to Met substitution results in an alteration of gene structure, which in turn leads to improper protein folding and reduced binding of BDNF to its associated receptors[35]. At a cellular level, this polymorphism alters intracellular trafficking and secretion of BDNF in the brain, such that BDNF secretion is *reduced* in Met allele carriers[40,44]. Taken together, these observations have guided the general assumption in the literature that possession of a Met allele is associated with detrimental clinical outcomes.

Within the context of neurocognitive functioning, several studies examining both healthy and clinical populations (i.e., those with neuropsychiatric and neurodegenerative disorders) have found significant associations between the Val66Met BDNF polymorphism and cognition—namely on tests of memory and executive functioning[40,45,46]. With regard to memory, early work suggested that Met allele carriers (those homozygous and heterozygous for the Met allele) demonstrated worse performance on episodic and working memory tasks relative to non-Met carriers (Val/Val homozygotes)[44,47–49]. Similarly, when compared to their non-Met counterparts, Met carriers also performed more poorly on tasks associated with executive functioning[50,51]. However, a 2012 meta-analysis of 31 independent samples of both healthy and clinical populations showed that there was *not* a consistent significant association between the Val66Met polymorphism and cognition[36].

Adding to the complex BDNF literature, a recent review examining the impact of BDNF on cognition in healthy and clinical samples (e.g., Alzheimer's disease, Parkinson's disease, schizophrenia, bipolar disorder, etc.) demonstrated that about half of the studies included in the review found an association between the Val66Met polymorphism and cognition[52]. Notably, memory was the cognitive domain most frequently associated with BDNF genotype, followed by executive functioning. However, the direction of the relationship was not consistent across studies, as some investigators found evidence for the Val allele to be associated with better cognition, whereas others demonstrated protective effects of the Met allele on cognition. Authors of the review concluded that existing studies are inconclusive; however, they pointed to a possible dissociation in the literature such that non-Met carriers generally show better performance relative to Met carriers on tests of memory, whereas Met carriers tended to show better performance than non-Met carriers on tasks of executive functioning[52].

Studies examining the BDNF Val66Met polymorphism and neurocognitive functioning in TBI samples are far less extensive, though available findings are similarly equivocal. Notably, McAllister and colleagues[43] reported *slower* processing speed in those with the BDNF Met allele across a sample comprised of those with and without mild to moderate TBI. Another study examining mTBI found that the Met allele, compared to Val/Val homozygotes, was associated with worse performance on the Neuropsychological Assessment Battery[53]. However, in the context of penetrating (severe) TBI, Krueger and colleagues[54] reported that carriers of the BDNF Met allele made greater gains in executive functioning over time following TBI relative to non-Met (i.e., Val/Val) carriers. Comparatively, no genotype differences in episodic memory or general intelligence were observed[54]. Finally, in another study examining participants with penetrating TBI, Barbey et al.[55] found that those with the Met allele outperformed their Val/Val allele counterparts on all aspects of general intelligence, including verbal comprehension, perceptual reasoning, working memory, and processing speed.

Taken together, the influence of the BDNF Val66Met polymorphism on neurocognitive functioning following TBI is unclear, and the relationship between the two is likely complex. Notable issues contributing to mixed findings in the literature are differences in injury-related variables and demographic characteristics across studies. In addition, time since injury, or chronicity, is a key variable that may be particularly important when examining genetic associations and clinical outcome. Moreover, cognitive outcomes of interest have varied widely across studies, and many studies have not included a non-TBI control group for comparison. Given the heterogeneous and inconclusive findings in the literature, we sought to further clarify the relationship between the BDNF Val66Met polymorphism and cognition using a well-characterized sample of participants *with* and *without* a remote history of mTBI. We hypothesized that the BDNF Val66Met polymorphism would influence neurocognitive functioning and that this relationship would be moderated by Veterans' mTBI status.

Materials and Methods

Participants and Procedures

Participants included 138 Veterans (n=75 mTBI; n=63 MC's) who had largely (91.3%) served in Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and/or Operation New Dawn (OND). Veterans with a history of mTBI were primarily recruited from various outpatient clinics within the Veterans Affairs San Diego Healthcare System (VASDHS), as well as through posted study advertisements and word-of-mouth, and MC Veterans were primarily recruited through study advertisements and word-of-mouth. Study procedures involved completion of (1) a clinical interview to determine TBI history, (2) self-report measures assessing psychiatric distress, and (3) a comprehensive neuropsychological assessment. Veterans were also asked to provide a DNA sample via buccal swab for BDNF genotyping. The VASDHS institutional review board approved this study and all Veterans provided informed consent prior to their research participation.

Inclusion/Exclusion Criteria

Inclusion criteria included being a military Veteran between the ages of 18–55 who completed all study procedures, including providing a buccal sample for genetic analysis. Exclusion criteria included the following: (1) diagnosis of a severe mental illness (e.g., bipolar disorder, schizophrenia, or other related disorders); (2) diagnosis of a severe neurological disorder or medical condition (e.g., multiple sclerosis, Parkinson's disease, stroke, myocardial infarction); (3) diagnosis of a moderate or severe TBI according to VA/DoD criteria[56]; (4) any recent (within 30 days) or current substance or alcohol abuse or dependence according to *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, Text Revision* (DSM-IV-TR) criteria[57]; and (5) suboptimal performance (defined by manual-specific guidelines) on the Test of Memory Malingering (TOMM) Trial 2 *or* Retention Trial[58] *or* the California Verbal Learning Test-II (CVLT-II)[59] Forced Choice Recognition subtest. Given our interest in examining Veterans with remote mTBI histories, anyone tested *within one year* of their most recent mTBI was also excluded.

Measures

Clinical Interview—A modified version of the VA Semi-Structured Clinical Interview for TBI[60] was used to assess Veterans' history of TBI. The interview gathered information pertaining to injury-severity characteristics, including presence and duration of loss of consciousness (LOC), alteration of consciousness (AOC), and posttraumatic amnesia (PTA); mechanism and setting of injury (blast versus blunt-force trauma; military/combat versus civilian-related injury); and dates of each injury reported. Importantly, Veterans were queried about any head injuries that occurred prior to, during, and after their military service. The clinical interviews were conducted by trained post-baccalaureate or graduate-level researchers under the supervision of a licensed psychologist/neuropsychologist. When available (i.e., for those Veterans who had specifically been evaluated by a TBI or polytrauma clinic within the VASDHS), medical records were also reviewed to verify TBI history. To determine whether an injury met criteria for a mTBI, the VA/DoD Clinical Practice Guideline for Management of Concussion/Mild TBI[56] definition was used. According to this definition, a mTBI occurs when at least one of the following criteria have been met: (1) any period of LOC ≤ 30 minutes; (2) any period of AOC up to 24 hours; and/or (3) any period of PTA ≤ 24 hours. If an injury met diagnostic criteria for a mTBI, the Veteran was classified as a TBI participant. Those without a history of mTBI were classified as a MC participant.

Self-Report Questionnaires—Current PTSD symptoms were measured using the Posttraumatic Stress Disorder Checklist – Military Version (PCL-M)[61]. The PCL-M, a 17-item self-report questionnaire, was designed to assess DSM-IV-TR diagnostic criteria for PTSD. Using a scale ranging from 1–5, with "1" indicating "not at all" and "5" indicating "extremely," participants were asked to evaluate how much they have been bothered by each symptom over the past month. A total score (possible range: 17–85) was calculated by adding together the selected values from each item; higher scores indicate greater PTSD symptoms. The PCL-M has been frequently used in studies of military Veterans and its psychometric properties have been well established.

Current depressive symptoms were measured using the Beck Depression Inventory-II (BDI-II)[67]. The BDI-II, a 21-item self-report questionnaire, measures depressive symptomatology occurring over the past two weeks. Participants were asked to rate each item using a scale ranging from 0–3, and a total score (possible range: 0–63) was calculated by totaling the selected responses from each item; higher scores indicate greater depressive symptoms. Similar to the PCL-M, the BDI-II has been frequently used in studies of military Veterans[62] and the measure has excellent psychometric properties[67,68].

Neuropsychological Assessment—To assess premorbid intellectual functioning, the Reading subtest from the Wide Range Achievement Test 4 (WRAT4)[69] was administered. Additionally, the following core neuropsychological tests were administered: California Verbal Learning Test-Second Edition (CVLT-II)[59]; Logical Memory and Visual Reproduction from the Wechsler Memory Scale-Fourth Edition (WMS-IV)[70]; Rey Complex Figure Test (RCFT)[71]; Design Fluency, Trail Making, and Verbal Fluency from the Delis-Kaplan Executive Function System (D-KEFS)[72]; Block Design from the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II)[73]; Coding and Symbol Search from the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV)[74]; and the Wisconsin Card Sorting Test-64 Card Version (WCST-64)[75]. Finally, the Test of Memory Malingering (TOMM)[58] was administered as a stand-alone performance validity test, and the CVLT-II Forced Choice Recognition subtest[59] was used as an embedded performance validity test.

In total, 25 variables of interest were generated from the above core battery, and domain-specific cognitive composite scores were computed to reduce the number of comparisons made. First, all individual raw scores were transformed to *z* scores and adjustments were made to ensure that all variables could be interpreted in a uniform manner—that is, all variables were calculated so that *higher* scores reflect *better* performance. A theory-driven approach was then used to generate three domain-specific cognitive composites, and Cronbach's alpha (α) was used to evaluate the internal consistency of each composite. Specifically, measures assessing learning and memory were grouped together to create the "memory" composite (8 items; α = 0.86); measures assessing aspects of executive functioning were grouped together to create the "executive functioning" composite (10 items; α = 0.82); and measures assessing visuospatial speed were group together to create the "visuospatial speed" composite (7 items; α = 0.78). Table 1 displays the specific tests associated with each cognitive composite and Table 2 lists descriptive statistics associated with each individual neuropsychological variable.

Laboratory Genotyping Procedures

Buccal samples were obtained from each Veteran and DNA was extracted and analyzed to determine participants' BDNF (rs6265) genotype (Qiagen QIAamp DNA Purification Kit, #51306). Samples were quantified (Invitrogen Qubit dsDNA HS Assay Kit # Q32854) for polymerase chain reaction (PCR) amplification of BDNF (BDNF PCR with Platinum Taq DNA Polymerase Kit [Invitrogen #10966018] and dNTP mix 10mM [Invitrogen #18427013] were used [C_11592758_10 for SNP rs6265]). BDNF genotyping results for the overall sample were as follows: Met/Met (*n*=3, 2.2%), Met/Val (*n*=46, 33.3%), and Val/Val (*n*=89, 64.5%). Based on these observed frequencies, Veterans were divided into two groups

—Met+ (Met/Met and Met/Val) and Met- (Val/Val). Veterans were not informed of their BDNF genotype.

Statistical Analyses

Descriptive statistics were run on the overall sample, and the mTBI BDNF Met+, mTBI BDNF Met-, MC BDNF Met+, and MC BDNF Met- groups were compared using analyses of variance (ANOVAs) and chi-square tests or Fisher's exact tests, as appropriate, to determine whether groups differed on any sample characteristics. Next, correlations were conducted to assess relationships between independent variables (group and BDNF genotype), dependent variables (cognitive composite scores), and relevant sample characteristics. Finally, two-way analyses of covariance (ANCOVAs) were conducted to evaluate the effect of group (mTBI versus MC) and BDNF genotype (Met+ versus Met-) across the three cognitive composites (memory, executive functioning, and visuospatial speed), adjusting for necessary covariates (see below under "Results"). Partial eta-squared values (η_p^2) were used to indicate effect sizes (interpreted as 0.01 = small, 0.06 = medium, and 0.14 = large). The Statistical Package for the Social Sciences (SPSS; Version 25) was used to conduct all analyses, and $p < .05$ was used as our criterion for significance.

Results

Sample Characteristics

The overall sample (N=138) included 75 Veterans with a history of mTBI (BDNF Met+ = 30, BDNF Met- = 45) and 63 MC participants without a history of mTBI (BDNF Met+ = 19, BDNF Met- = 44). Participants were predominantly male Veterans (78.3%) who served in the Navy (35.6%), Marines (33.3%), Army (23.7%), and Air Force (7.4%). On average, Veterans were 32.6 years of age (*SD* = 7.1; *Range* = 22–53 years) at the time of study participation and had completed 14.5 years of education (*SD* = 1.8; *Range* = 10–18 years).

Sample characteristics for the mTBI BDNF Met+, mTBI BDNF Met-, MC BDNF Met+, and MC BDNF Met- groups are displayed in Table 3. As expected, groups differed with respect to PTSD and depressive symptomatology, such that the mTBI groups endorsed significantly greater psychiatric distress relative to the MC groups. Additionally, groups differed on sex, such that the Met- groups had a higher proportion of females relative to the Met+ groups. Otherwise, there were no group differences with respect to age, years of education, WRAT4 Reading performance, and ethnicity/race.

Participants with mTBI were evaluated roughly 66.7 months (*SD* = 33.96; *Mdn* = 61; *Range* = 12–156 months) following their most *recent* mTBI; the two mTBI groups (mTBI BDNF Met+ and mTBI BDNF Met-) did not differ on this variable. The majority (77.0%) had a history of multiple (at least 2 or more) mTBIs, with an average of 2.5 lifetime mTBIs (*SD* = 1.37; *Mdn* = 2; *Range* = 1–8). With regard to injury severity characteristics, 57.3% of the sample experienced LOC during their most significant mTBI, 42.7% experienced AOC, and 52.0% experienced PTA. Finally, 65.3% of the mTBI sample reported a history of blast exposure.

Selection of Covariates

To determine relevant covariates for our main analyses, we evaluated relationships between independent variables, dependent variables, and sample characteristics. Correlation analyses are presented in Table 4. Regarding our independent variables of interest, group status (mTBI vs. MC) was significantly associated with the memory composite, years of education, and the PCL-M and BDI-II total scores; BDNF genotype (Met+ vs. Met-) was significantly associated with sex. Additionally, all three cognitive composite scores (our dependent variables of interest) were significantly associated with each other, as well as performance on the WRAT4 Reading subtest, the PCL-M and BDI-II total scores, sex, and ethnicity/race. Given these significant associations, the PCL-M (i.e., PTSD symptoms)[1], sex, years of education, and ethnicity/race were used as covariates in our main analyses.

Neurocognitive Functioning

Results of a 2×2 ANCOVA adjusting for PTSD symptoms, sex, years of education, and ethnicity/race did not yield significant main effects for group (mTBI versus MC; $p = .587$; $\eta_p^2 = .002$) or BDNF genotype (Met+ versus Met-; $p = .682$; $\eta_p^2 = .001$) on the memory composite. However, a significant interaction was found ($F(1, 130) = 5.23$, $p = .024$; $\eta_p^2 = .039$) such that the Met+ mTBI group demonstrated better performance than the Met- mTBI group on the memory composite, whereas the Met+ MC group demonstrated worse performance relative to the Met- MC group on the memory composite. Figure 1a shows adjusted means and standard errors for the memory composite, and unadjusted means and standard deviations are presented in Table 5.

Given that the memory composite may be confounded by executive functioning (as demonstrated by the high correlation between the memory and executive functioning composites; see Table 4), a follow-up 2×2 ANCOVA was conducted to further isolate memory, adding the executive functioning composite as an additional covariate. Results of this ANCOVA (adjusting for PTSD symptoms, sex, years of education, ethnicity/race, and the executive functioning composite) no longer revealed a significant group × BDNF genotype interaction ($F(1, 129) = 1.68$, $p = .197$; $\eta_p^2 = .013$).

When the executive functioning composite was evaluated as the dependent variable, results of a 2×2 ANCOVA adjusting for PTSD symptoms, sex, years of education, and ethnicity/race did not yield significant main effects for group ($p = .089$; $\eta_p^2 = .022$) or BDNF genotype ($p = .845$; $\eta_p^2 < .001$). However, a significant interaction was found ($F(1, 130) = 6.78$, $p = .010$; $\eta_p^2 = .050$) such that the Met+ mTBI group exhibited better performance than the Met- mTBI group on the executive functioning composite, whereas the Met+ MC group showed poorer performance relative to the Met- MC group on the executive functioning composite. Figure 1b shows adjusted means and standard errors for the executive functioning composite, and unadjusted means and standard deviations are presented in Table 5.

[1]The PCL-M and BDI-II total scores were highly associated with one another; as a result, only one measure of psychiatric distress was used as a covariate in the main analyses. In this case, the PCL-M was selected as a covariate due to its overall greater associations with the independent and dependent variables (see Table 4).

Given that the executive functioning composite may be confounded by the visuospatial speed composite (as demonstrated by the high correlation between the executive functioning and visuospatial speed composites; see Table 4), a follow-up 2×2 ANCOVA was conducted to further isolate executive functioning, adding the visuospatial speed composite as an additional covariate. When this additional covariate was added, results remained significant ($F(1, 129) = 8.60$, $p = .004$; $\eta_p^2 = .063$).

Finally, results of a 2×2 ANCOVA adjusting for PTSD symptoms, sex, years of education, and ethnicity/race did not yield significant main effects for group ($p = .160$; $\eta_p^2 = .015$) or BDNF genotype ($p = .860$; $\eta_p^2 < .001$) on the visuospatial speed composite, and the interaction was also not significant ($p = .938$; $\eta_p^2 < .001$). Figure 1c shows adjusted means and standard errors for the visuospatial speed composite, and unadjusted means and standard deviations are presented in Table 5.

Results for all analyses held when the BDI-II was added as a covariate in follow-up 2×2 ANCOVAs. Specifically, there continued to be a significant group by genotype interaction on the memory ($p = .031$, $\eta_p^2 = .036$) and executive functioning ($p = .011$, $\eta_p^2 = .050$) composites when PTSD symptom, depression symptoms, sex, years of education, and ethnicity/race were included as covariates.

Discussion

Previous studies examining the relationship between BDNF genotype and neuropsychological functioning following TBI have used disparate, heterogeneous samples and the focus has been on more severely injured samples. Furthermore, prior studies have examined a wide range of time intervals (acute/post-acute to remote TBI) for post-injury assessment and have inconsistently included a comparison control group. Given that these methodological differences have resulted in conflicting and inconsistent findings in the literature, our primary objective was to use a well-defined sample of participants with and without a history of remote mTBI to examine the influence of the BDNF Val66Met polymorphism on cognitive functioning. Using this approach, our preliminary results suggest a dissociation of BDNF genotype on neuropsychological performance across groups studied. Specifically, among Veterans with a history of mTBI, BDNF Met carriers showed *better* performance relative to non-carriers on measures of memory and executive functioning, whereas the opposite was true for our military control Veterans—that is, BDNF Met carriers showed *worse* performance relative to non-carriers on measures of memory and executive functioning. Our findings lend support to the notion that the Met allele may be protective in the context of remote mTBI but less beneficial in Veterans without a history of neurotrauma.

To our knowledge, the present study is the first to establish an interaction between history of TBI and BDNF genotype on cognitive functioning in the context of *mild* TBI among Veterans. Few prior studies have examined this interaction—even in the broader TBI literature—and findings from these available studies are largely equivocal. Somewhat consistent with our results, Krueger et al.[54] showed that relative to non-Met carriers (i.e., Val/Val homozygotes), Met carriers demonstrated *better* cognition—specifically, better

executive functioning—in those with a remote history of penetrating TBI, although they found no effects of BDNF in their control group. In contrast, McAllister et al.[43] demonstrated that the Met allele was associated with *poorer* processing speed across participants with and without a history of mild to moderate TBI; however, no differences in processing speed were observed between Met carriers and non-carriers when the sample was limited to only the TBI sample[43]. Furthermore, study authors found that the Val66Met polymorphism was *not* associated with memory measures in either the TBI or control group. Interestingly, both our study and Krueger et al.[54] examined military Veterans with *remote* TBI histories whereas McAllister et al.[43] examined participants one month post-injury, which could explain the disparate findings. Additionally, BDNF genotype groups were defined differently in the above studies; whereas McAllister et al.[43] examined all three genotype groups (Met/Met, Met/Val, and Val/Val), we combined the two Met allele groups into a single "Met+" group (Met/Met + Met/Val) due to the low frequency of Met homozygotes in our sample. Krueger et al.[54] utilized a similar approach as ours, suggesting that this methodological difference may have also contributed to the inconsistent findings.

In addition to the above studies, others have evaluated the relationship between the BDNF Val66Met polymorphism and cognition using only a TBI sample. For example, Barbey et al.[55] showed that the Met allele was associated with *better* general intelligence (i.e., verbal comprehension, perceptual reasoning, working memory, and processing speed) in military Veterans with a history of penetrating TBI who were evaluated in the chronic phase of injury. However, another study evaluating BDNF genotype and cognition in the context of civilian mTBI found that Met carriers performed more poorly than non-Met carriers on the Neuropsychological Assessment Battery both acutely (~5 hours) and at six months following injury[53]. Given these findings coupled with our observations in the current study, it is possible that the effect of the Val66Met polymorphism on cognitive functioning is dependent upon injury-specific variables (i.e., injury severity, mechanism of injury, chronicity of injury, etc.) that synergistically influence recovery and outcome following TBI. While it is difficult to disentangle variables that may be contributing to the discrepant findings in the literature, it is notable that release of BDNF is activity-dependent, and its secretion varies by brain region[76]. Therefore, given that injury due to head-trauma is highly heterogeneous, it is possible that BDNF secretion may be contingent upon whether or not particular brain regions were injured during the initial insult and the extent of neural injury. Clearly, the link between the BDNF Val66Met polymorphism and cognition following TBI is complex, and future studies are needed to further tease apart these relationships.

From a mechanistic perspective, studies have shown that the Val to Met substitution occurs in the portion of the BDNF gene that encodes the precursor peptide (pro-BDNF), which is later cleaved to form the mature neurotrophin (mature-BDNF)[44,76]. Notably, the Val66Met polymorphism has been shown to directly influence the processing and release of pro-BDNF, but indirectly affects activity-dependent secretion of mature-BDNF[76]. Pro- and mature-BDNF interact with different receptors (tumor necrosis factor receptor [p75NTR] versus a receptor of the tyrosine kinase group [TrkB], respectively) and thus are associated with different functions within the central nervous system; whereas pro-BDNF promotes apoptosis and suppression of axonal growth, mature-BDNF regulates neuronal survival, dendritic branching, and synaptic plasticity.[78] Importantly, prior research has shown that

pro-BDNF is upregulated in the central nervous system following neurotrauma[55]. As such, decreased pro-BDNF secretion may limit apoptosis of surviving cells, suggesting that the Met allele may potentially have a protective role in the context of neurotrauma[76,78–80]. Other studies investigating different clinical samples (e.g., multiple sclerosis, systemic lupus erythematosus) have also demonstrated similar protective effects of the Met allele on cognition[55], and a mouse model of experimental stroke showed that long-term functional recovery was enhanced in Met carriers[81,82]. Moreover, another study found that Met but not Val allele status was protective against depression in the presence of greater physical exercise[88], raising the possibility that neurobehavioral outcomes may be modified by important environmental variables in a manner specific to Met allele carriers. Taken together, there appears to be growing support for the possibility of differential effects of the Met allele on neuropsychological outcomes in clinical versus healthy samples, and this may further speak to the possible underlying mechanisms associated with the dissociation of the Val66Met polymorphism on cognition that we observed in the present study among our mTBI and healthy control Veterans. Additionally, age at time of injury may also be a salient factor in this relationship, as previous studies have suggested that the association between BDNF genotype and cognition may be age-dependent[54,55,76,77]. If this is true, perhaps age interacts with the ratio of pro- and mature-BDNF levels, which may ultimately have differential effects on cognition. Although future studies are needed in order to further investigate the underlying mechanisms associated with this relationship using both human and animal models, there appears to be some evidence to suggest that the balance between pro- and mature-BDNF plays an important role in clinical outcomes such as cognitive functioning[78].

Finally, neuroimaging studies may also help to elucidate the neural underpinnings of the relationship between the BDNF Val66Met polymorphism and cognitive functioning in those with and without a history of mTBI. Although prior imaging research has been conducted examining the relationship between BDNF and gray and white matter morphometry in healthy samples[83–86], few studies have investigated such relationships in the context of mild TBI. Thus, an important next step may be to examine the structural neural correlates of the present findings to help clarify the potential protective role of the Met allele in the context of mTBI. It is also important to consider that the association between the BDNF Val66Met polymorphism and cognition may also be contingent on additional factors (i.e., age, sex, time since injury, number of previous TBIs) that synergistically influence recovery and outcome following TBI[76].

Our study has several strengths including a carefully characterized, well-defined sample of Veterans with a history of remote mTBI and the inclusion of a military control group that allowed for the examination of group by BDNF genotype interactions on neurocognitive functioning. However, there are some important limitations that should be considered when interpreting the results. First, we specifically evaluated military Veterans and therefore it is unknown how our findings may generalize to non-Veteran samples. Relatedly, our focus was on evaluating the influence of the BDNF Val66Met polymorphism on neurocognitive functioning in those with a *remote* history of mTBI (i.e., at least one year or more post-injury); thus, our results may have less relevance for those who are evaluated in the acute phase of injury. As indicated previously, time since injury may play an important role in the

relationship between BDNF genotype and cognition, and ongoing studies are necessary to address whether the BDNF Val66Met polymorphism differentially impacts cognitive outcome in those with acute versus chronic TBIs. Furthermore, determining the relationship between genetics, injury chronicity, and lifetime number of mTBIs may also be an important avenue of future research.

Beyond issues of generalizability, other limitations include a smaller sample size and therefore insufficient power, which has been a common limitation noted across the TBI-genetics literature[43,53]. Of note, Ioannidis and colleagues[87] indicated that caution must be taken when interpreting findings from genetic studies that are likely underpowered; thus, we caution readers to interpret our findings as preliminary, and we suggest that larger-scale/population-based studies are needed in order to confirm the associations identified in the current study. It should also be noted that due to the low frequency of Met homozygotes in our sample, we combined Met/Met-carriers with Met/Val-carriers into a single "Met+" group and compared those participants to Val homozygotes. Future research with larger samples is needed in order to evaluate Met homozygotes as well as the contribution of other genetic polymorphisms (e.g., APOE) that may interact with BDNF to influence outcomes. Finally, the data from this study were cross-sectional, and future studies will need to employ longitudinal designs in order to more fully understand the association of the BDNF Val66Met polymorphisms and cognitive functioning following TBI.

In summary, findings from the present study revealed a dissociation such that BDNF Met carriers with a history of mTBI showed *better* performance relative to non-Met carriers on measures of memory and executive functioning, whereas BDNF Met carriers without a history of mTBI showed *worse* performance relative to non-Met carriers on measures of memory and executive functioning, offering preliminary evidence to suggest that the Met allele may be protective in the context of mTBI but less beneficial in Veterans without an mTBI history. In addition to establishing this important group by genotype interaction, results from our study suggest that continuing to explore genetic influences on cognitive outcome following mTBI may have important clinical implications. For example, determining the extent to which genetic factors contribute to post-injury outcome has the potential to offer critical information to healthcare providers and patients. Importantly, this information could have profound relevance to treatments that are currently being developed and optimized within a precision medicine approach in order to help those at greatest risk for poor recovery and outcome following mTBI. As this research continues to evolve, it will also be necessary to examine gene by gene and gene by environment interactions on cognitive outcome following TBI. This avenue of research promises to be a rich area of study that will undoubtedly have important clinical implications, especially as we move toward a more personalized approach to medicine.

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References

1. DVBIC. DoD Numbers for Traumatic Brain Injury In: (AFHSB) AFHSC, ed. Falls Church VA: Defense and Veterans Brain Injury Center; 2018.
2. Vanderploeg RD, Silva MA, Soble JR, et al. The structure of postconcussion symptoms on the Neurobehavioral Symptom Inventory: A comparison of alternative models. Journal of Head Trauma Rehabilitation. 2015;30(1):1–11. [PubMed: 24263177]
3. Dolan S, Martindale S, Robinson J, et al. Neuropsychological sequelae of PTSD and TBI following war deployment among OEF/OIF veterans. Neuropsychology Review. 2012;22(1):21–34. [PubMed: 22350690]
4. Belanger HG, Curtiss G, Demery JA, Lebowitz BK, Vanderploeg RD. Factors moderating neuropsychological outcomes following mild traumatic brain injury: A meta-analysis. Journal of the International Neuropsychological Society. 2005;11(3):215–227. [PubMed: 15892898]
5. Kelly MP, Coldren RL, Parish RV, Dretsch MN, Russell ML. Assessment of acute concussion in the combat environment. Archives of Clinical Neuropsychology. 2012;27(4):375–388. [PubMed: 22491730]
6. O'Neil ME, Carlson KF, Storzbach D, et al. Factors associated with mild traumatic brain injury in veterans and military personnel: A systematic review. Journal of the International Neuropsychological Society. 2014;20(3):249–261. [PubMed: 24622505]
7. Schretlen DJ, Shapiro AM. A quantitative review of the effects of traumatic brain injury on cognitive functioning. International Review of Psychiatry. 2003;15(4):341–349. [PubMed: 15276955]
8. Dikmen S, Machamer J, Fann JR, Temkin NR. Rates of symptom reporting following traumatic brain injury. Journal of the International Neuropsychological Society. 2010;16(3):401–411. [PubMed: 20188017]
9. McInnes K, Friesen CL, MacKenzie DE, Westwood DA, Boe SG. Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. PloS one. 2017;12(4):e0174847.
10. MacDonald CL, Barber J, Jordan M, et al. Early clinical predictors of 5-year outcome after concussive blast traumatic brain injury. JAMA Neurology. 2017;74(4):821–829. [PubMed: 28459953]
11. Boosman H, Winkens I, van Heugten C, Rasquin S, Heijnen V, Visser-Meily J. Predictors of health-related quality of life and participation after brain injury rehabilitation: The role of neuropsychological factors. Neuropsychological Rehabilitation. 2017;27(4):581–598. [PubMed: 26609798]
12. Dikmen S, Machamer J, Temkin N. Mild traumatic brain injury: longitudinal study of cognition, functional status, and post-traumatic symptoms. Journal of Neurotrauma. 2017;34(8):1524–1530. [PubMed: 27785968]
13. Taylor BC, Hagel EM, Carlson KF, et al. Prevalence and costs of co-occurring traumatic brain injury with and without psychiatric disturbance and pain among Afghanistan and Iraq War Veteran VA users. Medical Care. 2012;50(4):342–346. [PubMed: 22228249]
14. Belanger HG, Tate DF, Vanderploeg R. Concussion and Mild Traumatic Brain Injury In: Morgan JE, Ricker JH, eds. Textbook of Clinical Neuropsychology, Second Edition New York: Routledge (Taylor & Francis Group); 2018.
15. Albrecht MA, Masters CL, Ames D, Foster JK, Group AR. Impact of mild head injury on neuropsychological performance in healthy older adults: longitudinal assessment in the AIBL cohort. Frontiers in Aging Neuroscience. 2016;8:105. [PubMed: 27242516]
16. Brickell TA, Lippa SM, French LM, Kennedy JE, Bailie JM, Lange RT. Female service members and symptom reporting after combat and non-combat-related mild traumatic brain injury. Journal of Neurotrauma. 2017;34(2):300–312. [PubMed: 27368356]
17. Dretsch MN, Silverberg ND, Iverson GL. Multiple past concussions are associated with ongoing post-concussive symptoms but not cognitive impairment in active-duty army soldiers. Journal of Neurotrauma. 2015;32(17):1301–1306. [PubMed: 25763565]
18. Marx BP, Doron-Lamarca S, Proctor SP, Vasterling JJ. The influence of pre-deployment neurocognitive functioning on post-deployment PTSD symptom outcomes among Iraq-deployed

Army soldiers. Journal of the International Neuropsychological Society. 2009;15(6):840–852. [PubMed: 19891817]

19. Merritt VC, Lange RT, French LM. Resilience and symptom reporting following mild traumatic brain injury in military service members. Brain Injury. 2015;29(11):1325–1336. [PubMed: 26204318]
20. Ponsford J Factors contributing to outcome following traumatic brain injury. NeuroRehabilitation. 2013;32(4):803–815. [PubMed: 23867406]
21. Cooper DB, Kennedy JE, Cullen MA, Critchfield E, Amador RR, Bowles AO. Association between combat stress and post-concussive symptom reporting in OEF/OIF service members with mild traumatic brain injuries. Brain Injury. 2011;25(1):1–7. [PubMed: 21117916]
22. Lange RT, Brickell T, French LM, et al. Risk factors for postconcussion symptom reporting after traumatic brain injury in US military service members. Journal of Neurotrauma. 2013;30(4):237–246. [PubMed: 23126461]
23. Reid MW, Miller KJ, Lange RT, et al. A multisite study of the relationships between blast exposures and symptom reporting in a post-deployment active duty military population with mild traumatic brain injury. Journal of Neurotrauma. 2014;31(23):1899–1906. [PubMed: 25036531]
24. Lawrence DW, Comper P, Hutchison MG, Sharma B. The role of apolipoprotein E episilon (ε)-4 allele on outcome following traumatic brain injury: A systematic review. Brain Injury. 2015;29(9):1018–1031. [PubMed: 25915580]
25. Zhou W, Xu D, Peng X, Zhang Q, Jia J, Crutcher KA. Meta-analysis of APOE 4 allele and outcome after traumatic brain injury. Journal of Neurotrauma. 2008;25(4):279–290. [PubMed: 18373478]
26. Bennett ER, Reuter-Rice K, Laskowitz DT. Genetic influences in traumatic brain injury In: Laskowitz D, Grant G, eds. Translational Research in Traumatic Brain Injury. Boca Raton, Florida: CRCPress/Taylor and Francis Group; 2016:1–32.
27. Merritt VC, Clark A, Sorg S, et al. Apolipoprotein E (APOE) ε4 genotype is associated with reduced neuropsychological performance in military veterans with a history of mild traumatic brain injury. Journal of Clinical and Experimental Neuropsychology. 2018.
28. McFadyen C, Zeiler FA, Newcombe V, et al. The Apolipoprotein E4 polymorphism and outcomes from traumatic brain injury: a living systematic review and meta-analysis. Journal of Neurotrauma. 2019;[epub ahead of print].
29. Koponen S, Taiminen T, Kairisto V, et al. APOE-ε4 predicts dementia but not other psychiatric disorders after traumatic brain injury. Neurology. 2004;63(4):749–750. [PubMed: 15326261]
30. Isoniemi H, Tenovuo O, Portin R, Himanen L, Kairisto V. Outcome of traumatic brain injury after three decades—relationship to ApoE genotype. Journal of Neurotrauma. 2006;23(11):1600–1608. [PubMed: 17115907]
31. Griesbach GS, Masel BE, Helvie RE, Ashley MJ. The impact of traumatic brain injury on later life: Effects on normal aging and neurodegenerative diseases. Journal of Neurotrauma. 2018;35(1):17–24. [PubMed: 28920532]
32. Bath KG, Lee FS. Variant BDNF (Val66Met) impact on brain structure and function. Cognitive, Affective, & Behavioral Neuroscience. 2006;6(1):79–85.
33. Huang EJ, Reichardt LF. Neurotrophins: Roles in neuronal development and function. Annual Review of Neuroscience. 2001;24(1):677–736.
34. Lipsky RH, Marini AM. Brain-derived neurotrophic factor in neuronal survival and behavior-related plasticity. Annals of the New York Academy of Sciences. 2007;1122(1):130–143. [PubMed: 18077569]
35. Shen T, You Y, Joseph C, et al. BDNF polymorphism: A review of its diagnostic and clinical relevance in neurodegenerative disorders. Aging and Disease. 2018;9(3):523–536. [PubMed: 29896439]
36. Mandelman SD, Grigorenko EL. BDNF Val66Met and cognition: all, none, or some? A meta-analysis of the genetic association. Genes, Brain and Behavior. 2012;11(2):127–136.
37. Chen Z, Bath K, McEwen B, Hempstead B, Lee F. Impact of genetic variant BDNF (Val66Met) on brain structure and function. Novartis Foundation Symposia 2008;289:180–195.

38. Park H, Poo M-m. Neurotrophin regulation of neural circuit development and function. Nature Reviews Neuroscience. 2013;14(1):7–23. [PubMed: 23254191]
39. Cohen-Cory S, Kidane AH, Shirkey NJ, Marshak S. Brain-derived neurotrophic factor and the development of structural neuronal connectivity. Developmental Neurobiology. 2010;70(5):271–288. [PubMed: 20186709]
40. Dincheva I, Glatt CE, Lee FS. Impact of the BDNF Val66Met polymorphism on cognition: implications for behavioral genetics. The Neuroscientist. 2012;18(5):439–451. [PubMed: 22367929]
41. Gratacòs M, González JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X. Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. Biological Psychiatry. 2007;61(7):911–922. [PubMed: 17217930]
42. Adachi N, Numakawa T, Richards M, Nakajima S, Kunugi H. New insight in expression, transport, and secretion of brain-derived neurotrophic factor: implications in brain-related diseases. World journal of biological chemistry. 2014;5(4):409–428. [PubMed: 25426265]
43. McAllister TW, Tyler AL, Flashman LA, et al. Polymorphisms in the brain-derived neurotrophic factor gene influence memory and processing speed one month after brain injury. Journal of Neurotrauma. 2012;29(6):1111–1118. [PubMed: 22188054]
44. Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003;112(2):257–269. [PubMed: 12553913]
45. Pezawas L, Verchinski BA, Mattay VS, et al. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. Journal of Neuroscience. 2004;24(45):10099–10102. [PubMed: 15537879]
46. Savitz J, Solms M, Ramesar R. The molecular genetics of cognition: Dopamine, COMT and BDNF. Genes, Brain and Behavior. 2006;5(4):311–328.
47. Ho B-C, Milev P, O'Leary DS, Librant A, Andreasen NC, Wassink TH. Cognitive and magnetic resonance imaging brain morphometric correlates of brain-derived neurotrophic factor Val66Met gene polymorphism in patients with schizophrenia and healthy volunteers. Archives of General Psychiatry. 2006;63(7):731–740. [PubMed: 16818862]
48. Hariri AR, Goldberg TE, Mattay VS, et al. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. Journal of Neuroscience. 2003;23(17):6690–6694. [PubMed: 12890761]
49. Dempster E, Toulopoulou T, McDonald C, et al. Association between BDNF val66 met genotype and episodic memory. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2005;134(1):73–75.
50. Rybakowski JK, Borkowska A, Czerski PM, Skibińska M, Hauser J. Polymorphism of the brain-derived neurotrophic factor gene and performance on a cognitive prefrontal test in bipolar patients. Bipolar Disorders. 2003;5(6):468–472. [PubMed: 14636373]
51. Rybakowski JK, Borkowska A, Skibinska M, et al. Prefrontal cognition in schizophrenia and bipolar illness in relation to Val66Met polymorphism of the brain-derived neurotrophic factor gene. Psychiatry and Clinical Neurosciences. 2006;60(1):70–76. [PubMed: 16472361]
52. Toh YL, Ng T, Tan M, Tan A, Chan A. Impact of brain-derived neurotrophic factor genetic polymorphism on cognition: A systematic review. Brain and Behavior. 2018;8:e01009.
53. Narayanan V, Veeramuthu V, Ahmad-Annuar A, et al. Missense mutation of brain derived neurotrophic factor (BDNF) alters neurocognitive performance in patients with mild traumatic brain injury: A longitudinal study. PloS One. 2016;11(7):e0158838.
54. Krueger F, Pardini M, Huey ED, et al. The role of the Met66 brain-derived neurotrophic factor allele in the recovery of executive functioning after combat-related traumatic brain injury. Journal of Neuroscience. 2011;31(2):598–606. [PubMed: 21228168]
55. Barbey AK, Colom R, Paul E, et al. Preservation of general intelligence following traumatic brain injury: contributions of the Met66 brain-derived neurotrophic factor. PLoS One. 2014;9(2):e88733.
56. The Management of Concussion-mild Traumatic Brain Injury Working Group. VA/DoD Clinical Practice Guideline for the Management of Concussion-Mild Traumatic Brain Injury. 2016.

57. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, forth edition, text revision. Washington, DC: American Psychiatic Association; 2000.
58. Tombaugh TN. Test of Memory Malingering: TOMM. Tonawanda, NY: Multi-Health Systems North 1996.
59. Delis D, Kramer J, Kaplan E, Ober B. California Verbal Learning Test: Adult version manual (2nd ed.). San Antonio, TX 2000.
60. Vanderploeg RD, Groer S, Belanger HG. Initial developmental process of a VA semistructured clinical interview for TBI identification. Journal of Rehabilitation Research & Development. 2012;49(4):545–556. [PubMed: 22773258]
61. Weathers FW, Huska JA, Keane TM. PCL-M for DSM-IV. 1991; Boston, MA.
62. Morissette SB, Woodward M, Kimbrel NA, et al. Deployment-related TBI, persistent postconcussive symptoms, PTSD, and depression in OEF/OIF veterans. Rehabilitation Psychology. 2011;56(4):340–350. [PubMed: 22121940]
63. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD Checklist (PCL). Behaviour Research and Therapy. 1996;34(8):669–673. [PubMed: 8870294]
64. Bliese PD, Wright KM, Adler AB, Cabrera O, Castro CA, Hoge CW. Validating the primary care posttraumatic stress disorder screen and the Posttraumatic Stress Disorder Checklist with soldiers returning from combat. Journal of Consulting and Clinical Psychology. 2008;76(2):272–281. [PubMed: 18377123]
65. Keen SM, Kutter CJ, Niles BL, Krinsley KE. Psychometric properties of PTSD Checklist in sample of male veterans. Journal of Rehabilitation Research & Development. 2008;45(3).
66. Wilkins KC, Lang AJ, Norman SB. Synthesis of the psychometric properties of the PTSD checklist (PCL) military, civilian, and specific versions. Depression and Anxiety. 2011;28(7):596–606. [PubMed: 21681864]
67. Beck AT, Steer RA, Brown G. Manual for the Beck Depression Inventory Second Edition (BDI-II). San Antonio: Psychological Corporation; 1996.
68. Storch EA, Roberti JW, Roth DA. Factor structure, concurrent validity, and internal consistency of the beck depression inventory—second edition in a sample of college students. Depression and Anxiety. 2004;19(3):187–189. [PubMed: 15129421]
69. Wilkinson GS, Robertson G. Wide Range Achievement Test 4 (WRAT4). Lutz, FL: Psychological Assessment Resources, Inc.; 2006.
70. Wechsler D Wechsler Memory Scale–Fourth Edition (WMS–IV). San Antonio, TX NCS Pearson; 2009.
71. Meyers JE, Meyers KR. Rey Complex Figure Test and Recognition Trial: Professional Manual. Lutz, FL: Psychological Assessment Resources, Inc.; 1995.
72. Delis D, Kaplan E, Kramer J. Delis-Kaplan Executive Function System (D-KEFS). San Antonio, TX: The Psychological Corporation; 2001.
73. Wechsler D Wechsler Abbreviated Scale of Intelligence–Second Edition (WASI-II). NCS Pearson: San Antonio, TX; 2011.
74. Wechsler D Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV). San Antonio, TX: NCS Pearson; 2008.
75. Kongs SK, Thompson LL, Iverson GL, Heaton R. Wisconsin Card Sorting Test-64 Card Version (WCST-64). Odessa, FL: Psychological Assessment Resources; 2000.
76. Finan JD, Udani SV, Patel V, Bailes JE. The Influence of the Val66Met Polymorphism of Brain-Derived Neurotrophic Factor on Neurological Function after Traumatic Brain Injury. Journal of Alzheimer's Disease. 2018;65(4):1055–1064.
77. Failla MD, Kumar RG, Peitzman AB, Conley YP, Ferrell RE, Wagner AK. Variation in the BDNF gene interacts with age to predict mortality in a prospective, longitudinal cohort with severe TBI. Neurorehabilitation and Neural Repair. 2015;29(3):234–246. [PubMed: 25063686]
78. Borodinova A, Salozhin S. Differences in the Biological Functions of BDNF and proBDNF in the Central Nervous System. Neuroscience and Behavioral Physiology. 2017;47(3):251–265.
79. Poo M-m. Neurotrophins as synaptic modulators. Nature Reviews Neuroscience. 2001;2(1):24–32. [PubMed: 11253356]

80. Bekinschtein P, Cammarota M, Izquierdo I, Medina JH. BDNF and memory formation and storage. The Neuroscientist. 2008;14(2):147–156. [PubMed: 17911219]

81. Qin L, Jing D, Parauda S, et al. An adaptive role for BDNF Val66Met polymorphism in motor recovery in chronic stroke. Journal of Neuroscience. 2014;34(7):2493–2502. [PubMed: 24523540]

82. Qin L, Kim E, Ratan R, Lee FS, Cho S. Genetic variant of BDNF (Val66Met) polymorphism attenuates stroke-induced angiogenic responses by enhancing anti-angiogenic mediator CD36 expression. Journal of Neuroscience. 2011;31(2):775–783. [PubMed: 21228186]

83. Kim SN, Kang D-H, Yun J-Y, et al. Impact of the BDNF Val66Met polymorphism on regional brain gray matter volumes: Relevance to the stress response. Psychiatry Investigation. 2013;10(2):173. [PubMed: 23798966]

84. Tost H, Alam T, Geramita M, et al. Effects of the BDNF val 66 met polymorphism on white matter microstructure in healthy adults. Neuropsychopharmacology. 2013;38(3):525–532. [PubMed: 23132269]

85. Forde NJ, Ronan L, Suckling J, et al. Structural neuroimaging correlates of allelic variation of the BDNF val66met polymorphism. Neuroimage. 2014;90:280–289. [PubMed: 24384148]

86. Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, Zubieta J-K. BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. Biological Psychiatry. 2006;59(9):812–815. [PubMed: 16442082]

87. Ioannidis JP, Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG. Genetic associations in large versus small studies: an empirical assessment. The Lancet. 2003;361(9357):567–571.

88. Mata J Thompson RJ, & Gotlib IH BDNF genotype moderates the relation between physical activity and depressive symptoms. Health Psychology. 2010;29(2):130–133. [PubMed: 20230085]

(a)

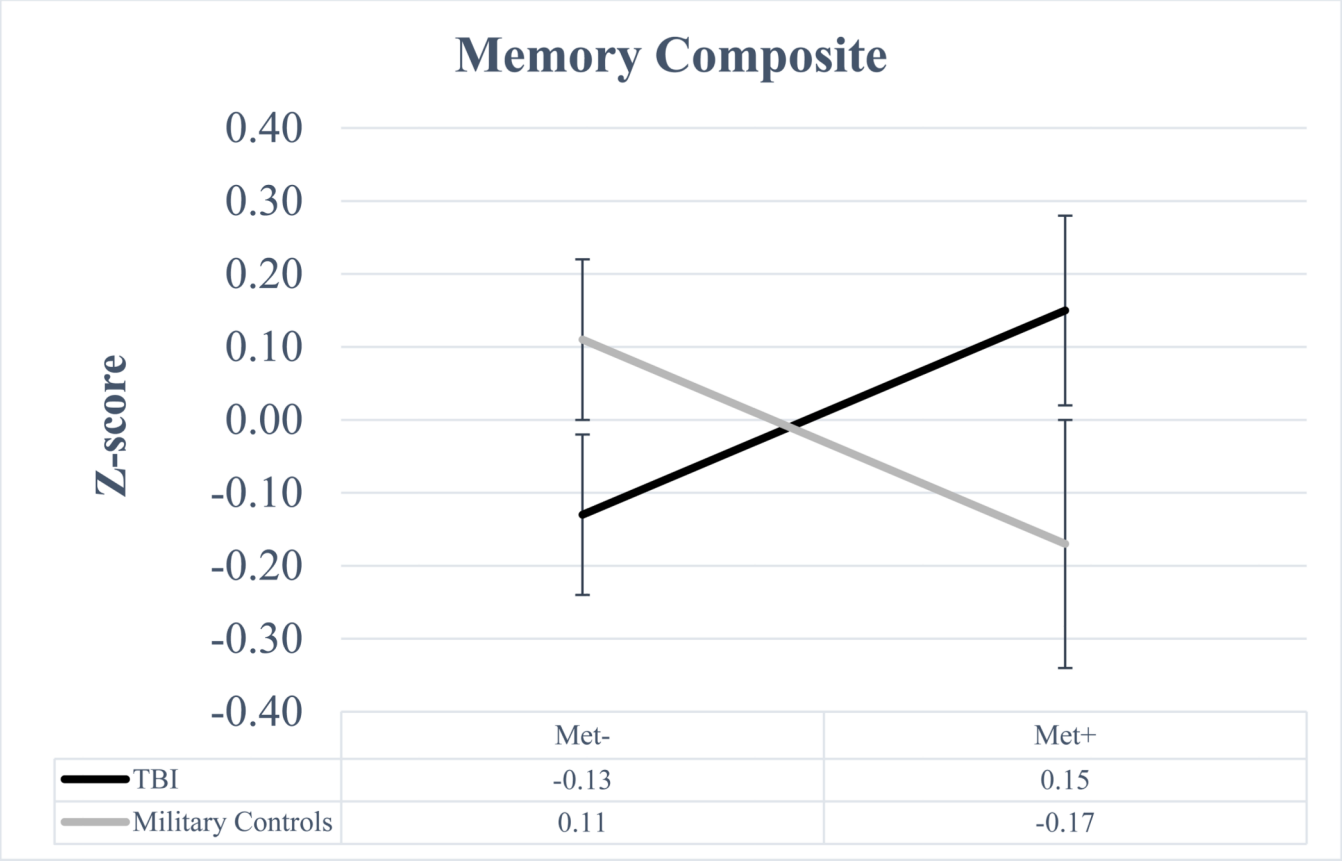

Figure 1a.

Memory cognitive composite scores across traumatic brain injury (TBI) and military control (MC) participants by BDNF genotype (Met+ versus Met-). Mean scores (adjusted) with standard errors are displayed.

(b)

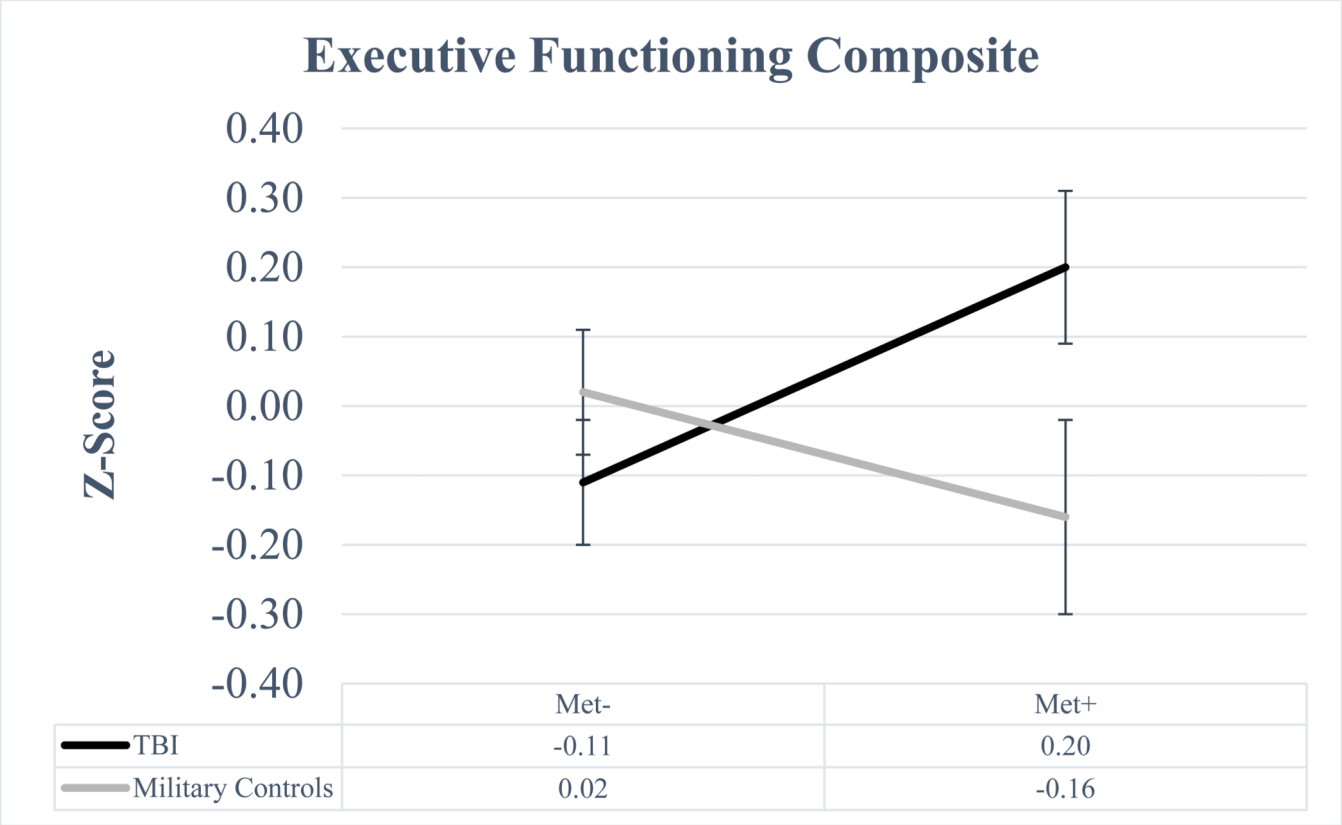

Figure 1b.

Executive functioning cognitive composite scores across traumatic brain injury (TBI) and military control (MC) participants by BDNF genotype (Met+ versus Met-). Mean scores (adjusted) with standard errors are displayed.

(c)

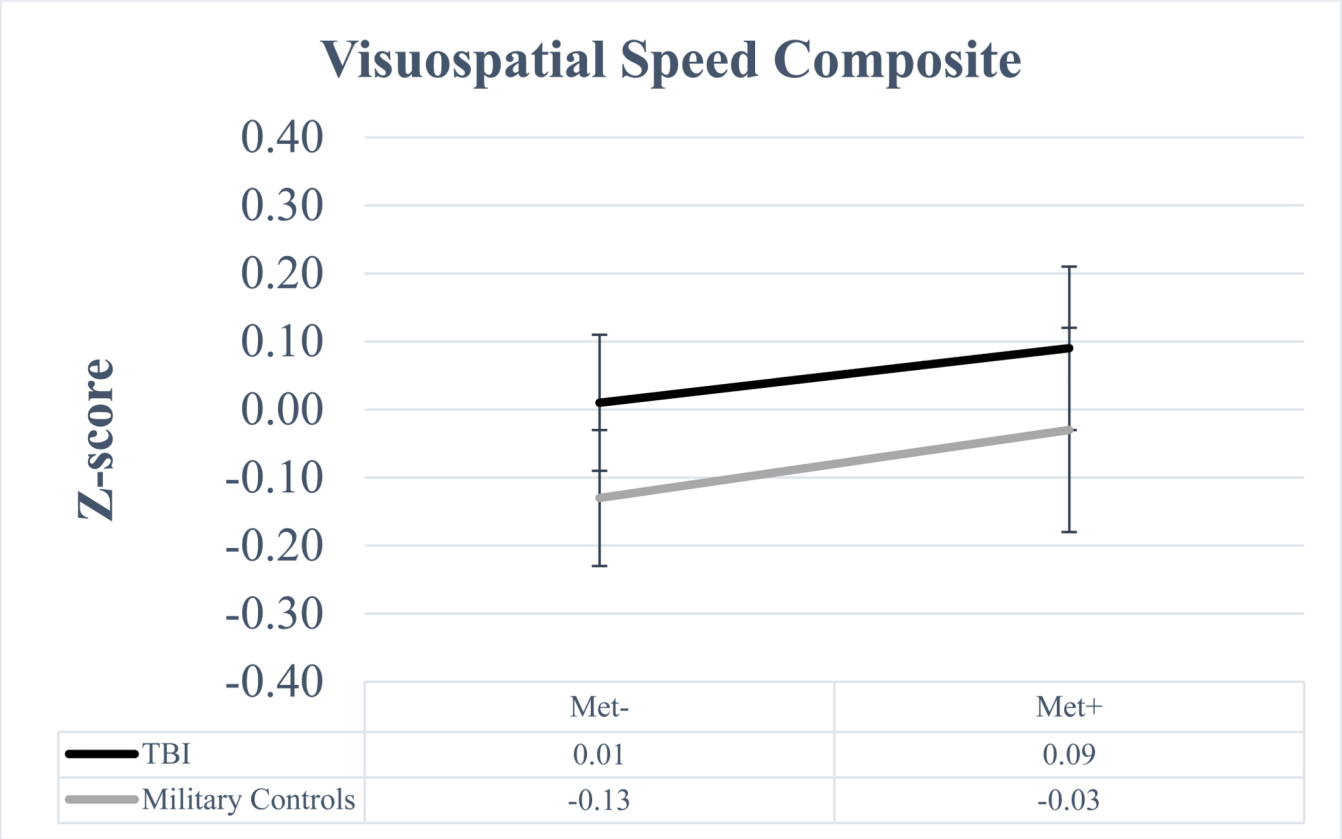

Figure 1c.

Visuospatial speed cognitive composite scores across traumatic brain injury (TBI) and military control (MC) participants by BDNF genotype (Met+ versus Met-). Mean scores (adjusted) with standard errors are displayed.

Table 1.

Variables comprising each domain-specific cognitive composite.

Memory Composite	Executive Functioning Composite	Visuospatial Speed Composite
CVLT-II Trials 1–5 Total Recall	WCST-64 Perseverative Responses	WAIS-IV Coding
CVLT-II Short Delay Free Recall	WCST-64 Total Errors	WAIS-IV Symbol Search
CVLT-II Long Delay Free Recall	D-KEFS Verbal Fluency Letter	D-KEFS TMT Visual Scanning
WMS-IV Logical Memory I	D-KEFS Verbal Fluency Category	D-KEFS TMT Number Sequencing
WMS-IV Logical Memory II	D-KEFS Verbal Fluency Switching	D-KEFS TMT Letter Sequencing
WMS-IV Visual Reproduction I	D-KEFS Verbal Fluency Switching Accuracy	D-KEFS TMT Motor Speed
WMS-IV Visual Reproduction II	D-KEFS Design Fluency Filled	WASI-II Block Design
RCFT Delay	D-KEFS Design Fluency Empty	
	D-KEFS Design Fluency Switching	
	D-KEFS TMT Number-Letter Switching	
Cronbach's α = .86	**Cronbach's α = .82**	**Cronbach's α = .78**

Abbreviations: CVLT-II = California Verbal Learning Test - Second Edition; WMS-IV = Wechsler Memory Scale – Fourth Edition; RCFT = Rey Complex Figure Test; WCST-64 = Wisconsin Card Sorting Test-64 Card Version; D-KEFS = Delis-Kaplan Executive Function System; TMT = Trail Making Test; WAIS-IV = Wechsler Adult Intelligence Scale – Fourth Edition; WASI-II = Wechsler Abbreviated Scale of Intelligence – Second Edition.

Table 2.

Neuropsychological variables: Descriptive statistics.

Variable	Raw Score: Mean (SD)	Standard Score: Mean (SD)	Standard Score: Median
Memory Composite			
CVLT-II Trials 1–5 Total Recall[a]	50.47 (9.41)	50.25 (9.88)	50.00
CVLT-II Short Delay Free Recall[b]	10.75 (2.83)	−0.07 (0.99)	0.00
CVLT-II Long Delay Free Recall[b]	11.30 (2.92)	−0.09 (1.04)	0.00
WMS-IV Logical Memory I[c]	27.73 (7.19)	10.92 (2.91)	11.00
WMS-IV Logical Memory II[c]	24.58 (7.86)	10.74 (3.19)	11.00
WMS-IV Visual Reproduction I[c]	39.14 (3.81)	11.17 (2.39)	12.00
WMS-IV Visual Reproduction II[c]	31.28 (8.61)	11.22 (3.23)	11.00
RCFT Delay[d]	19.55 (6.95)	53.39 (29.17)	57.00
Executive Functioning Composite			
WCST-64 Perseverative Responses[a]	8.10 (6.93)	46.73 (8.12)	47.00
WCST-64 Total Errors[a]	14.06 (8.85)	50.11 (9.78)	51.00
D-KEFS Verbal Fluency Letter[c]	39.91 (10.12)	10.57 (3.02)	11.00
D-KEFS Verbal Fluency Category[c]	43.02 (7.71)	11.54 (3.15)	12.00
D-KEFS Verbal Fluency Switching[c]	14.55 (2.80)	10.98 (3.29)	11.00
D-KEFS Verbal Fluency Switching Accuracy[c]	13.24 (3.24)	11.16 (3.20)	11.00
D-KEFS Design Fluency Filled[c]	10.24 (3.24)	10.30 (2.69)	10.00
D-KEFS Design Fluency Empty[c]	11.41 (3.54)	10.51 (2.85)	11.00
D-KEFS Design Fluency Switching[c]	8.89 (2.56)	11.02 (2.71)	11.00
D-KEFS TMT Number-Letter Switching[c]	70.74 (24.38)	9.98 (2.59)	10.00
Visuospatial Speed Composite			
WAIS-IV Coding[c]	74.84 (12.66)	10.70 (2.40)	11.00
WAIS-IV Symbol Search[c]	33.61 (7.64)	10.22 (2.90)	10.00
D-KEFS TMT Visual Scanning[c]	18.72 (4.99)	11.04 (2.21)	11.00
D-KEFS TMT Number Sequencing[c]	26.72 (9.52)	11.16 (2.48)	12.00
D-KEFS TMT Letter Sequencing[c]	25.25 (8.84)	11.30 (2.44)	12.00
D-KEFS TMT Motor Speed[c]	20.19 (6.39)	12.08 (1.27)	12.00
WASI-II Block Design[a]	50.01 (12.54)	56.08 (8.20)	57.00

Abbreviations: CVLT-II = California Verbal Learning Test - Second Edition; WMS-IV = Wechsler Memory Scale – Fourth Edition; RCFT = Rey Complex Figure Test; WCST-64 = Wisconsin Card Sorting Test-64 Card Version; D-KEFS = Delis-Kaplan Executive Function System; TMT =

Trail Making Test; WAIS-IV = Wechsler Adult Intelligence Scale – Fourth Edition; WASI-II = Wechsler Abbreviated Scale of Intelligence – Second Edition.

Notes:

[a] Standard score values are presented as T-scores

[b] Standard score values are presented as *z*-scores

[c] Standard scores values are presented as scaled scores

[d] Standard score values are presented as percentiles.

Table 3.

Participant characteristics by group.

Variables	mTBI BDNF Met+[a] (n=30)		mTBI BDNF Met-[a] (n=45)		MC BDNF Met+[a] (n=19)		MC BDNF Met-[a] (n=44)		Omnibus Test Result[b]
	M (SD)	Range	M (SD)	Range	M (SD)	Range	M (SD)	Range	*p*
Age	31.77 (5.29)	24–46	33.62 (8.08)	23–53	34.21 (8.53)	23–49	31.36 (6.38)	22–49	.305
Years of Education	14.30 (1.82)	12–18	14.02 (1.64)	10–18	14.95 (2.12)	12–18	14.84 (1.86)	12–18	.111
WRAT4 Reading SS	103.41 (10.66)	82–134	100.18 (10.95)	80–133	104.53 (9.56)	93–123	103.66 (10.33)	79–126	.306
Time Since Injury (Months)[c]	65.40 (32.52)	12–121	67.62 (35.22)	16–156	--	--	--	--	.424
Number of mTBIs	2.41 (0.91)	1–4	2.60 (1.60)	1–8	--	--	--	--	.571
PCL-M Total Score	43.13 (18.35)	17–81	43.16 (15.06)	17–73	25.11 (11.75)	17–63	25.11 (13.09)	17–73	<.001
BDI-II Total Score	17.87 (11.92)	0–43	20.98 (12.73)	3–51	8.79 (11.39)	0–34	6.75 (10.49)	0–54	<.001
	N	%	N	%	N	%	N	%	*p*
Sex									
Male	27	90.0	36	80.0	17	89.5	28	63.6	.031
Female	3	10.0	9	20.0	2	10.5	16	36.4	
Ethnicity/Race									
White/European American	18	60.0	20	44.4	15	78.9	27	61.4	.070
Other	12	40.0	25	55.6	4	21.1	17	38.6	

Abbreviations: mTBI = mild traumatic brain injury; BDNF = brain-derived neurotrophic factor; MC = military control; WRAT4 = Wide Range Achievement Test 4; SS = standard score; PCL-M = Posttraumatic Stress Disorder (PTSD) Checklist – Military Version; BDI-II = Beck Depression Inventory-II.

Notes:

[a] The "Met+" grouping refers to those homozygous (Met/Met) and heterozygous (Met/Val) for the Met*A allele, and the "Met-" grouping refers to those homozygous (Val/Val) for the Val*G allele.

[b] Analyses of variance were used to evaluate whether groups differed on continuous variables and chi-square or Fisher's exact tests were used to evaluate whether groups differed on categorical variables.

[c] Time since injury refers to the time elapsed between Veterans' most *recent* injury and study enrollment.

Table 4.

Correlations of independent variables, dependent variables, and sample characteristics.

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Group (mTBI vs. MC)	-	.10	.18*	.13	.07	−.05	.20*	.12	-	−.52***	−.47***	.15	.16
2. BDNF Genotype (Met+ vs. Met-)	-	-	−.03	.02	.01	.01	.03	.09	−.07	.05	.02	−.21*	.14
3. Memory Composite	-	-	-	.53***	.31***	−.07	.06	.26**	.23*	−.26**	−.19*	.23**	.23**
4. Executive Functioning Composite	-	-	-	-	.55***	−.08	.20*	.40***	.07	−.26**	−.20*	.27***	.37***
5. Visuospatial Speed Composite	-	-	-	-	-	−.12	.11	.30***	.01	−.25**	−.24**	.24**	.29***
6. Age	-	-	-	-	-	-	.34***	.00	.05	.03	−.01	.00	−.03
7. Years of Education	-	-	-	-	-	-	-	.22*	.17	−.24**	−.28***	.13	.04
8. WRAT4 Reading SS	-	-	-	-	-	-	-	-	.17	−.20*	−.21*	.01	.28***
9. Number of mTBIs	-	-	-	-	-	-	-	-	-	−.01	−.06	−.12	.27*
10. PCL-M Total Score	-	-	-	-	-	-	-	-	-	-	.82***	−.10	−.14
11. BDI-II Total Score	-	-	-	-	-	-	-	-	-	-	-	.04	−.15
12. Sex	-	-	-	-	-	-	-	-	-	-	-	-	−.01
13. Ethnicity/Race	-	-	-	-	-	-	-	-	-	-	-	-	-

Notes:

* $p < .05$

** $p < .01$

*** $p \leq .001$

Table 5.

Neuropsychological composite scores (*z*-scores) by group.

Variables	mTBI BDNF Met+[a] (n=30)		mTBI BDNF Met−[a] (n=45)		MC BDNF Met+[a] (n=19)		MC BDNF Met−[a] (n=44)	
	M	SD	M	SD	M	SD	M	SD
Memory Composite	0.03	0.71	−0.21	0.73	−0.12	0.92	0.26	0.60
Executive Functioning Composite	0.08	0.50	−0.19	0.58	−0.11	0.66	0.17	0.66
Visuospatial Speed Composite	−0.05	0.74	−0.08	0.67	0.03	0.57	0.04	0.65

Abbreviations: mTBI = mild traumatic brain injury; BDNF = brain-derived neurotrophic factor; MC = military control.

Notes:

[a]The “Met+” grouping refers to those homozygous (Met/Met) and heterozygous (Met/Val) for the Met*A allele, and the “Met−“ grouping refers to those homozygous (Val/Val) for the Val*G allele. Values presented in the table are *unadjusted* means and standard deviations for the three cognitive composite scores.