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The Interactive Effects of Brain-Derived Neurotrophic Factor (BDNF) Polymorphisms and Posttraumatic Stress Disorder on Neurocognitive Functioning in U.S. Military Veterans

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THE INTERACTIVE EFFECTS OF BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) POLYMORPHISMS AND POSTTRAUMATIC STRESS DISORDER ON NEUROCOGNITIVE FUNCTIONING IN U.S. MILITARY VETERANS

THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
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at the University of Kentucky

By

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ABSTRACT OF THESIS

THE INTERACTIVE EFFECTS OF BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) POLYMORPHISMS AND POSTTRAUMATIC STRESS DISORDER ON NEUROCOGNITIVE FUNCTIONING IN U.S. MILITARY VETERANS

Posttraumatic Stress Disorder (PTSD) is associated with mild-to-moderate deficits in neurocognitive functioning. Single nucleotide polymorphisms (SNPs) in the brain-derived neurotrophic factor (BDNF) gene, namely, the Met allele, may also be associated with mild deficits in neurocognitive functioning. However, findings are inconsistent and may be sensitive to environmental epigenetic moderators such as psychopathology.

The current study analyzed data from European-American U.S. military veterans (n = 1,244) who participated in the 2011 National Health and Resilience in Veterans Study (NHRVS). Multivariate analyses of covariances were conducted to evaluate the unique and interactive effects of the Met allele and probable PTSD on objective and subjective neurocognitive functioning.

Significant ($p \leq .001$) interactions between Met allele carrier status and probable PTSD were observed in objective ($\eta_p^2 = .028$) and subjective neurocognitive functioning ($\eta_p^2 = .029$). In individuals without PTSD (n = 1113), the Met allele was not significantly associated with objective neurocognitive functioning ($p = .01$, $\eta_p^2 = .013$) or subjective neurocognitive functioning ($p = .17$, $\eta_p^2 = .009$). In individuals with PTSD (n = 131), the Met allele was significantly ($p < .01$) associated with poorer objective ($\eta_p^2 = .179$) and subjective neurocognitive functioning ($\eta_p^2 = .237$).

These findings suggest that associations between the Met allele and neurocognitive functioning are dependent on the presence of PTSD.

KEYWORDS: BDNF, neurocognition, PTSD, veterans, epigenetics

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DEDICATION

To Aeryn, my beloved wife. I would not have been able to complete this thesis without your love, support, and prayers.

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CHAPTER 1. INTRODUCTION

Posttraumatic Stress Disorder (PTSD) is a psychiatric disorder that can develop following exposure to traumatic event(s) involving actual or threatened death, serious injury, or sexual assault (American Psychiatric Association [APA], 2013). Characteristic symptoms of PTSD include trauma-related intrusions, avoidance of trauma-related stimuli, negative alterations in cognition and mood, and intensification of emotional arousal and reactivity (APA, 2013). Upwards of 89% of the population will experience trauma during their life (Goldstein et al., 2016; Kilpatrick et al., 2013) but the lifetime and 12-month prevalence of PTSD in the general population are 8% and 4%, respectively (Goldstein et al., 2016; Kilpatrick et al., 2013; Smith et al., 2016). Overall prevalence estimates are higher among groups that are more likely to encounter traumatic events than the general population, such as combat veterans and emergency health professionals (Iranmanesh et al., 2013; Smith et al., 2016; Weiss et al., 1992).

Neurocognitive Functioning and Posttraumatic Stress Disorder

A diagnosis of PTSD and PTSD symptomatology are associated with mild to moderate deficits in cognitive functioning (Gilbertson et al., 2001; Uddo et al.,1993). A meta-analysis involving 60 cross-sectional studies found that individuals with PTSD exhibited poorer verbal learning, processing speed, working memory, and verbal memory (Cohen's *d*s = .20 to .62) compared to trauma-exposed but psychiatrically healthy participants (Scott et al., 2015). Additionally, veterans with PTSD report poorer subjective neurocognitive functioning than trauma-exposed veterans without PTSD (Averill et al., 2019; Spencer et al., 2010).

Although deficits in neurocognitive functioning were originally thought to result from trauma exposure (Everly & Horton, 1989; Uddo et al., 1993), it is likely that trauma, PTSD symptoms, and neurocognitive functioning are reciprocally related to one another (Brewin, 2007; Brewin et al., 2010; McNally, 2006; Qureshi et al., 2011). Individuals with PTSD exhibit poorer learning and memory than psychiatrically healthy controls, even after controlling for pre-trauma IQ (Gil et al., 1990). Similarly, after adjusting for estimated pre-military IQ, working memory and sustained attention functioning were negatively correlated with PTSD severity in U.S. (United States) military veterans (Vasterling et al., 2002). Longitudinal research has shown that working memory, verbal intelligence, and processing speed performance among young adults (20-28 years old) prior to a natural disaster were inversely associated with re-experiencing and arousal symptoms three to eight months following the trauma (Parslow & Jorm, 2007). Similarly, pre-deployment immediate visual recall and verbal memory predicted post-deployment PTSD severity among U.S. military veterans (Marx et al., 2009). Taken together, the available literature suggests that neurocognitive deficits prior to a traumatic event may serve as a possible risk factor for the development of PTSD and is exacerbated by PTSD itself.

Brain-Derived Neurotrophic Factor Polymorphisms

Genetic research has identified multiple characteristics that can increase risk for neurocognitive deficits and accelerated age-related neurocognitive decline. Genetic characteristics such as the Apolipoprotein E ε4 gene, chromosome 14q24 presenilin-1 mutation, and amyloid precursor protein mutations have been associated with exacerbated age-related neurocognitive decline and Alzheimer's Disease (Hersi et al., 2017; Scapagnini, 2010; Tilley et al., 1998). Similarly, genetic polymorphisms on the

brain-derived neurotrophic factor (BDNF) gene are associated with neurocognitive deficits (Azeredo et al., 2017; Egan et al., 2003; Kennedy et al., 2015; Miyajima et al., 2008).

Brain-derived neurotrophic factor is a protein within the neurotrophin family located in the short (p) arm of chromosome 11 at position 14.1. It supports neuron differentiation, maintenance, and maturation (Bathina & Das, 2015). It has also shown neuroprotective effects against adverse neural conditions such as glutamatergic overstimulation and hypoglycemia (Maisonpierre et al., 1991). Brain-derived neurotrophic factor also regulates neural plasticity, such as axonal, dendritic, and synaptic growth (Bramham & Messaoudi, 2005; Calabrese et al., 2014; Lu et al., 2005). Accordingly, BDNF plays an important role in plasticity processes in several brain regions that are important to neurocognitive functioning, such as the hippocampus, striatum, and prefrontal cortex (Bath et al., 2012; Brigadski & Lessmann, 2014; Jing et al., 2017; Linnarsson et al., 1997; Notaras et al., 2017; Pattwell et al., 2012).

Common polymorphisms occur on the BDNF gene. These variations occur due to single nucleotide transitions from guanine to adenine at position 196 in exon 5 (rs6265; Cargill et al., 1999). This single nucleotide polymorphism (SNP), results in a substitution at the 66th codon from valine (Val) to methionine (Met). Because the substitution is genetic, this polymorphism can be inherited. As such, there are two opportunities for progeny to inherit this SNP: one from the mother and the other from the father. Possible genotypes include Val66Val (both standard alleles), Val66Met (one standard allele and one with rs6265), and Met66Met (both alleles with rs6265; Lichtblau, 2010). The frequency of the Met allele varies from 0 – 72% depending on geographic region and

ethnicity (Petryshen et al., 2010). For example, the frequency of the Met allele varies from 15% to 18% among white European-Americans (Hori et al., 2020; Zhang et al., 2006) to over 45% in Cambodia (Petryshen et al., 2010).

PTSD and BDNF Polymorphisms

Cross-sectional studies suggest that carriers of the Met allele are at an increased risk for PTSD compared to homozygote Val allele counterparts (Bruenig et al., 2016; Li et al., 2016; Zhang et al., 2014; Zhang et al., 2016); though not all studies have reported significant associations (Bountress et al., 2017; Lee et al., 2006). Research also suggests that Met allele carriers report more severe PTSD symptom severity than non-Met carriers (Pitts et al., 2019). Further, the Met allele may help explain the variance between responders and non-responders to behavioral (Felmingham et al., 2013) and pharmacological intervention for PTSD (Malikowska-Racia & Salat, 2019). Together, these data suggest that the Met allele may influence the etiology, maintenance, and treatment of PTSD symptomatology for some trauma-exposed individuals.

BDNF and Neurocognitive Functioning

Human studies investigating the associations between BDNF SNPs and neurocognitive functioning have yielded mixed results. Some studies found that, relative to non-Met carriers, Met carriers exhibited poorer attentional capacities, processing speed, and memory performance (Azeredo et al., 2017; Egan et al., 2003; McAllister et al., 2012; Miyajima et al., 2008). Furthermore, some studies suggest that the Met allele adversely impacts self-reported neurocognitive functioning (Pitts et al., 2020). Other studies found no associations between the Met allele and objective attentional capacities, processing speed, and memory performance (Benjamin et al., 2010; Karnik et al., 2010; Mandelman & Grigorenko, 2012). One study even reported better objective

neurocognitive functioning among Met allele carriers compared to non-Met carriers (Alfimova et al., 2012). These inconsistencies can be partly attributed to study limitations; lower statistical power, heterogeneous samples, and neurocognitive measures with psychometric shortcomings (Mandelman & Grigorenko, 2012). Most studies did not control for or model important individual differences that may also affect neurocognitive functioning (Alfimova et al., 2012; Benjamin et al., 2010; Egan et al., 2003; Karnik et al., 2010). This includes, but is not limited to education level, stress and trauma exposure, and psychopathology, including PTSD (Boals & Banks, 2012; van Hooren et al., 2007; Inzelberg et al., 2007; Leibovici et al., 1996; Scott et al., 2015).

Environmental Epigenetic Factors and BDNF Polymorphisms

Environmental factors can modify gene expression without altering the underlying genetic sequence to impact phenotypic expression in a process known as epigenetics (McEwen, 2016). The most well-understood epigenetic mechanism is DNA methylation (Ho et al., 2012). Methylation occurs when a methyl group is added to the 5' position of a gene sequence on the promoter region – a region that controls upregulation or suppression of gene transcription – by an enzyme called methyltransferase (Moore, Le, & Fan, 2013). When a promoter region becomes methylated, the ribonucleic acid polymerase – the enzyme that initiates gene transcription – cannot bind to the DNA strand, thus preventing protein manufacturing (Moore, Le, & Fan, 2013). The methyl group will remain on the gene until it is removed or altered by an enzyme (Moore, Le, & Fan, 2013).

Gene methylation allows cells to adapt to different environmental stimuli and modify cellular functions. For example, methylation is important for energy conservation; allowing cells to silence genes and allocate resources elsewhere when needed (Varriale,

2014). Although gene methylation serves an adaptive function, methylation is sustained after meiotic division and therefore can have long-lasting effects (Hitchins & Ward, 2007). As such, high frequency and long-term exposure to adverse cellular or environmental stimuli can have longstanding consequences on gene expression.

Environmental factors such as exposure to tobacco smoke, infectious pathogens, infectious fungi, and radiation, have been shown to influence gene methylation across the lifespan (Ho et al., 2012). Stress and trauma have also been implicated as a trigger for epigenetic interactions with promoter regions on genes (Ho et al., 2012; Logue et al., 2016; Wolf et al., 2016). Psychopathology is implicated as another factor that can influence DNA methylation (O'Donnell & Meaney, 2020; Wolf et al., 2019; Zheleznyakova et al., 2016; Weder et al., 2014). Posttraumatic stress disorder severity is associated with accelerated cellular aging and DNA methylation, which is linked to poorer working memory capacity (Wolf et al., 2016). The apolipoprotein ε4 gene – a hallmark risk factor for dementia that is reliably associated with accelerated age-related cognitive decline (Ward et al., 2012) – has been shown to interact with PTSD among U.S. military veterans, such that the synergistic effects of ε4 and PTSD on subjective neurocognitive difficulties is two-to-four-fold the independent effect of either factor (Averill et al., 2019). It was suggested that this interaction is the result of the degeneration of neurocognitive-relevant brain regions associated with PTSD and ε4 (Averill et al., 2019). Furthermore, this interaction may be due to increased methylation of the ε4 allele, which PTSD symptomatology has been shown to accelerate (Wolf et al., 2016).

Psychopathologies such as anxiety, depression, schizophrenia, and borderline personality disorder are associated with methylation of the BDNF gene (Zheleznyakova et al., 2016). Depression severity is associated with BDNF methylation in maltreated children (Weder et al., 2014). Similarly, individuals with bipolar disorder exhibit significantly higher rates of DNA methylation on the promoter region of the BDNF gene than psychiatrically healthy controls (Mill et al., 2008; Zheleznyakova et al., 2016). Likewise, veterans with PTSD exhibit higher levels of BDNF methylation (Kim et al., 2017).

Subjective neurocognitive deficits associated with the Met allele are moderated by depression symptoms, such that the association between the Met allele and subjective neurocognitive deficits is modest (d = .16) unless observed in conjunction with depressive symptoms (d = .77 Pitts et al., 2020). Specifically, veterans with significant depressive symptoms and the Met allele reported poorer reasoning, concentration, and processing speed abilities compared to Val/Val and/or non-depressed counterparts (Pitts et al., 2020). Likewise, veterans with significant depressive symptoms and the Met allele performed poorer on objective working memory and visual learning tasks than Val/Val and/or non-depressed counterparts (Pitts et al., 2020).

One study has examined the unique and interactive effects of the Met allele and PTSD on neurocognitive functioning (Mestrovic et al., 2020). Findings suggested that, in a sample of 315 Croatian military veterans, the Met allele was significantly associated with poorer visual short-term memory and visual object manipulation performance on the Rey-Osterrieth Complex Figure Test among veterans with PTSD, but not among veterans without PTSD (Mestrovic et al., 2020). To our knowledge, no studies have replicated

these findings or examined the interactive effects of the Met allele and PTSD on other objective measures of neurocognitive functions (e.g., visual learning and attention) or subjective neurocognitive functioning. This is important given that subjective neurocognitive functioning may be more strongly associated with clinically significant neurocognitive impairment and decline than objective measures (Hess et al., 2020; Savard & Ganz, 2016; Pietrzak et al., 2015; Waldorff et al., 2012). Additionally, the study published on the effects of the Met allele and PTSD on neurocognitive functioning did not conduct contrasts evaluating the effects of PTSD split by Met allele carrier status (Mestrovic et al., 2020). Exploring this addresses an important gap, because previous literature suggests that the Met allele may influence the etiology, maintenance, and treatment of PTSD symptomatology (Bruenig et al., 2016; Felmingham et al., 2013; Li et al., 2016; Malikowska-Racia & Salat, 2019; Zhang et al., 2014; Zhang et al., 2016). Similarly, it is possible that the Met allele may influence the impact of PTSD on neurocognitive functioning.

Current Study

The proposed study aims to examine the main and interactive effects of the Met allele and probable past-month PTSD on objective and subjective neurocognitive functions using data from the 2011 National Health and Resilience in Veterans Study (NHRVS; Pietrzak, 2011). Exploratory analyses will examine these effects on specific measures of objective (processing speed, attention, visual learning, and working memory) and subjective (confusion, attention, memory, reasoning, concentration, and psychomotor speed) neurocognitive functions. It is hypothesized that there will be a significant association between probable PTSD and neurocognitive functioning, such that individuals reporting probable PTSD will perform poorer on neurocognitive functioning

tasks and report poorer neurocognitive functioning than those not reporting probable PTSD. It is also hypothesized that there will be a significant association between BDNF SNPs and neurocognitive functioning, such that Met carriers will perform poorer on neurocognitive functioning tasks and report poorer neurocognitive functioning than non-Met carriers. It is also hypothesized that BDNF SNPs and probable PTSD will interact such that the effect of the Met allele on objective and subjective neurocognitive functioning will be greater for those reporting probable PTSD relative to those not reporting probable PTSD. Lastly, it is hypothesized that the effect of PTSD on objective and subjective neurocognitive functioning will be greater for Met allele carriers relative to Val homozygote counterparts.

CHAPTER 2. METHODS

Procedure

The NHRVS was approved by the Human Subjects Subcommittee of the Veterans Affairs Connecticut Healthcare System and Office of Research & Development. Data from the NHRVS were drawn from KnowledgePanel, a survey research panel representing households with or without telephone or internet access (GfK Knowledge Networks, Menlo Park, California, U.S.A.); participants were provided with computer and internet access to participate if they could not provide their own. GfK Knowledge Networks uses probability-based sampling of household addresses from the U.S. Postal Service's Delivery Sequence File, which improves population coverage. GfK Knowledge Networks operates an incentive program for research participation. Participants of the

NHRVS were provided with 50,000 points, which is equal to 50 USD for participation. All participants provided informed consent before completing any study procedures.

Participants completed a large battery of questionnaires, including those used for the present analyses. This was followed by the Cogstate Brief Battery (Cogstate Inc., Melbourne, Australia). After completing the Cogstate Brief Battery, the participants were debriefed electronically. A subset of participants was selected to participate in genetic testing. Participants who consented to genetic testing were sent Oragene DNA (OG-250) kits and instructed to follow manufacture directions.

Participants

Participants were included in the analyses if they participated in the first wave of the NHRVS collected in 2011 and completed the THS (Carlson et al., 2011), PCL-IV-S (Weathers et al., 1993), CogState Brief Battery (Cogstate Inc., New Haven, CT, USA), the MOS-Cog (Stewart et al., 1992) and DNA testing. The sample consists of 1,244 Caucasian/European American U.S military veterans who were recruited as part of the NHRVS in 2011 (total NHRVS $n = 3157$). See Table 2.1 for full sample characteristics. Post-stratification weights were applied based on the population demographic distribution of U.S. Veterans (age, education, metropolitan area, and Census region) in the GfK Knowledge survey panel (GfK Knowledge Networks, Menlo Park, California, USA) and adjusted to align with U.S. Census data.

Measures

Trauma History Screen. Trauma histories were assessed using the Trauma History Screen (THS; Carlson et al., 2011). The THS is a 14-item self-report measure of potential Diagnostic and Statistical Manual-IV (DSM-IV; American Psychiatric Association, 1994) criterion A1 traumatic events. The THS asks each respondent to

indicate whether a listed traumatic event was experienced or directly witnessed ("yes" or "no"), and to mark the number of times each endorsed event happened. THS exhibited high levels of one-week test-retest reliability (r = .93) for detecting trauma (Carlson et al., 2011). Additionally, the THS demonstrated convergent validity when compared to other validated trauma questionnaires, such as the Traumatic Events Questionnaire (r = .76; Carlson et al., 2011). Cumulative trauma load on the THS is calculated by summing the number of lifetime DSM-IV criterion A1 traumatic events and the number of times each endorsed event happened.

Posttraumatic Stress Disorder Checklist. To assess probable PTSD symptoms, the past-month DSM-IV version of the PTSD Checklist-Specific version (PCL-IV-S; Weathers et al., 1993) was administered. The PCL-IV-S is a 17-item Likert-like self-report measure of DSM-IV PTSD symptom severity. Item's responses range from 1 – "Not at all" to 5 – "Extremely". A continuous PTSD symptom severity score is computed by summing all items. The PCL-IV-S was administered to all participants who endorsed at least one traumatic event on the THS. Participants were instructed to answer PCL-IV-S questions concerning their most severe traumatic experience endorsed on the THS. A score of 17 was imputed for participants who did not endorse at least one traumatic event on the THS. The total score of the PCL-IV-S displays convergent validity with other gold-standard measures of PTSD severity such as the Clinician-Administered PTSD Scale for DSM-IV (r = .79, p < .001) and the Mississippi Scale for Combat-related PTSD (r = .90, p < .001; Keen et al., 2008). The PCL-IV-S total score has also demonstrated high test-retest reliability one hour following the initial assessment (r = .92, p < .001), at a one week interval (r = .88, p < .001), and at a two week interval (r = .68, p < .001;

Ruggiero et al., 2003). A cut-off score of 35 on the PCL-IV-S yields a sensitivity of .71 and a specificity of .84 for the detection of PTSD in the general population (Walker et al., 2002).

Mini International Neuropsychiatric Interview. The Mini International Neuropsychiatric Interview for DSM-IV (MINI) was adapted for self-report and used to assess past-month major depressive disorder and lifetime alcohol abuse and drug abuse disorders (Sheehan et al., 1998). The major depressive disorder module of the clinician-administered MINI yields a sensitivity of .77 and a specificity of .79 in the detection of current major depressive disorder (Sheehan et al., 1998). The substance use modules of the clinician-administered MINI yield a sensitivity of .89 and .69 and a specificity of .93 and .99 to detect lifetime alcohol use disorder and lifetime substance use disorder, respectively (Sheehan et al., 1998).

Medical Outcomes Study – Cognitive Functioning Scale. To assess subjective past-month neurocognitive functioning, the Medical Outcome Study – Cognitive Functioning Scale (MOS-Cog; Stewart et al., 1992) was administered. The MOS-Cog is a 6-item scale that assesses subjective neurocognitive dysfunction over the past month. Each of the six questions on the MOS-Cog assesses a domain of neurocognitive functioning over the past-month: memory (i.e., forgetfulness), reasoning, attention, confusion, psychomotor speed, and concentration. Responses use a Likert-type scale that ranges from 0 “All of the time” to 6 (“None of the time”). Scores on the MOS-Cog predict Trail Making Test scores (Revicki, Chan, & Gevirts, 1998) and are moderately correlated with objective psychomotor speed (i.e., letter-digit substitution test), attention

(i.e., concept shifting test), and memory performance (i.e., visual-verbal learning test; Klein et al., 2002).

Cogstate Brief Battery. The Cogstate Brief Battery is a computerized neuropsychological battery developed by Cogstate Inc. (Cogstate Inc., Melbourne, Australia) used to assess four neurocognitive domains: processing speed, attention, visual learning, and working memory (Darby et al., 2012). The Cogstate Brief Battery consists of four tests administered in a fixed order: Detection Test, Identification Test, One Card Learning Test, and the One Back Test. Prior to each Cogstate Brief Battery test, participants were given instructions and completed a practice trial. On every trial of each test, a playing card stimulus is presented in the center of the computer screen. Participants are occasionally prompted to respond to questions about these cards. Questions and responses vary by test, as do the values, color, and suit of each card.

To assess processing speed, the *Detection Test* was used. In this test, the participants are instructed to attend to a single playing card in the center of the screen. Occasionally, the card will turn over and reveal a "joker" and participants are instructed to respond to the question: "Has the card turned over?" as quickly as possible. Participants indicate "K" (yes) with a single keypress. This test continues until 25 correct responses are made or two minutes elapses. To assess attention, the *Identification Test* was used. In this test, participants are instructed to respond to the question "Is the card red?" as quickly as possible. Participants indicate "K" (yes) or "D" (no) with a keypress. Red and black "joker" cards are displayed in equivalent numbers in random order. This test proceeds until 35 correct answers have been recorded or the maximum time (two minutes) is reached.

On the Detection Test and the Identification Test, the primary measure is response time. The response time on the Identification Test and Detection Test are measured in milliseconds. Scores on reaction time tests were inverted, such that lower scores are indicative of poorer neurocognitive functioning. Additionally, reaction time scores were transformed using a logarithmic base 10 ($\log_{10}$) to account for the negatively skewed distribution values (Lim et al., 2012). This transformation helps mitigate violations of the assumption of normality for most statistical tests.

To assess visual learning, the *One Card Learning Test* was used. In this test, participants are instructed to attend to the card presented and respond to "Have you seen this card before in this task?" Participants indicate "K" (yes) or "D" (no) with a keypress. The cards presented are non-joker playing cards. To assess working memory, the *One-Back Test* is used. In this test, participants are instructed to attend to the card in the center of the screen and respond to "Is this card the same as that on the immediately previous trial?" Participants indicate "K" (yes) or "D" (no) with a keypress. Although specific keys were identified during each of the test instructions, keys that surrounded the "K" key (e.g., U, I, O, J, L, M, "," and "." keys) were sensitive to "yes" responses and the keys that surrounded the "D" key (e.g., W, E, R, S, X, F, V, and C keys) were sensitive to "no" responses.

Forty-two cards are shown in the One Card Learning Test and the One-Back Test. Target stimuli appear on 50% of the trials. Both tasks present three blocks of 14 cards and a block is discontinued if three minutes pass. Visual learning is measured by the proportion of correct answers, which is transformed using an arcsine square root. Working memory is measured by the proportion of correct answers and the response

time, which are transformed using an arcsine square root and logarithmic base 10, respectively.

The Cogstate Brief Battery has shown utility for detecting mild neurocognitive impairment in aging populations (Fredrickson et al., 2010). The total score of each test is automatically transformed to be normally distributed and is then converted into a z-score. Z-scores from each test can also be combined to compute an overall composite score that represents overall neurocognitive functioning. Scores on the Cogstate Brief Battery are stable up to a year after the initial assessment, as indicated by high intraclass correlations (*ICC's* = .79 - .91) between test administrations (Fredrickson et al., 2010). Scores on the Cogstate Brief Battery do not differ when participants were supervised or unsupervised by a research assistant (Cromer et al., 2015).

The Cogstate Brief Battery tests show strong convergent validity with traditional neuropsychological tests (Maruff et al., 2009). Detection Test scores are correlated with scores on measures of processing speed such as the grooved pegboard task ($r = .81$, $p < .001$; Maruff et al., 2009). Identification Test scores are correlated with scores on measures of attention such as the Trail Making Test ($r = .78$, $p < .001$; Maruff et al., 2009). One-Back Test scores are correlated with scores on measures of working memory such as the Symbol Digit Modalities Test and the Wechsler Memory Scale spatial span task (*r's* = .80 - .81, *p's* < .01; Maruff et al., 2009). Lastly, One Card Learning Test scores are correlated with scores on measures of visual memory such as the Brief Visual Memory Test and the Rey Complex Figure Test (*r's* = .69 - .83, *p's* < .01; Maruff et al., 2009). The Cogstate Brief Battery tests also demonstrated adequate discriminant validity when compared to other neurocognitive tasks that measure different functions. The

Detection Test and Identification Test were not significantly correlated to measures of memory such as the Brief Visual Memory Test (*r's* = .04 - .17, *p's* > .01). Additionally, the One-Back Test and the Visual Learning Test scores were not correlated with measures of attention such as grooved pegboard task scores (*r's* = .13 - .17, *p's* > .01; Maruff et al., 2009). There is overlap between the Cogstate Brief Battery tests, where different battery tests are correlated with the same validated neuropsychological test. For example, both the Identification Test and the Detection Test scores are both highly correlated with the Trail Making Test (*r's* = .76 - .70, *p*'s > .001; Maruff et al., 2009). This pattern of multiple associations is expected, due to the extensive overlap between neurocognitive functions (Chan et al., 2008; Friedman & Miyake, 2004; Miyake et al., 2000).

BDNF Val66Met genotyping. To determine BDNF SNPs, saliva samples were collected using Oragene DNA (OG-250) kits (DNA Genotek, Ontario, Canada). All subjects recruited were Caucasian/European to reduce genetic variance between groups. Following directions included in the kit, participants were instructed to unscrew the saliva collection container and begin spitting into the container. Following collection, participants were instructed to close the container and shake for 10 seconds. Saliva samples were shipped to DNA Genotek (Ontario, Canada) to have the DNA extracted and genotyped. Participants were instructed to avoid eating, drinking, smoking, or chewing gum 30 minutes prior to saliva collection to avoid degradation of the saliva samples. OG-250 kits maximize DNA yield compared to other types of genetic genotyping techniques, such as buccal swabs and blood extraction (Looi et al., 2012), and remain stable at room temperature over eight months (Nunes et al., 2012). DNA was extracted using prepIT-

L2P reagent (DNA Genotek, Ontario, Canada) and was genotyped with a PsychChip GWAS array. Genotypes were called using GenomeStudio software V2011.1 and genotyping module V1.8.4 (Illumina, San Diego, CA, USA). Principal components (PC) for GWAS data were computed using EIGENSOFT (Price et al., 2006) based on a common set of SNPs with Hapmap3, which were in low linkage disequilibrium with one another. Due to manufacturer protocol, outliers from the genetic data (95 subjects) were automatically discarded from the PC analysis. Outliers were defined as individuals whose ancestry was at least three standard deviations from the mean on the two largest PCs.

CHAPTER 3. ANALYTIC APPROACH

All statistical analyses were completed with SPSS Software Version 26 (International Business Machines Corporation, Armonk, NY, USA). PCL-IV-S scores were dichotomized – probable PTSD (PCL-IV-S ≥ 35) and no probable PTSD (PCL-IV-S < 35) – due to severe positive skew of PCL-IV-S scores in the present sample (Figure 1). The main effect of the Met allele was dichotomized by contrasting Met+ veterans (Val66Met and Met66Met) with Met- veterans (Val66Val). Val66Met and Met66Met groups are commonly combined due to the low base rate of Met66Met (Martin et al., 2018; Teo et al., 2014; Vulturar et al., 2016). Furthermore, in the present sample, only four participants would be included in the Met66Met and PTSD group ($n = 4$). There was no relationship between probable PTSD status and Met allele carrier status ($X^2 = .663$, $p = .415$) in this sample. Descriptive statistics such as mean scores and standard deviations of Cogstate Brief Battery and MOS-Cog scores were calculated for the entire sample and for PTSD (PCL-IV-S ≥ 35 and PCL-IV-S < 35) and BDNF SNP (Met carrier and non-Met carrier) sub-groups.

Post-stratification weights were applied to statistical analyses based on the population demographic distribution of U.S. veterans (age, education, metropolitan area, and Census region) in the GfK Knowledge survey panel (GfK Knowledge Networks, Menlo Park, California, USA) and then adjusted to align with U.S. Census data. Hypotheses were tested with multivariate analyses of covariance (MANCOVA). The models included BDNF SNP, probable PTSD, and their interaction term as fixed effects, age, sex, highest education level (dichotomized into less than high school and some college or higher), income (dichotomized into annual household income of 59,999 or less and 60,000 or more), probable current major depressive disorder, probable lifetime alcohol or substance use disorder, military combat exposure, and cumulative trauma load as covariates. Covariates were selected due to their association with neurocognitive functioning (Boals & Banks, 2012; Bruijnen et al., 2019; Hooren et al., 2007; Leibovici et al., 1996; Martindale et al., 2017; Pitts et al., 2020; Weiss, 2003). Each of the Cogstate Brief Battery tests (Detection Test, Identification Test, One Card Learning Test, and One-Back Test) were entered as dependent variables for the first MANCOVA and each question on the MOS-Cog (psychomotor speed, attention, confusion, concentration, reasoning, and memory) were be entered as dependent variables for the second MANCOVA. Alpha level was set at .01 to control for type I error rate.

Post-hoc MANCOVAs were conducted by splitting the sample by probable PTSD status and by splitting the sample by Met allele carrier status to probe significant interactive effects. Similarly, post-hoc analyses of covariance (ANCOVA) were conducted after splitting the sample to probe significant main and interaction effects of probable PTSD and Met allele carrier status on individual objective neurocognitive

functions – attention, processing speed, visual learning, and working memory and individual domains of subjective neurocognitive functions – psychomotor speed, attention, confusion, concentration, reasoning, and memory.

A multivariate analysis of variance sensitivity power analysis (MANOVA) in G*Power (Faul et al., 2007) was conducted to determine the effect size needed to reject the null hypotheses for 2 main effects and one interactive effect. Given the sample size (n = 1,244), desired power (.9), number of groups (4), number of predictors (6), and max number of response variables (6), a small effect size (d = .1) would be required to detect statistically significant (α = .01) main and interaction effects.

Missing data were multiply imputed using Markov Chain Monte Carlo algorithms. Item-level imputation required at least 50% available data for imputation. Outliers were identified using Mahalanobis Distance for each dependent variable. Mahalanobis Distance values were compared to a chi-square distribution with degrees of freedom equal to the number of factors (k = 2). Any participant with a p-value below .001 was discarded from the analysis. In total, 93 participants were identified as outliers on either the MOS-Cog and/or the Cogstate Brief Battery and discarded from the analysis. Participants with probable PTSD were more likely to be outliers than individuals without probable PTSD ($p < .01$). There was no relationship between BDNF SNPs and outlier status.

There are four assumptions for the MANCOVA: independent observations, multivariate normality, multicollinearity, homogeneity of covariance. The assumption of independent t observations is met because the data are cross-sectional and between-subjects. Further, each participant was only counted as one observation as ensured by the

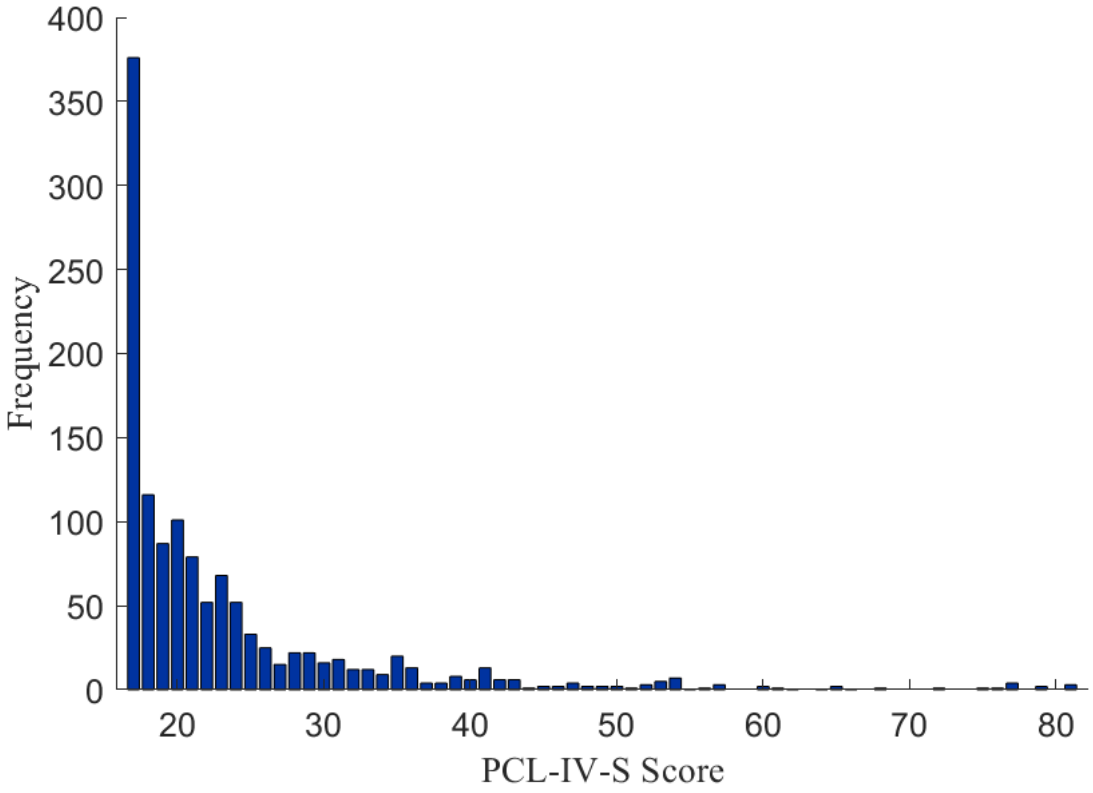
GfK Knowledge Survey panel (GfK Knowledge Networks, Menlo Park, California, USA). Kolmogorov-Smirnov Tests of Normality revealed that all dependent variables were non-normal ($p < .01$), therefore multivariate normality cannot be assumed. Bivariate correlations were conducted to evaluate multicollinearity between MOS-Cog questions (r's = .49 - .81). Bivariate correlations were also conducted to evaluate multicollinearity between individual Cogstate tests (r's = .07 - .59). Utilizing the multicollinearity cut-off of .8 as suggested in the literature (Berry & Feldman, 2006), all dependent variables were deemed non-multicollinear except for subjective attention and concentration ($r = .81$). Box's Test of Equality of Covariance was conducted to test for homogeneity of covariance. Because Box's Test of Equality of Covariance was ($p < .001$) for both MANCOVAs, the covariance matrices of the dependent variables are not equal across groups. Because there were violations of the assumptions of both the assumption of multivariate normality and the assumption of homogeneity of covariance, Pillai's Trace was interpreted for all multivariate effects.

Table 1. Sociodemographic and Psychiatric Characteristics (*n* [Weighted %] or Weighted *M* [*SD*])

	PTSD -	PTSD +	Met -	Met +	Full Sample
Total *n*	1113 (89.4%)	131 (10.6%)	860 (69.1%)	384 (30.9%)	1244
Genetic Characteristics					
Met -	770 (69.2%)	90 (68.8%)	-	-	-
Met +	343 (30.8%)	41 (31.2%)	-	-	-
Sociodemographic					
Age	62.7 (13.8)	53.9 (16.7)	62.4 (14.5)	60.4 (14.0)	61.8 (14.3)
Male	1029 (92.5%)	116 (88.1%)	794 (92.4%)	351 (91.4%)	1145 (92.1%)
Female	83 (7.5%)	16 (11.9%)	66 (7.6%)	33 (8.6%)	99 (7.9%)
Married/cohabitating	868 (78.0%)	77 (58.6%)	656 (76.3%)	289 (75.2%)	945 (75.9%)
Annual income ≥ 60,000	525 (47.2%)	29 (21.9%)	379 (44.1%)	175 (45.6%)	554 (44.5%)
Education level					
High school or less	345 (31.0%)	48 (36.7%)	274 (31.9%)	119 (31.0%)	393 (31.6%)
Some college	385 (34.6%)	59 (44.9%)	308 (35.8%)	136 (35.4%)	444 (35.7%)
Bachelor's degree or higher	383 (34.4%)	24 (18.4%)	278 (32.3%)	129 (33.6)	407 (32.7%)
Clinical characteristics					
Cumulative trauma	3.0 (2.4)	6.3 (3.2)	3.3 (2.7)	3.3 (2.7)	3.3 (2.7)
Probable lifetime AUD/DUD	233 (20.9%)	60 (45.5%)	209 (24.3%)	84 (21.8%)	293 (23.5%)
Probable current MDD	139 (12.5%)	77 (58.2%)	146 (17.0%)	70 (18.2%)	216 (17.3)
Military characteristics					
Years in military	7.2 (7.7)	6.2 (6.5)	7.0 (7.6)	7.3 (7.5)	7.1 (7.6)
Combat veteran	337 (30.4%)	64 (48.4%)	294 (34.3%)	107 (27.8%)	401 (32.3%)

Note. Probable PTSD defined as PCL-IV-S ≥ 35. AUD = alcohol use disorder; DUD = drug use disorder; MDD = major depressive disorder; PTSD = posttraumatic stress disorder

Figure 1. Distribution of PCL-IV-S Scores Within the Entire Sample



Note. PCL-IV-S = Posttraumatic Stress Disorder Checklist (DSM-IV Version) – Specific

CHAPTER 4. RESULTS

Cogstate Brief Battery

A MANCOVA exploring the impact of probable PTSD and Met allele carrier status on the Cogstate Brief Battery revealed a significant effect of PTSD on overall objective neurocognitive functioning [$F(5, 1064) = 4.237$, $p = .001$, $\eta_p^2 = .020$], such that individuals with probable PTSD displayed poorer neurocognitive functioning ($M = -.106$, $SE = .072$) than individuals without probable PTSD ($M = .097$, $SE = .020$). A significant effect of Met allele carrier status on overall objective neurocognitive functioning [$F(5, 1064) = 3.802$, $p = .002$, $\eta_p^2 = .018$] was observed, such that individuals with the Met allele displayed poorer neurocognitive functioning ($M = -.020$, $SE = .057$) than individuals without the Met allele ($M = .012$, $SE = .042$). A significant Met*PTSD interaction on overall objective neurocognitive functioning was observed [$F(5, 1064) = 6.215$, $p < .001$, $\eta_p^2 = .028$]. Follow-up ANCOVAS revealed that the Met*PTSD interaction was significant for attention performance [$F(1, 1068) = 9.683$, $p = .002$, $\eta_p^2 = .009$].

To probe the significant Met*PTSD interaction, the sample was split by probable PTSD status, then a MANCOVA was conducted to examine the main effects of the Met allele among veterans with and without probable PTSD. A significant main effect of Met allele carrier status suggested that the Met allele impacted objective neurocognitive functioning among individuals with probable PTSD [$F(5, 74) = 3.729$, $p = .008$, $\eta_p^2 = .168$]. Among individuals with probable PTSD, Met allele carriers displayed poorer neurocognitive functioning ($M = -.107$, $SE = .84$) than non-Met carriers ($M = .035$, $SE = .060$). Although the main effect of Met allele carrier status was not significant among

individuals without probable PTSD [$F(5, 980) = 2.975$, $p = .01$, $\eta_p^2 = .013$], it was trending in the opposite direction.

The sample was also split by Met allele carrier status, then MANCOVA were conducted to examine the main effects of PTSD among veterans with and without the Met allele. Significant main effects of PTSD suggested that PTSD impacted objective neurocognitive functioning among Met allele carriers [$F(5, 312) = 3.318$, $p = .006$, $\eta_p^2 = .050$] and non-Met allele carriers [$F(5, 740) = 10.548$, $p < .001$, $\eta_p^2 = .067$], such that probable PTSD status was similarly associated with poorer neurocognitive functioning in both groups. Among individuals with the Met allele, individuals with probable PTSD displayed poorer neurocognitive functioning ($M = -.227$, $SE = .108$) than individuals without PTSD ($M = .148$, $SE = .030$). Similarly, among individuals without the Met allele, individuals with probable PTSD displayed poorer neurocognitive functioning ($M = -.022$, $SE = .088$) than individuals without PTSD ($M = .061$, $SE = .023$). See Figure 2.

After splitting the sample by probable PTSD status, follow-up ANCOVAs suggest that the Met allele was not significantly associated attention functioning in individuals with probable PTSD [$F(1, 983) = 1.629$, $p = .115$, $\eta_p^2 = .003$] or without probable PTSD [$F(1, 77) = 3.933$, $p = .012$, $\eta_p^2 = .078$]. After splitting the sample by Met allele carrier status, follow-up ANCOVAs suggest that PTSD was not significantly associated with attention functioning in individuals with the Met allele [$F(1, 316) = 5.113$, $p = .024$, $\eta_p^2 = .016$] or without the Met allele [$F(1, 744) = 4.497$, $p = .034$, $\eta_p^2 = .006$]. See Table 2.

Medical Outcomes Study – Cognitive Functioning Scale

A MANCOVA exploring the impact of probable PTSD and Met allele carrier status on the MOS-Cog revealed a significant effect of PTSD on overall subjective neurocognitive functioning [$F(6, 1063) = 23.629$, $p < .001$, $\eta_p^2 = .118$], such that individuals with probable PTSD reported poorer neurocognitive functioning ($M = -.751$, $SE = .085$) than individuals without probable PTSD ($M = .172$, $SE = .024$). A significant effect of Met allele carrier status on overall subjective neurocognitive functioning [$F(6, 1063) = 7.683$, $p < .001$, $\eta_p^2 = .042$] was observed, such that Met allele carriers reported poorer neurocognitive functioning ($M = -.345$, $SE = .068$), than non-Met carriers ($M = -.234$, $SE = .50$). A significant Met*PTSD interaction on overall subjective neurocognitive functioning was observed [$F(6, 1063) = 5.310$, $p < .001$, $\eta_p^2 = .029$]. Follow-up ANCOVAS revealed that the Met*PTSD interaction was significant for psychomotor speed [$F(1, 1068) = 14.979$, $p < .001$, $\eta_p^2 = .014$] and concentration $F(1, 1068) = 7.526$, $p = .006$, $\eta_p^2 = .007$].

To probe the significant Met*PTSD interaction, the sample was split by probable PTSD status, then a MANCOVA was conducted to examine the main effects of the Met allele among participants with and without probable PTSD. A significant main effect of Met allele status suggested that, among individuals with probable PTSD [$F(6, 72) = 3.730$, $p = .003$, $\eta_p^2 = .237$], Met carriers reported poorer subjective neurocognitive functioning ($M = -.988$ $SE = .186$) compared to non-Met carriers ($M = -.830$, $SE = .133$). There was not a significant effect of the Met allele on subjective neurocognitive functioning among individuals without probable PTSD [$F(6, 978) = 1.515$, $p = .170$, $\eta_p^2 = .009$].

The sample was also split by Met allele carrier status, then a MANCOVA was conducted to examine the main effects of PTSD among veterans with and without the Met allele. Significant main effects of PTSD among non-Met allele carriers [$F(6, 739) = 10.423$, $p < .001$, $\eta_p^2 = .078$] and Met allele carriers [$F(6, 311) = 15.892$, $p < .001$, $\eta_p^2 = .235$] suggested that, regardless of Met allele status, subjective neurocognitive functioning was poorer for individuals with probable PTSD than for those without; however, the effect size among Met allele carriers was nearly three times larger. Among individuals with the Met allele, those with probable PTSD displayed poorer neurocognitive functioning ($M = -.948$, $SE = .149$) than those without PTSD ($M = .203$, $SE = .041$). Similarly, among individuals without the Met allele, those with probable PTSD displayed poorer neurocognitive functioning ($M = -.599$, $SE = .026$) than those without PTSD ($M = .148$, $SE = .026$). See Figure 3.

After splitting the sample by probable PTSD status, follow-up ANCOVAs suggest that among veterans without probable PTSD, the Met allele was not significantly associated with psychomotor speed [$F(1,983) = .061$, $p = .805$, $\eta_p^2 < .001$] or concentration [$F(1, 983) = .003$, $p = .959$, $\eta_p^2 < .001$]. Among individuals with probable PTSD, the Met allele was significantly associated with subjective psychomotor speed [$F(1, 77) = 8.111$, $p = .006$, $\eta_p^2 = .095$], such that individuals with probable PTSD and the Met allele reported poorer psychomotor speed than individuals with probable PTSD but without the Met allele (Table 3). After splitting the sample by Met allele carrier status, ANCOVAs revealed that, among non-Met carriers, probable PTSD was significantly associated with concentration [$F(1, 744) = 34.479$, $p < .001$, $\eta_p^2 = .044$], and psychomotor speed [$F(1, 744) = 26.227$, $p < .001$, $\eta_p^2 = .034$], such that individuals without the Met

allele and with probable PTSD reported poorer psychomotor speed and concentration than individuals without the Met allele and without probable PTSD (Table 3). Similarly, among Met carriers, probable PTSD was significantly associated with concentration [$F(1, 316) = 53.212$, $p < .001$, $\eta_p^2 = .144$] and psychomotor speed [$F(1, 316) = 58.705$, $p < .001$, $\eta_p^2 = .157$], such that individuals with the Met allele and with probable PTSD reported poorer psychomotor speed and concentration than individuals with the Met allele and without probable PTSD (Table 4.2).

Table 2. Estimated Marginal Means of Multivariate Analysis of Covariance on Objective Neurocognitive Functioning

	Processing Speed		Attention		Visual Learning		Working Memory Accuracy		Working Memory Reaction	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
PTSD -, Met -	.094	.028	.040	.031	.000	.037	.100	.033	.079	.033
PTSD -, Met +	.164	.043	.130	.048	.128	.057	.021	.051	.018	.050
PTSD +, Met -	-.168	.103	.270	.116	-.050	.138	-.388	.123	-.269	.122
PTSD +, Met +	.042	.139	-.239	.115	-.313	.186	-.297	.166	-.220	.164

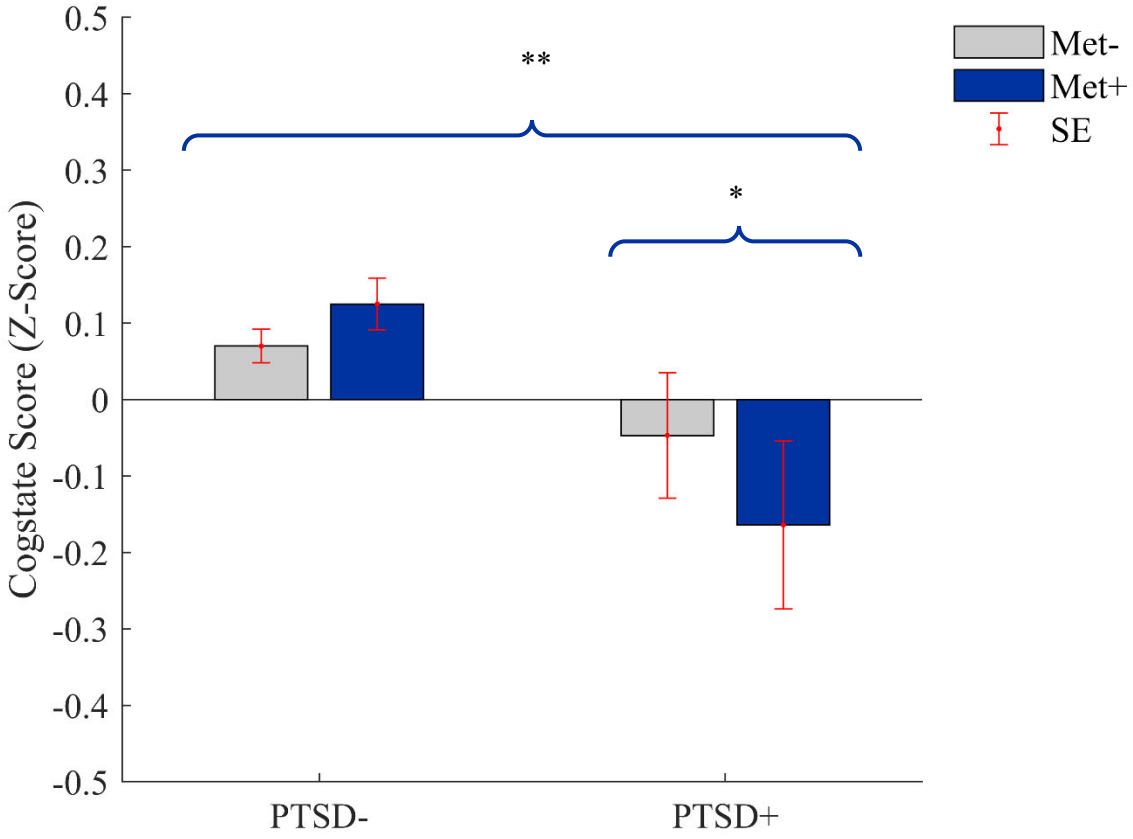
Note. Results adjusted for cumulative trauma load, sex, income, educational attainment, probable current major depressive disorder, probable lifetime alcohol use disorder or drug use disorder, and military combat exposure. Means are displayed as Z-scores.
M = mean, *SE* = standard error, PTSD = posttraumatic stress disorder

Table 3. Estimated Marginal Means of Multivariate Analysis of Covariance on Subjective Neurocognitive Functioning

	Psychomotor Speed		Memory		Reasoning		Concentration		Confusion		Attention	
	M	*SE*	*M*	SE	*M*	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
PTSD -, Met -	.173	.025	.141	.031	.107	.027	.187	.027	.194	.024	.174	.027
PTSD -, Met +	.184	.036	.168	.048	.190	.041	.188	.041	.194	.036	.243	.042
PTSD +, Met -	-.353	.094	-.520	.116	-.389	.100	-.459	.099	-.440	.088	-.633	.102
PTSD +, Met +	-.955	.127	-.560	.156	-.179	.135	-.912	.133	-.718	.119	-.797	.138

Note. Results adjusted for cumulative trauma load, sex, income, educational attainment, probable current major depressive disorder, probable lifetime alcohol use disorder or drug use disorder, and military combat exposure. *M* = mean; *SE* = standard error; PTSD = posttraumatic stress disorder

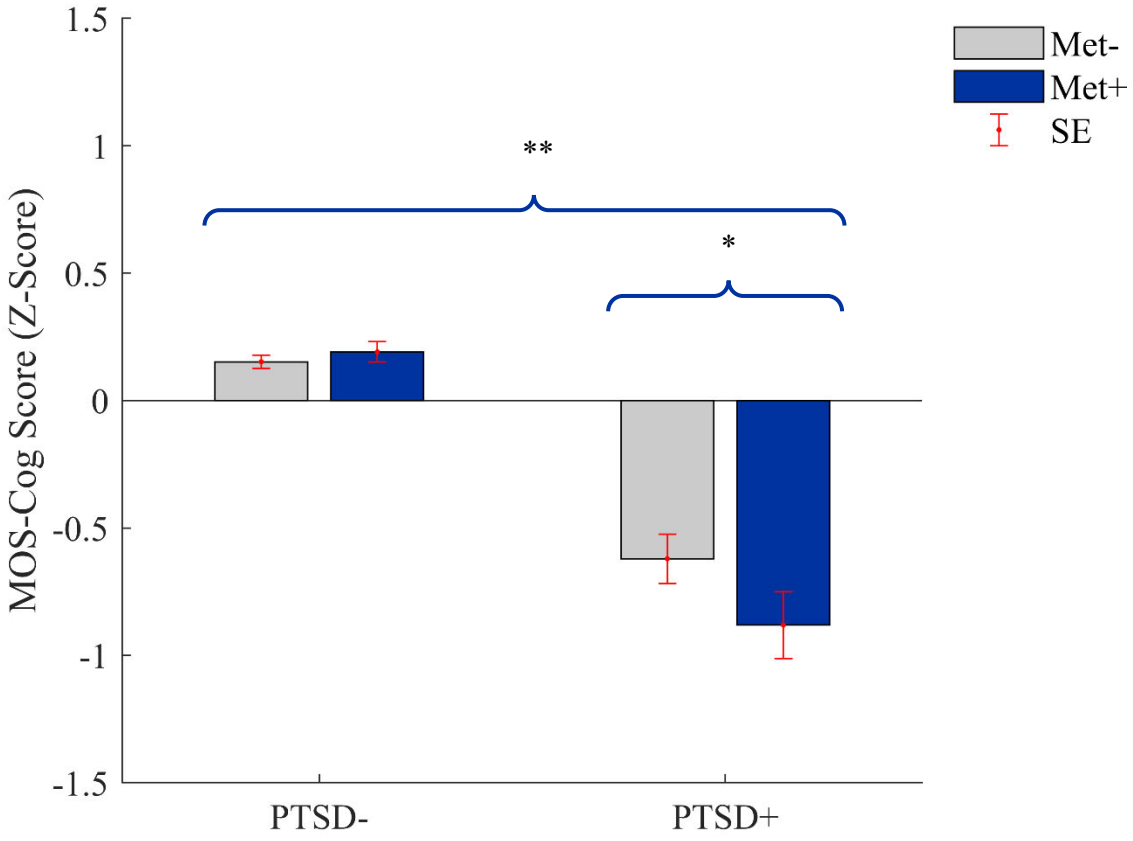
Figure 2. Estimated Marginal Means of PTSD and the Met Allele on Overall Objective Neurocognitive Functioning.



* = $p < .01$, ** = $p < .001$

Note. PTSD = posttraumatic stress disorder, *SE* = standard error

Figure 3. Estimated Marginal Means of PTSD and the Met Allele on Overall Subjective Neurocognitive Functioning



* = $p < .01$, ** = $p < .001$

Note. PTSD = posttraumatic stress disorder, *SE* = standard error

CHAPTER 5. DISCUSSION

This study examined the effects of the SNPs on the BDNF gene and probable PTSD on objective and subjective neurocognitive functioning in a nationally representative sample of U.S. military veterans. Met allele carrier status and probable PTSD interacted, such that the effects of the Met allele on neurocognitive functioning are dependent on the presence of PTSD, such that individuals with the Met allele and probable PTSD display poorer neurocognitive functioning relative to non-PTSD counterparts and/or non-Met carriers. Additionally, the impact of PTSD on neurocognitive functioning was significant regardless of Met allele carrier status, but the impact of PTSD on subjective neurocognitive functioning was three times greater among Met allele carriers than non-Met carriers.

The present results replicate the previously reported interaction between PTSD and the Met allele on neurocognitive functioning (Mestrovic et al., 2020) and extend the literature by employing a measure with improved psychometric properties and by exploring domains not assessed by the Rey-Osterrieth Complex Figure (i.e., attention and processing speed). Mestrovic and colleagues found that Val66Val served a protective function in veterans with PTSD with short-term memory and visual object manipulation compared to veterans with Met allele and PTSD (Mestrovic et al., 2020). Similarly, the present study found that the Val66Val served a protective function; however, planned contrasts suggest this effect was not significantly confined to a specific neurocognitive domain. The present data suggest that PTSD and the Met allele interact to negatively impact overall neurocognitive functioning broadly. Additionally, this study extends the literature by examining the differential impact of PTSD on neurocognitive functioning

depending on the presence or absence of the Met allele, which has not been previously reported. Lastly, this study extends the literature by examining the interactive impact of the Met allele and PTSD on objective and subjective neurocognitive functioning concurrently. Statistically significant objective neurocognitive deficits do not always equate to clinically significant deficits in neurocognition-relevant domains of functioning. Small effect size deficits in objective neurocognitive functioning have low clinical significance unless accompanied by subjective reductions (Savard & Ganz, 2016). By evaluating both objective and subjective neurocognitive functioning concurrently, the current study was able to detect salient neurocognitive concerns among the U.S. veteran population.

Methylation of the CpG islands on the Met allele is common among individuals with psychopathology (O'Donnell & Meaney, 2020, Zheleznyakova et al., 2016) and has been observed in individuals with PTSD (Wolf et al., 2019). It is hypothesized that the stressors associated with psychopathology are frequent and severe enough to demethylate stress-related genes and methylate genes involved in higher-order processes (Ho et al., 2012). If a gene associated with neural plasticity or higher-order thinking is methylated due to stress, it is unlikely that the gene will demethylate until the individual is removed from the stressor (Ho et al., 2012). Therefore, not producing BDNF due to stress-related methylation of BDNF CpG islands, would likely result in reductions in neurocognitive functioning beyond the effect of SNPs alone. As such, it is possible that the interaction between current probable PTSD and the Met allele on subjective and objective neurocognitive function is due to methylation of the CpG island on the Met allele. The present study did not assess for methylation. As such, future research should explore the

possibility of a mediated moderation, where the interaction between the Met allele and PTSD on neurocognitive functioning is itself mediated by BDNF CpG island methylation. Other epigenetic mechanisms may explain the current results. For example, microRNA expression responds to environmental changes (e.g., stress) and can impact the expression of a gene (Ho et al., 2012). MicroRNA has been implicated as an important regulator of several brain processes, such as neurogenesis, synaptic plasticity, and neurocognitive functioning (Luoni & Riva, 2016; Xu, Hsu, Karayiorgou, & Gogos, 2012). Gathering data on DNA methylation and microRNA functioning could better inform the relationship between PTSD and the Met allele on subjective and objective neurocognitive functioning.

Significant interactions between PTSD and the Met allele on neurocognitive functioning may also be driven by mutual degeneration of neurocognition-relevant brain regions and stunted neural plasticity. The Met allele is theorized to impact neurocognitive functioning because of its detrimental effect on BDNF secretion (Kennedy et al., 2015). Secretion of BDNF is crucial to neurocognitive functioning because it regulates long-term potentiation and synaptic plasticity (Bramham & Messaoudi, 2005; Calabrese et al., 2014; Lu et al., 2005). Additionally, BDNF secretion is associated with prefrontal grey matter volume (Pezawas et al., 2004), which can influence the ability to regulate neurocognitive abilities (Depue et al., 2010). As such, if lower levels of BDNF are secreted in the prefrontal cortex because of the Met allele, it could result in poorer neurocognitive functioning. PTSD is similarly associated with lower prefrontal grey matter volume (Holmes et al., 2018). The interactive impact of PTSD and the Met allele may be the result of concurrent volumetric grey matter reductions and reduced neural

plasticity, which may exhibit an exacerbating effect. Future research should utilize neuroimaging to examine neurological differences among individuals with PTSD with and without the Met allele.

This study possesses several strengths. First, the dataset is large, and nationally representative for Caucasian U.S. military veterans and all analyses utilized poststratification weights to align the sample with U.S. census data. Additionally, the findings of this study were significant after controlling for possible confounding variables including age, sex, cumulative trauma load, income, probable past-month major depressive disorder, military combat exposure, probable lifetime substance/alcohol use disorder, and education level. Another strength of this study is the mean age of the sample (M = 61.8). Not only is this age representative of U.S. military veterans, but the older sample allows inferences to be drawn regarding characteristics that put an individual at risk of age-related cognitive deficits.

Due to the increased birthrate following World War II and advancements in medicine, there has been a significant shift in the age distribution in the U.S. (Shay, 2015). This age distribution shift contributed to an increase in the national median age from 35.3 in 2000 to 38.4 in 2019 (Jordan, 2020; Meyer, 2001). U.S. military veterans are, by comparison, much older than the general population (Eibner et al., 2015; Villa et al., 2005). In 2000, the median age of U.S. veterans was 57 (Richardon & Waldrop, 2003). In 2020, the median age of veterans was 65 years (Vespa, 2020). A forward age distribution shift among U.S. veterans is likely associated with an increased prevalence of age-related neurocognitive decline among veterans (Parkar, 2015). Age-related neurocognitive decline is a chief concern among the elderly, as it is associated with a

diversity of adverse outcomes such as poorer quality of life and increased burden on caretakers and family members (Harada et al., 2014; Schneider, 2001). As such, research is needed to compare the impact of the Met allele and PTSD on neurocognitive functioning throughout the lifespan to determine if the efforts reported herein worsen with age. SNPs may exhibit an antagonistic pleiotropic effect; said otherwise, a gene may offer a protective function during early life stages and become detrimental at later life stages or vice versa. For example, the APOE e4 allele – a hallmark risk factor for dementia – has been associated with superior verbal fluency in 6-to-15-year-olds compared to non-e4 carriers in the same age group but is associated with significant neurocognitive deficits later in life (Dik et al., 2001). Therefore, the possibility exists that the effect of the Met allele on neurocognitive functioning may change throughout the lifespan. Furthermore, the Met allele may interact with PTSD differently depending on the age group assessed. Further research should examine a moderating effect of age on the unique and interactive effects of PTSD and the Met allele.

One inherent weakness of this study is the poor divergent validity of the Cogstate Brief Battery. Often, neurocognitive measures exhibit poor divergent validity, making it difficult to separate overall neurocognitive functioning into individual domains (Chan et al., 2008; Friedman & Miyake, 2004; Miyake et al., 2000); though this weakness is offset by the use of MANCOVAs for hypothesis tests. In this dataset, objective attention performance and objective processing speed performance were highly correlated ($r = .59$, $p < .001$), likely because they are both measured in reaction time. Because attention and processing speed are highly correlated, it is difficult to discern whether performance on the Identification Test or the Detection Test are due to processing speed, attention, or a

combination of the two. As such, future research may examine the interactive impact of the Met allele and PTSD on neurocognitive functioning using a more comprehensive battery of neurocognitive measures with stronger discriminant validity such as the executive function battery posed by Miyake and colleagues (2000). Future research employing such an executive function battery may provide deeper insight into exact neurocognitive abilities affected by PTSD and the Met allele.

Another limitation of the study is that the MOS-Cog and the Cogstate Brief Battery had non-normal distributions and heterogeneous variances. For example, the One-Back Test exhibited a severe ceiling effect (skewness = -2.2, kurtosis = 9.1). There were 23.7% of participants (n = 298) who received the maximum score on working memory accuracy performance. Although the One-Back Test can be used to detect severe working memory deficits (Maruff et al., 2009), in a relatively healthy sample the One-Back Test may not be sufficiently sensitive to detect deficits or group differences. A similar ceiling effect was observed on each question of the MOS-Cog. As such, future research may examine the impact of PTSD and the Met allele using more sensitive measures such as the Subjective Cognitive Decline Questionnaire (Rami et al., 2014) for subjective neurocognitive functioning and/or the executive functioning battery posed by Miyake and colleagues (2000).

Another important limitation is that the data are cross-sectional, and therefore do not allow us to conclude the directional associations among the variables assessed. As referenced earlier, there are data suggesting that neurocognitive deficits are both risk factors for and consequences of PTSD (Aupperle et al., 2012; Gil et al., 1990; Gilbertson et al., 2001; Parslow & Jorm 2007; Vasterling et al., 2002). These data can suggest a

directional relationship between the Met allele and neurocognitive deficits, given that inheritance of the Met allele occurs prior to the presence of neurocognitive functioning or PTSD. However, these data cannot inform the directional nature of the relationship between PTSD and neurocognitive functioning. Further longitudinal research that assesses genetic SNPs and neurocognitive functioning before and after trauma exposure and PTSD could help inform causality and the direction of the interaction between PTSD and the Met allele on neurocognitive functioning.

The current study has important implications for the treatment and prevention of age-related cognitive decline. There are multiple modifiable factors that combat the progression of age-related cognitive decline, such as nutrition, physical exercise, and neurocognitive training (Andrade & Radhakrishnan, 2009). However, few studies have observed the impact of treating psychopathology among individuals who are at risk for accelerated age-related cognitive decline. There is some evidence that treating PTSD can improve neurocognitive function (Jak et al., 2018). For example, a single case study found that cognitive processing therapy improved processing speed and attention alongside improvements in PTSD symptoms (Boyd et al., 2016). Additionally, a small study (n = 15) found that individual trauma-focused therapy was associated with clinically significant improvements in memory and executive functioning (Walter et al., 2010). As such, therapeutic intervention for PTSD may eliminate the adverse effects of the Met allele on neurocognitive functioning among individuals with PTSD. For example, reductions in PTSD symptoms may demethylate neurocognition-relevant CpG islands, resulting in a positive impact on neurocognitive functioning; however, further research is needed to support this claim.

Future studies examining the effect of the Met allele on neurocognitive functioning should also examine other psychiatric disorders. The current study speculates that the interaction between PTSD and the Met allele on neurocognitive functioning is due to DNA methylation from PTSD-related stressors. Significant levels of methylation on the BDNF gene are seen in other psychopathologies such as major depressive disorder, schizophrenia, and borderline personality disorder (O'Donnell & Meaney, 2020; Zheleznyakova et al., 2016). As such, other forms of psychopathology or combinations of psychopathology can methylate the BDNF allele and display similar interactive effects on neurocognitive functioning.

These results highlight the importance of assessing psychopathological factors when evaluating the impact of genetic SNPs on phenotypic effects. Stress has a major impact on gene expression which can introduce significant error when evaluating the impact of genetics on any observable outcome (Ho et al., 2012). It is hypothesized that studies searching for candidate gene-disease associations typically yield small effect sizes due to unknown gene-gene interactions (Ioannidis et al., 2006). Alternatively, failed candidate gene studies may be the result of ignoring the impact of psychopathology on gene expression. As such, researchers should broadly assess psychopathology when exploring the impact of a gene or SNP on neurocognitive outcomes.

CHAPTER 6. CONCLUSION

As neurocognitive dysfunction is a salient concern among aging U.S. military veterans, it is important to understand modifiable factors that impact neurocognitive functioning for individuals who are at risk for neurocognitive dysfunction. The present results replicated a previously reported interaction between the Met allele and PTSD on

objective neurocognitive functioning and extended the literature by showing a similar interaction on subjective neurocognitive functioning in a large, nationally representative sample of Caucasian U.S. military veterans. These results suggest that the stressors associated with PTSD may impact BDNF allele expression, likely resulting in downstream effects on neurocognitive functioning; however further longitudinal epigenetic research is needed to support this inference. These results highlight the importance of assessing psychopathology as a possible confound in genetic research. Additionally, these results underscore the importance of assessing and treating PTSD in individuals who are at genetic risk for neurocognitive deficits. Although modern therapeutic intervention cannot change one's genetic code, treating current PTSD may reduce the impact of genetic risk factors for neurocognitive deficits.

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