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Short communication

BDNF Val66Met polymorphism and posttraumatic stress symptoms in U.S. military veterans: Protective effect of physical exercise

Barbara L. Pitts[a], Julia M. Whealin[a,b], Ilan Harpaz-Rotem[c,d], Ronald S. Duman[d,e], John H. Krystal[c,d], Steven M. Southwick[c,d], Robert H. Pietrzak[c,d,*]

[a] U.S. Department of Veterans Affairs VA Pacific Islands Healthcare System, Honolulu, HI, USA
[b] University of Hawaii School of Medicine, Manoa, HI, USA
[c] U.S. Department of Veterans Affairs National Center for Posttraumatic Stress Disorder, Clinical Neurosciences Division, VA Connecticut Healthcare System, West Haven, CT, USA
[d] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
[e] Department of Neurobiology, Yale University School of Medicine, New Haven, CT, USA

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ABSTRACT

The Met allele of the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with reduced levels of BDNF release, heightened hypothalamic-pituitary-adrenal axis reactivity, and impaired fear extinction. As a result, Met allele carriers may be at risk for greater severity of posttraumatic stress disorder (PTSD) symptoms. In this study, we examined the relationship between the BDNF Val66Met polymorphism and PTSD symptoms in two nationally representative samples of European American U.S. military veterans (main sample, $n = 1386$; replication sample, $n = 509$). Results revealed that, relative to Val/Val homozygotes, Met allele carriers reported greater severity of lifetime and current PTSD symptoms, specifically re-experiencing symptoms. Met allele carriers with high trauma burden also reported greater severity of lifetime and past-month PTSD symptoms. Greater engagement in physical exercise moderated this gene-by-environment interaction. Specifically, among veterans with high lifetime trauma burden, Met allele carriers who exercised had significantly lower severity of PTSD symptoms compared to those who did not exercise. These findings suggest that interventions designed to bolster engagement in physical exercise may help mitigate PTSD symptoms in veterans who are Met allele carriers and highly exposed to trauma.

1. Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder characterized by intrusive symptoms, avoidance of trauma reminders, negative thoughts and mood, and alterations in arousal and reactivity that affects approximately 8% of U.S. military veterans in their lifetimes (Wisco et al., 2016). There is increasing interest in identifying genetic markers for PTSD, and understanding how these markers may be moderated by environmental and psychosocial risk and protective factors (e.g., Mota et al., 2018). While genome-wide association studies have identified some gene variants associated with PTSD risk, very large sample sizes are needed to identify specific risk loci (Duncan et al., 2017), and these studies often do not assess environmental and psychosocial moderators of genetic risk.

Genetic studies have implicated a specific polymorphism in the brain-derived neurotrophic factor (BDNF) gene as a potential risk factor for PTSD (Bountress et al., 2017; Bruenig et al., 2016) and moderator of the relationship between PTSD and fear extinction learning (Flemingham et al., 2018). BDNF is a neurotrophin that plays a role in synaptic plasticity, differentiation, and neuronal function throughout life (Frielingsdorf et al., 2010). A functional single-nucleotide polymorphism of the BDNF gene (Val66Met), which results in an amino acid change from valine (Val) to methionine (Met) at position 66 on the BDNF protein has been identified (Egan et al., 2003). Animal studies have found that the replacement of Val by Met is linked to reduced processing and neuronal-activity dependent secretion of BDNF in the brain, which is in turn associated with increased anxiety-like behaviors in stressful situations (Chen et al., 2006). Further, human studies have shown that Met allele carriers have impaired fear extinction, as well as reduced hippocampal volume and function, which are also observed in

* Corresponding author at: U.S. Department of Veterans Affairs National Center for PTSD, Clinical Neurosciences Division, VA Connecticut Healthcare System, 950 Campbell Ave 161E, West Haven, CT, USA.
E-mail address: robert.pietrzak@yale.edu (R.H. Pietrzak).

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individuals with PTSD (Frielingsdorf et al., 2010; Flemingham et al., 2018).

Recent meta-analyses have yielded conflicting evidence of the association between the BDNF Vall66Met polymorphism and PTSD risk. While some studies found that Met allele carriers do not have increased risk of PTSD relative to Val/Val homozygotes, significant findings do emerge when more restrictive inclusion criteria are used (Bountress et al., 2017). For example, Met allele carriers were more likely to have PTSD than Val/Val homozygotes after removing studies that violated Hardy-Weinberg equilibrium (HWE) expectations (Bruenig et al., 2016). Results of these meta-analyses highlight the need for studies of large samples with BDNF Val66Met genotype frequencies that do not deviate from HWE expectations and employ more refined phenotyping approaches that examine dimensions of PTSD symptomatology.

Surprisingly few studies have examined the protective role of psychosocial factors with respect to genetic risk for PTSD. Characterization of such factors can help inform risk models of PTSD, as well as targets for prevention and treatment efforts in individuals at increased genetic and environmental (e.g., high trauma burden) risk for this disorder. One protective factor that may moderate the effect of BDNF Met allele carrier status on PTSD risk is physical exercise. In rodent models, exercise increases hippocampal BDNF expression and is associated with enhanced consolidation of fear extinction memory; in humans, physical exercise is associated with increased plasma BDNF levels, hippocampal neurogenesis, improved memory function, and reduced depressive and PTSD symptoms (Bouchet et al., 2017; Erickson et al., 2012; Liu and Nusslock, 2018; Rosenbaum et al., 2015; Tanner et al., 2018). Given that Met allele carrier status is associated with increased anxiety symptoms and possibly PTSD risk, modifiable protective factors that help moderate these symptoms, such as physical exercise (Liu and Nusslock, 2018), may help mitigate PTSD symptoms in this population. To date, however, no known study has evaluated this possibility.

We had three aims in the current study: (1) To examine the direct effect of the BDNF Val66Met genotype on PTSD symptoms; (2) to evaluate the interaction between the BDNF Val66Met genotype and lifetime trauma burden on severity of PTSD symptoms; and (3) to assess whether physical exercise may moderate the effects of the BDNF Val66Met genotype on severity of PTSD symptoms in veterans with high trauma burden.

2. Method

2.1. Participants

The main sample consisted of 1386 trauma-exposed European American (EA) U.S. military veterans from the National Health and Resilience in Veterans Study (NHRVS), a nationally representative study of U.S. veterans, conducted in 2011. The replication sample was an independent sample (n = 509) of trauma-exposed EA U.S. military veterans from a second baseline cohort survey of the NHRVS conducted in 2013. Post-stratification weights were applied based on the demographic distribution of veterans (age, sex, education, race/ethnicity, metropolitan area, and Census region) in the GfK Knowledge Networks survey panel and calibrated against U.S. Census data. The NHRVS was approved by the Veterans Affairs Connecticut Healthcare System and Office of Research & Development.

2.2. Assessments

2.2.1. BDNF Val66Met genotyping

Saliva was collected using Oragene DNA (OG-250) kits. DNA was extracted using prepIT-L2P reagent (DNA Genotek, Ontario, Canada) according to manufacturer's directions and genotyped with the PsychChip GWAS array. Genotypes were called using GenomeStudio software V2011.1 and genotyping module V1.8.4 (Illumina, San Diego, CA, USA). We computed principal components (PC) for the GWAS data using EIGENSOFT based on a common set SNPs (64,219) with Hapmap3, which were in low linkage disequilibrium (LD) with one another and had a MAF > 0.01. We detected and removed 95 outliers from the PC analysis. The *BDNF* Val66Met (rs6265) SNP was directly genotyped, and a dichotomous variable of 0 versus 1 or 2 Met alleles was generated for analyses. Additional details regarding genotyping are available elsewhere (Mota et al., 2018).

2.2.2. Trauma exposure and PTSD symptoms

Trauma histories were assessed using the Trauma History Screen (Carlson et al., 2011), which assesses potentially traumatic events across the lifespan, including childhood (e.g., physical abuse) and adulthood (e.g., motor vehicle accident) events. PTSD symptoms were assessed using lifetime and past-month versions of the PTSD Checklist; the DSM-IV version (Weathers et al., 1993) was used in the main sample and the DSM-5 version (Weathers et al., 2013) was used in the replication sample. Symptom clusters were computed by summing PCL items corresponding to a four-factor model of re-experiencing/intrusion, avoidance, emotional numbing/negative cognitions and mood, and hyperarousal symptoms.

2.2.3. Physical exercise

Engagement in physical exercise was assessed using the following question from a self-report inventory of typical weekly frequency of engagement in various activities: "How many days per week do you typically engage in the following activities: sports/exercise" (Montross et al., 2006). Given the non-normal and positively skewed distribution of this variable, it was dichotomized into "No Exercise" and "Any Exercise" for analyses; the "Any Exercise" group reporting a median of three days of exercise per week (interquartile range = 3).

2.3. Data analysis

Univariate analyses of covariance (ANCOVAs) were conducted to evaluate the relationship between Met allele carrier status, lifetime trauma burden, and their interaction, with severity of lifetime and past-month PTSD symptoms in the main and replication samples. Covariates included age, sex, top 10 PCs from population stratification analysis, combat exposure (i.e., combat veteran vs. non-combat veteran), nature of 'worst' traumatic event (i.e., assaultive [e.g., physical attack] vs. non-assaultive [e.g., unexpected loss of a loved one]), and history of mental health treatment (i.e., No (coded "0″) vs. Yes (coded "1″) history of psychotropic medication and/or psychotherapy/counseling; Bjorkholm and Monteggia, 2016; Perroud et al., 2013). To evaluate the role of physical exercise as a potential moderator of the interaction between *BDNF* Met allele carrier status x lifetime trauma burden, we incorporated Met allele carrier status x trauma burden x physical exercise interaction terms into the ANCOVAs. Post-hoc analyses of PTSD symptom clusters were limited to lifetime severity due to the low prevalence and variance of past-month PTSD symptom clusters. Reported raw frequencies are unweighted; means, percentages, and inferential statistics are post-stratification weighted to reflect the general population of U.S. veterans.

3. Results

3.1. Sample

Table 1 shows sociodemographic, military, and clinical characteristics of the main and replication samples. On average, the samples were 62–63 years of age, had some college or higher education, were married/cohabitating and retired, had household incomes < $60,000/year, were non-combat veterans, and spent an average of seven years in the military. Both samples reported an average of about four potentially traumatic life events, and 7.1–10.0% screened positive for lifetime PTSD and 3.5%–3.8% for past-month PTSD.

Table 1
Sociodemographic, military, trauma and clinical characteristics and associations between BDNF genotype, trauma burden, and PTSD symptoms in main and replication samples of U.S. European-ancestry military veteran.

	Main Sample (n = 1386) Weighted mean (SD) or n (weighted %)	Replication Sample (n = 509) Weighted mean (SD) or n (weighted %)
Sociodemographic Characteristics		
Age	62.6 (14.3)	62.4 (15.6)
Male sex	1,260 (92.8%)	457 (90.7%)
Some college or higher education	1,183 (66.0%)	428 (65.4%)
Married/living with partner	1,084 (74.9%)	379 (72.3%)
Currently employed	536 (36.1%)	152 (30.3%)
Household income ≥ $60,000/year	728 (42.4%)	255 (44.0%)
Military Characteristics		
Combat veteran	479 (32.7%)	213 (42.0%)
Number of years in military	6.8 (7.5)	7.0 (7.2)
Trauma and Clinical Characteristics		
Number of lifetime traumatic events	3.8 (2.5)	3.7 (2.5)
Index traumatic event		
Sudden death, close family member/ friend	451 (34.4%)	151 (32.7%)
Life-threatening illness or injury	226 (16.6%)	84 (14.2%)
Military-related trauma	113 (7.9%)	42 (9.5%)
Child physical or sexual abuse	59 (3.2%)	23 (5.4%)
Other traumatic event	537 (37.9%)	209 (38.2%)
Lifetime PCL score*	28.4 (11.4)	15.2 (15.2)
Positive screen for lifetime PTSD	95 (7.1%)	44 (10.0%)
Past-month PCL score*	24.2 (10.1)	9.4 (12.1)
Positive screen for past-month PTSD	41 (3.8%)	15 (3.5%)
BDNF Val66Met genotype		
Val/Val	945 (69.9%)	348 (68.2%)
Val/Met	389 (26.9%)	144 (27.9%)
Met/Met	52 (3.2%)	17 (3.9%)

Results of Multivariable Analyses of Variance Examining Associations between BDNF Val66Met Genotype, Trauma Burden, and PTSD Symptoms

Main Sample (n = 1386)	Lifetime PTSD Symptoms		Past month PTSD Symptoms		Re-experiencing		Avoidance		Emotional Numbing		Hyperarousal	
	F	p	F	p	F	p	F	p	F	p	F	p
BDNF Met allele carrier	**5.26**	**0.022**	**11.20**	**0.001**	**9.73**	**0.002**	6.93	0.009	2.33	0.13	0.49	0.48
BDNF Met allele carrier x Cumulative trauma burden	**8.08**	**0.005**	**24.65**	**< 0.001**	**11.83**	**0.001**	7.56	0.006	4.10	0.043	1.96	0.16
Replication Sample (n = 509)	Lifetime PTSD Symptoms		Past Month PTSD Symptoms		Intrusions		Avoidance		Negative Cognitions and Mood		Alterations in Arousal and Reactivity	
	F	p	F	p	F	p	F	p	F	p	F	p
BDNF Met allele carrier	**6.64**	**0.010**	1.86	0.17	4.18	0.041	2.57	0.11	4.27	0.039	3.06	0.081
BDNF Met allele carrier x Cumulative trauma burden	**9.04**	**0.003**	**4.39**	**0.037**	4.36	0.037	1.02	0.31	6.98	0.009	2.57	0.11

Note. PCL = PTSD Checklist; PTSD = posttraumatic stress disorder; *BDNF* = brain-derived neurotrophic factor.
The DSM-IV version of the PCL was used in the main sample (score range = 17–85) and the DSM-5 version of the PCL was used in the replication sample (score range = 0–80).
Distributions of *BDNF* Val66Met genotypes did not differ from Hardy-Weinberg expectations in the main (X^2 = 2.25, p = 0.13) and replication (X^2 = 0.20, p = 0.66) samples.
Multivariable analyses of variance results are adjusted for age, sex, ancestral proportion scores, combat veteran status, nature of index trauma (assaultive vs. non-assaultive), and history of mental health treatment.
Significance level for post-hoc analyses of lifetime PTSD symptoms was p = 0.003 (Bonferroni-corrected α = 0.05/16 main and interaction effect terms).

3.2. Effects of BDNF and trauma load on PTSD symptoms

The bottom panel of Table 1 shows results of multivariable ANCOVAs evaluating associations between main and interactive effects of BDNF Val66Met genotype and trauma load in predicting severity of PTSD symptoms. Results revealed a significant main effect of Met allele carrier status in predicting lifetime PTSD symptoms in both the main and replication samples, and past-month PTSD symptoms in the main sample; and a significant interaction of Met allele carrier status x trauma load in predicting lifetime and past-month PTSD symptoms in both samples. Post-hoc analyses of lifetime PTSD symptom clusters, with $p < 0.003$ considered significant (Bonferroni-corrected $\alpha = 0.05/16$ main and interaction effect terms), revealed a significant main effect of Met allele carrier status and Met allele carrier status x trauma load in predicting severity of re-experiencing symptoms in the main sample.

3.3. Protective effects of physical exercise

A moderation analysis examined the role of physical exercise as a potential moderator of the relation between Met allele carrier status and trauma load. Incorporation of genotype x trauma load x physical

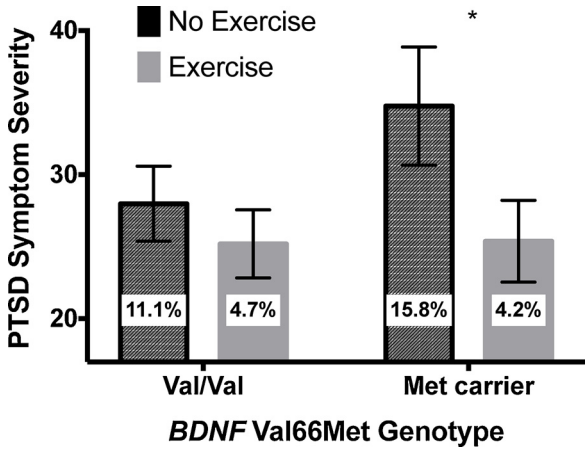

Fig. 1. Effect of exercise in moderating effect of *BDNF* Val66Met genotype on severity of past-month PTSD symptoms in highly trauma-exposed veterans in the main sample (n = 602).
Note. BDNF = brain-derived neurotropic factor. PTSD = posttraumatic stress disorder. Exercise = regular weekly engagement in at least one day of exercise or sporting activity.
The median number of days of exercise among veterans who reported exercising was 3 (interquartile range = 3).
Prevalences of probable PTSD (i.e., score ≥ 50 on the DSM-IV version of the PTSD Checklist) are embedded in bar graphs; Means are adjusted for age, sex, ancestral proportion scores, combat veteran status, type of index trauma—assaultive vs. non-assaultive, and history of mental health treatment.
*Significant difference, $p < 0.01$; Error bars reflect 95% confidence intervals.

exercise interaction terms revealed that engagement in physical exercise moderated the association between Met allele carrier status x trauma load on severity of past-month PTSD symptoms in the main ($F = 9.49$, $p < 0.001$) and replication ($F = 12.83$, $p < 0.001$) samples. Fig. 1, illustrates the interaction of Met allele carrier status x trauma load x physical exercise in predicting severity of past-month PTSD symptoms in the main sample.

4. Discussion

This study examined the relation between the BDNF Val66Met polymorphism and PTSD symptoms in two nationally representative samples of European American U.S. military veterans. Compared to veterans homozygous for the Val allele, those who carried either one or two copies of the Met allele reported greater severity of lifetime PTSD symptoms in the main and replication samples, and past-month PTSD symptoms in the main sample. These findings are consistent with prior findings suggesting that BDNF plays a role in brain functions implicated in PTSD, such as fear extinction (Frielingsdorf et al., 2010). A gene-by-environment interaction was also observed, with Met allele carriers with high cumulative trauma burden reporting greater severity of PTSD symptoms relative to Val/Val homozygotes with high cumulative trauma burden.

The finding that Met allele carrier status and the interaction of Met allele carrier status and cumulative trauma burden were uniquely related to severity of re-experiencing symptoms in the main sample suggests that the BDNF Val66Met polymorphism may be associated with specific aspects of the multi-faceted PTSD phenotype, particularly symptoms associated with fear learning and stress reactivity (Frielingsdorf et al., 2010). This finding may account for some of the inconsistencies in prior work (Bountress et al., 2017), which has analyzed PTSD as a homogeneous construct. Volumetric reductions and functional alterations of the hippocampus may underlie and possibly mediate the relation between Val66Met polymorphism and re-experiencing symptoms, as this polymorphism and hippocampal changes are implicated in impaired fear extinction and PTSD (Bueller et al., 2006; Woon et al., 2010). Taken together, these findings underscore the importance of genetic imaging studies to examine associations between BDNF Val66Met polymorphisms, hippocampal structure and function, and the heterogeneous phenotypic expression of PTSD symptoms.

Engagement in sports/exercise moderated the GxE association between Met allele carrier status and cumulative trauma burden in predicting PTSD symptoms. One explanation for this finding is that engagement in physical exercise may help promote hippocampal neurogenesis, size and function, increase BDNF levels, and improve aspects of executive function (Liu and Nusslock, 2018; Toh et al., 2018). Improvement in aspects of executive function may help trauma survivors better inhibit responses to and disengage attention from trauma-related stimuli (Aupperle et al., 2012), which may in turn lead to reduced severity of PTSD symptoms, although further research is needed to evaluate this possibility. Of note, the median number of days of exercise among veterans who reported engaging in physical exercise was three per week, which suggests that regular, weekly exercise may be necessary in order to help mitigate the deleterious effect of Met allele carriage and high trauma burden on severity of PTSD symptoms. Collectively, these results suggest that interventions designed to bolster engagement in exercise may help mitigate PTSD symptoms in veterans who are Met allele carriers and highly exposed to trauma. Further research is needed to evaluate this possibility.

Limitations of this study must be noted. First, because the sample was comprised predominantly of male veterans, there was not enough statistical power to assess potential moderating effects of sex. In light of data suggesting sex differences in diurnal variation and levels of plasma BDNF (Piccinni et al., 2008), further research is needed to evaluate the role of sex as a moderator of BDNF Val66Met polymorphisms, trauma load, and physical exercise in predicting PTSD symptoms. Second, the measure of physical exercise was based on a single-item measure of typical weekly frequency of engagement in sports/exercise (Montross et al., 2006). Given that physical activity, exercise, and physical fitness are distinct (Caspersen et al., 1985); and that self-reports of physical activity may not provide accurate estimates of the absolute amount of physical activity (Sallis and Saelens, 2000), additional research using more objective measures of physical activity, exercise, and fitness is needed to evaluate the replicability of the current findings.

5. Conclusions

Notwithstanding the limitations noted above, results of this study replicate prior work suggesting that the BDNF Val66Met polymorphism may be linked to severity of PTSD symptoms. They extend this work to suggest that genetic susceptibility of Met allele carriers may be greatest for those who experience a high number of traumatic events in their lifetimes and may be uniquely related to re-experiencing symptoms. Results further suggest that engagement in physical exercise may help mitigate PTSD symptoms in Met allele carriers with high trauma burden. Additional research is needed to replicate these results in more diverse samples of veterans and other trauma-affected populations; identify biological mediators of BDNF Val66Met polymorphisms and the heterogeneous phenotypic expression of PTSD symptoms; and evaluate the efficacy of interventions designed to promote engagement in physical exercise in mitigating PTSD symptoms in Met allele carriers with high trauma burden.

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Conflict of interest

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Credit author statement

Barbara Pitts: Conceptualization, Writing–original draft preparation, Writing–review & editing.

Julia Whealin: Conceptualization, Writing–original draft preparation, Writing–review & editing.

Ilan Harpaz-Rotem: Writing–review & editing.

Ronald Duman: Writing–review & editing.

John Krystal: Methodology, Investigation, Writing–review & editing, Supervision, Funding Acquisition.

Steven Southwick: Methodology, Investigation, Writing–review & editing, Supervision, Funding Acquisition.

Robert Pietrzak: Conceptualization, Methodology, Investigation, Writing–original draft preparation, Writing–review & editing, Formal Analysis, Visualization, Funding Acquisition, Project Administration.

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