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# Genetic predictor of current suicidal ideation in US service members deployed to Iraq and Afghanistan

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ABSTRACT

*Objective:* Suicide is one of the ten leading causes of death in United States and the suicide rate in the military population has increased since the start of the Iraq and Afghanistan wars. However, few biomarkers for current suicidal ideation (CSI) have been identified. The current study examined the association of four candidate genes with CSI in active duty US Army Special Operations Command and National Guard units (n = 3,889) who served in Iraq and Afghanistan between November 2009 and July 2014.

*Methods:* Current PTSD symptoms and CSI were assessed using the PTSD Checklist (PCL) and PHQ-9, respectively. Traumatic events were assessed using items from the Life Events Checklist (LEC) that met the DSM-IV PTSD criteria of a traumatic stressor. All genotypes of saliva DNA were discriminated using the TaqMan 5′-exonuclease assay.

*Results:* The associations between CSI and brain-derived neurotrophic factor (BDNF), FK506 binding protein (FKBP5), catechol-O-methyltransferase (COMT), or S100A10 (p11) were examined. We found CSI was associated with BDNF (OR = 1.5, 95% CI = 1.5–1.8, P = 0.0002), but not FKBP5, COMT and p11. Female soldiers reported CSI more often than males ($\chi2 = 7.403$, p = 0.0065), although gender did not affect CSI severity. In addition, associations were found between CSI and depression, PTSD, and BDNF, but not traumatic events. The BDNF Val66Met contributed to the severity of CSI even after adjusting to PTSD, depression and LEC.

*Conclusions:* The associations of BDNF with CSI and its severity suggest that BDNF may be a predictor of suicidal risk and present an opportunity to develop laboratory tools with clinical implications in suicide prevention and treatment.

## 1. Introduction

Suicidal behavior is a major public health concern (Hawton et al., 2001; Hawton and van Heeringen, 2009; Nock et al., 2008). It is characterized as a spectrum that includes suicidal ideation, suicide plans, suicide attempts, and completed suicide (Moscicki, 1997). Completed suicide (or suicide death) represents 1.8% of the global burden of disease and is one of the ten leading causes of death. In 2002 alone, potentially preventable suicides accounted for 877,000 deaths worldwide (WHO, 2012). In the United State, suicide rates have increased from 1999 through 2014, with greater annual percent increases after 2006 (http://www.cdc.gov/nchs/data/databriefs/db241_table.pdf#1). There are 421,200 to 842,400 suicide attempts per year among those aged 15 to 24 (Wilcox et al., 2009). However, suicidal ideation (i.e., suicidal thoughts) is more common than suicide attempts or completed suicides. The annual incidence of suicidal ideation in the US is estimated to be ∼5.6% (Crosby et al., 1999). Over 13.0% of Americans experience suicidal ideation at some point in their life (Kessler et al., 1999). Recently, increased rates of suicide in the active duty Army, as well as in the veteran population have drawn attention to suicide risk in these populations (Ursano et al., 2015). During the Iraq and Afghanistan wars, suicide rates in the US Army increased from 12.4 per 100,000 in 2003 to 18.1 per 100,000 in 2008 (Tanielian and Jaycox, 2008; Ursano et al., 2015). The rate in the National Guard

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reached 28.9 per 100,000 in 2013 (Gerrick, 2013).

Nearly 90% of the people who commit suicide are estimated to have a psychiatric disorder (Cavanagh et al., 2003). Depression and PTSD are comorbid with, and considerably increase the risk of, suicidal ideation (Hemelrijk et al., 2012; Ramsawh et al., 2014). A heritable component of suicidal behavior has been demonstrated in twin studies (Fu et al., 2002; Statham et al., 1998), adoptions (Wender et al., 1986), and families (Powell et al., 2000). For example, one study found that among 62 monozygotic twin pairs, 7 were concordant for suicide compared with 2 among 114 dizygotic twin pairs (11.3% vs 1.8%) (Roy et al., 1991). Approximately 43% of the variance of the occurrence of suicide may be attributed to genetic influences (Fu et al., 2002; Statham et al., 1998). A meta-analysis of the functional BDNF SNP Val66Met (rs6265, 196G > A) found that Met-carriers have a higher risk for a suicide attempt (Zai et al., 2012). In addition, depressed patients show reduced levels of hippocampal and cortical BDNF in postmortem studies (Yoshimura et al., 2010). There is also data demonstrating that blood BDNF levels are decreased in depressed patients (Yoshimura et al., 2010). A significantly negative correlation was observed between the HAMD scores and serum BDNF levels. Moreover, treatment with antidepressants, ECT, and rTMS increased the blood levels of BDNF. Fluvoxamine, paroxetine, milnacipran, and sertraline all increased serum BDNF levels (Yoshimura et al., 2010). At the time of death, over-expression of BDNF in subjects on antidepressant medication was also found in several brain regions associated with depression compared to untreated subjects (Dunham et al., 2009). These data suggest that blood (plasma and serum) BDNF level may be a biological marker for a depressive state (Yoshimura et al., 2010).

In addition, FKBP5 has been associated with suicide (De la Cruz-Cano, 2017). COMT, which catalyzes the transfer of a methyl group to catecholamines and degrades dopamine, norepinephrine and epinephrine, has been associated with both suicide attempts and completed suicide (Baud et al., 2007; Du et al., 2014; Ono et al., 2004). Although the COMT Val108/158Met polymorphism has also been associated with psychiatric disorders characterized by an increased risk of suicidal attempt and suicide (Baud et al., 2007; Du et al., 2014; Ono et al., 2004), a meta-analysis of 12 independent studies was unable to confirm the role of the polymorphism in suicide (Russ et al., 2000). Finally, p11 (annexin II light chain), a member of the S-100 calcium binding protein family (Gerke and Weber, 1985; Johnsson et al., 1990; Jost et al., 1997; Munz et al., 1997; Rescher and Gerke, 2008; Semich et al., 1989) and a potential biomarker for PTSD (Zhang et al., 2012) and depression (Svenningsson et al., 2006), is also associated with suicidal behavior. P11 blood transcripts were significantly lower in suicide attempters with PTSD compared to healthy controls (Zhang et al., 2011).

Genetic research about complex psychological disorders, such as suicidal ideation, PTSD, and depression, in US service members requires substantial resources and time to collect large samples, precisely defined phenotypes, and high quality specimens. In this study, 3,889 DNA samples were collected from US soldiers deployed during the Iraq and Afghanistan wars to address specific questions of the SNPs in functional candidate genes, traumatic life events, PTSD, and depression as predictors of suicidal ideation. We sought to investigate the association of current suicidal ideation (CSI) with four candidate genes (BDNF, FKBP5, COMT and p11). The four 'candidate genes' were identified based on previously published papers and demonstrate potential biological, physiological, or functional relevance to suicide (Cheng et al., 2006; Dell'osso et al., 2013; Du et al., 2014; Dwivedi, 2009; Perez-Ortiz et al., 2013; Roy et al., 2010; Supriyanto et al., 2011; Zhang et al., 2011). We also examined the effects of the interactions among the genes, environmental factors (traumatic life events), and mental health status (depression or PTSD) on CSI as well as its severity.

## 2. Method

### 2.1. Participants

Between November 2009 and July 2014, 3,889 volunteers were enrolled from active duty US Army Special Operations Command and National Guard units who had been deployed in Iraq and Afghanistan. The average age of the subjects with or without CSI were 29.0 ± 8.2 and 29.4 ± 8.4 years, respectively. The Institutional Review Board of the Uniformed Services University of the Health Sciences approved the protocol. All respondents were provided with a study briefing and written informed consent.

### 2.2. PTSD, depression, CSI and traumatic life events

Current PTSD symptoms were assessed using the PTSD Checklist (PCL), a 17-item Diagnostic and Statistical Manual Fourth Edition (DSM-IV) based self-report measure with well-established validity and reliability (Gelaye et al., 2017; Karstoft et al., 2017). The total PCL score determined PTSD symptom severity. Probable PTSD was determined based on endorsement of DSM-IV criteria and PCL score ≥ 50 (Gelaye et al., 2017; Karstoft et al., 2017). Depression was assessed with the PHQ-9. PHQ-9 is a depression module, which scores each of the 9 DSM-IV criteria from 0 (not at all) to 3 (nearly every day) (Kroenke et al., 2001). CSI was assessed with a PHQ-9 item: 'Thoughts that you would be better off dead or of hurting yourself' (during last two weeks). The respondents were considered to have CSI if they chose one of the responses: "Several days", "More than half the days", or "Nearly every day". Severity of CSI was determined by PHQ-9 (suicidal ideation) scores using a 1 to 4 scale (not at all, several days, more than half the days and nearly every day).

Lifetime traumatic events or trauma exposure were assessed using the Life Events Checklist (LEC), a commonly used self-report measure assessing experiences that meet the DSM-IV PTSD definition of a traumatic stressor. The number of life-time stressful events was the total number of 'happened to me' events.

### 2.3. Saliva sample collection, DNA extraction and genotyping

Saliva samples were collected using Oragene™ DNA Self-Collection Kits according to the manufacturer's instructions (DNA Genotek). Saliva DNA was extracted using the manufacturer's protocol. Briefly, the 2-ml samples were incubated in a water bath for 1 h at 50 °C, and then Purifier was added. Each tube was mixed well and incubated on ice for 10 min. The tubes were centrifuged at 15,000 × *g* for 5 min. The supernatant was removed and transferred to a fresh tube; an equal volume of room temperature 99.9% ethanol was added. The sample was mixed by inversion and allowed to stand at room temperature for 10 min. The sample was centrifuged at 15,000 × *g* for 2 min and the supernatant was removed and discarded. The DNA pellet was dissolved in 100-μL of TE buffer and the concentration was measured using Nanodrop.

All genotypes were discriminated with 7900HT Fast Real-Time PCR system using the TaqMan 5′-exonuclease assay. The primers of BDNF, p11, FKBP5, COMT, and NPY are shown in Table 1. The allele-discriminating probe was capable of hybridizing. The fluorescent probes were labeled at the 5′ end with either FAM or VIC.

The total 5-μl of PCR mixture contained 5-ng DNA, 120-nM ADP 1 × Master Mix (ABI), and 1 × SNP assay. Amplification conditions were 2 min at 50 °C, 10 min at 95 °C, and then 40 cycles at 96 °C for 15 s and at 62.5 °C for 90s. Genotypes were generated using the ABI PRISM 7900 Sequence Detection system software. To evaluate genotyping accuracy, one-quarter of the samples, randomly selected, were genotyped in duplicate. The error rate was < 0.005, and the completion rate

**Table 1**
List of polymorphisms of candidate genes for the association analysis.

| Gene | SNP ID | Assay ID | Sequences including SNP [allele 2/allele 1] |
|---|---|---|---|
| BDNF | rs6265 | C_11592758_10 | TCCTCATCCAACAGCTCTTCTATCA[C/T]GTGTTCGAAAGTGTCAGCCAATGAT |
| S100A10 | rs11204922 | C_26672722_10 | TGCAGCAGGGTAAGGACCTCTAAAT[C/T]TTAAAAAGGCTAATTTTAGGAGGTT |
| | rs3791153 | C_26672725_10 | ACCAGGATGTGGCATCTCCACCACC[A/G]GGTTTTTGGACCTGAAGGTAGCCAT |
| | rs2338019 | C_9624346_10_M | AAAAGTATAGCAGCAGCATTTCCCA[T/C]ATGAGCACTGCAAACTCCTACTCTA |
| FKBP5 | rs9470080 | C_92160_10 | ATAATTACCATTTGTCCAAAGTCAA[C/T]CTCTGAGCTAAAACACAATGTTTTT |
| | rs1360780 | C_8852038_10 | GAAGGCTTTCACATAAGCAAAGTTA[C/T]ACAAAACAAAAATTCTTACTTGCTA |
| | rs3800373 | C_27489960_10 | GAAGAGCAACTATTTATTTGTCAAC[A/C]CTACAGATTTTGTTTTTAAAAATTA |
| | rs9296158 | C_1256775_10 | CCTGGTAATATCACTCTCAATATCA[A/G]TATAGTCCAGAAACCAGCTTCAAAT |
| COMT | rs4633 | C_2538747_20 | CCAAGGAGCAGCGCATCCTGAACCA[C/T]GTGCTGCAGCATGCGGAGCCCGGGA |
| | rs4680 | C_25746809_50 | CCAGCGGATGGTGGATTTCGCTGGC[A/G]TGAAGGACAAGGTGTGCATGCCTGA |
| | rs737865 | C_2255420_10 | GCTTTTTGGATTTTTCCAGCCAGGG[A/G]TTTTTGTGTCCTGTTGCTTTTTATT |

was > 0.95 (Applied Biosystems).

### 2.4. Statistics

All analyses were performed with SPSS version 18. Student t-tests were performed in order to examine the age difference between the respondents with and without CSI. Chi-square tests were used to test differences of gender and ethnicity between groups and the association between CSI and the polymorphisms of the candidate genes. For candidate gene polymorphism (BDNF) with a significant association with CSI we then examined several independent predictors and models of CSI and CSI severity. We used univariate and multivariate logistic regression to examine whether each dependent variable was associated with the CSI (0 = No, 1 = Yes), particularly the relationships between CSI and the CSI-associated polymorphism of BDNF, age, gender, ethnicity, number of lifetime traumatic events, PTSD, and depression. In addition, univariate and multivariate linear regressions were conducted to examine the relationships between CSI severity and BDNF, gender, age, ethnicity, number of lifetime traumatic events, PTSD and depression. We conducted the mediation analysis using procedures of Baron and Kenny (1986). This model establishes two pathways which influences Y by direct effect and indirect effect. In direct effect, pathway leads from X to Y without passing M. In indirect effect, a pathway of X to Y is lead through M (Baron and Kenny, 1986).

## 3. Results

The demographics and characteristics of respondents with and without CSI are presented in Table 2. The study population consisted of 266 and 3,623 respondents with and without CSI, respectively. Females (9.7%; 47 out of 481) had significant higher CSI rate than males did (6.4%, 219 out of 3408) ($\chi^2 = 7.403$, $P < 0.01$). The depression and PTSD rates were significantly higher in those with CSI than those without CSI (Table 2). No sex-related differences of the PTSD or depression rates were observed (Table 2). No statistically significant differences of age and ethnicity were observed between the CSI group and non-CSI group.

**Table 2**
Demographic data of subjects.

| | Respondents with CSI N = 266 | Respondents without CSI N = 3623 |
|---|---|---|
| Age | 29.0 ± 8.2 | 29.4 ± 8.4 |
| Gender | | |
| Male | 219 | 3189[a] |
| Female | 47 | 434 |
| Ethnic | | |
| White | 187 | 2477 |
| Black | 22 | 270 |
| Asian | 38 | 712 |
| American Indian | 7 | 51 |
| Multiracial | 15 | 131 |

[a] $\chi^2 = 7.403$; $P = 0.00651$.

Genotype and allele frequencies of BDNF A198G (Val66Met) were compared in the 266 subjects with CSI and the 3623 subjects without CSI. The distributions of genotype frequencies were significantly different between the respondents with CSI and without CSI ($P < 0.001$) (Table 3). The percentage of Val/Met and Met/Met carriers in those with CSI (50.7%) was higher than that in controls (39.7%) (OR: 1.56, 95%1.22–2.01, p = 0.0005). The frequency of the 198G (66Met) allele was higher in individuals with CSI than in controls (29.8% *vs* 22.6%, $\chi^2 = 14.1$, p = 0.0002, OR: 1.5, 95% CI: 1.2–1.8). No different distributions of genotype frequencies and allele frequencies were found between those with CSI and controls in p11, FKBP5, and COMT (Table 3).

To analyze the association of the between genes and CSI, a series of logistic regressions were performed (Table 4). CSI was assigned as a condition dependent variable, and the polymorphism of BDNF and age, gender, ethnicity, traumatic events, PTSD, and depression were examined as independent variables. Univariate logistic regression analysis showed the CSI was significantly related to gender, depression, PTSD, BDNF, BDNF x depression, and BDNF x PTSD, but not traumatic events (Table 4). Furthermore, multivariate logistic regression analyses indicated that the CSI was significantly related to BDNF (and depression) even after controlling for age, gender and PTSD. (Table 4). In addition, the regression analysis showed significant associations between severity of CSI and the polymorphism of BDNF, PTSD, depression, traumatic life events, BDNF x depression, and BDNF x PTSD (Table 5). Multivariate regression analysis demonstrated that the severity of CSI was related positively to depression, PTSD, and BDNF, but negatively to traumatic life events (Table 5). The suicidal ideation risk associated with BDNF was increased by 32% (Table 4) and 59% (Table 5) when PTSD and depression were added, respectively. Mediation analysis showed that first, BDNF was positive correlated with CSI ($\beta = 0.08$, $p < 0.001$), indicating a significant total effect. Second, BDNF was correlated with depression ($\beta = 0.09$, $p < 0.001$) or PTSD ($\beta = 0.06$, $P < 0.001$). Third, depression ($\beta = 0.04$, $p < 0.01$) and PTSD ($\beta = 0.06$, $p < 0.01$) were both correlated with CSI, with controlling for BDNF.

## 4. Discussion

In this study, we found that the genotype and allele distributions of BDNF Val66Met were significantly different between the subjects with CSI and the subjects without CSI. The subjects with CSI were more likely to carry the Met allele than those without CSI. There was no significant association of FKBP5, COMT, or p11 with CSI. The findings on the BDNF gene provides evidence that the BDNF Val66Met is related to CSI and may have clinical relevance as a biological predictor for risk of CSI. The negative data on the associations between CSI and the candidate genes of FKBP5, COMT and p11 are inconsistent with other

**Table 3**
Genotype frequencies distribution of SNPs in case and control.

| Gene | SNP ID | Group | Genotype frequency | | | | Allele frequency | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 11 | 12 | 22 | P value | 1 | 2 | P value |
| BDNF | rs6265 | Control | 2185 | 1240 | 200 | 0.001 | 5610 | 1640 | 0.0002 |
| | | Suicide_ideation_current | 128 | 109 | 23 | | 23 | 155 | |
| p11 | rs3791153 | Control | 271 | 1457 | 1971 | 0.98 | 1999 | 5399 | 0.89 |
| | | Suicide_ideation_current | 19 | 107 | 145 | | 145 | 397 | |
| | rs11204922 | Control | 1064 | 1634 | 649 | 0.12 | 3762 | 2932 | 0.74 |
| | | Suicide_ideation_current | 85 | 99 | 52 | | 269 | 203 | |
| | rs2338019 | Control | 570 | 1969 | 1049 | 0.78 | 3109 | 4067 | 0.65 |
| | | Suicide_ideation_current | 37 | 146 | 77 | | 220 | 300 | |
| FKBP5 | rs1360780 | Control | 386 | 1680 | 1586 | 0.92 | 2452 | 4852 | 0.87 |
| | | suicide_ideation_current | 27 | 119 | 118 | | 173 | 337 | |
| | rs3800373 | Control | 363 | 1641 | 1611 | 0.96 | 2367 | 4863 | 0.89 |
| | | Suicide_ideation_current | 28 | 119 | 118 | | 175 | 355 | |
| | rs9296158 | Control | 1485 | 1725 | 447 | 0.84 | 4695 | 2619 | 0.58 |
| | | Suicide_ideation_current | 113 | 127 | 30 | | 353 | 187 | |
| | rs9470080 | Control | 432 | 1731 | 1385 | 0.80 | 2595 | 4501 | 0.52 |
| | | Suicide_ideation_current | 35 | 129 | 98 | | 199 | 325 | |
| COMT | rs4633 | Control | 722 | 1640 | 1128 | 0.37 | 3084 | 3896 | 0.24 |
| | | Suicide_ideation_current | 62 | 114 | 78 | | 238 | 270 | |
| | rs4680 | Control | 1099 | 1704 | 688 | 0.49 | 3902 | 3080 | 0.39 |
| | | Suicide_ideation_current | 71 | 132 | 51 | | 274 | 234 | |
| | rs165599 | Control | 617 | 1584 | 1239 | 0.97 | 2818 | 4062 | 0.97 |
| | | Suicide_ideation_current | 47 | 116 | 93 | | 210 | 210 | |

**Table 4**
Logistic regression analysis to detect predictors for suicide ideation.

| Independent variable | B | SE | Exp(B) | 95% CI for Exp(B) | P |
|---|---|---|---|---|---|
| **Univariate** | | | | | |
| Age | −0.007 | 0.007 | 0.993 | 0.979 to 1.007 | 0.350 |
| Gender | 0.393 | 0.160 | 1.481 | 1.083 to 2.024 | 0.014 |
| Race ethnicity | 0.026 | 0.027 | 1.026 | 0.974 to 1.082 | 0.329 |
| Depression | −0.258 | −0.011 | 1.295 | 1.267 to 1.324 | 0.000 |
| PTSD | 2.265 | 0.132 | 9.630 | 7.437 to 12.470 | 0.000 |
| Traumatic life events | −0.412 | 0.256 | 1.510 | 0.915 to 2.494 | 0.107 |
| BDNF | 0.082 | 0.018 | 1.085 | 1.047 to 1.125 | 0.000 |
| BDNF x depression | −3.005 | 0.072 | 1.227 | 1.198 to 1.257 | 0.000 |
| BDNF x PTSD | −3.031 | 0.074 | 0.048 | 1.159 to 1.210 | 0.000 |
| **Multiple variate model one** | | | | | |
| Age | −0.011 | 0.009 | 0.989 | 0.972 to 1.007 | 0.218 |
| Gender | 0.451 | 0.191 | 1.570 | 1.079 to 2.286 | 0.018 |
| Race ethnicity | −0.026 | 0.033 | 0.974 | 0.913 to 1.039 | 0.424 |
| Depression | 1.435 | 0.702 | 4.198 | 1.061 to 16.616 | 0.041 |
| PTSD | 2.362 | 0.722 | 10.612 | 2.578 to 43.680 | 0.001 |
| Traumatic life events | −0.031 | 0.018 | 0.970 | 0.935 to 1.005 | 0.092 |
| BDNF | 0.050 | 0.024 | 1.051 | 1.003 to 1.102 | 0.037 |
| BDNF x depression | 0.054 | 0.053 | 1.056 | 0.952 to 1.171 | 0.304 |
| BDNF x PTSD | −0.067 | 0.056 | 0.935 | 0.838 to 1.043 | 0.230 |
| **Multiple variate model two** | | | | | |
| Gender | 0.357 | 0.205 | 1.429 | 0.956 to 2.137 | 0.082 |
| Depression | 0.258 | 0.014 | 1.294 | 1.258 to 1.331 | 0.000 |
| PTSD | 0.010 | 0.201 | 1.010 | 0.681 to 1.498 | 0.960 |
| BDNF | 0.050 | 0.024 | 1.052 | 1.003 to 1.102 | 0.035 |

**Table 5**
Linear regression analysis of predictors for severity of CSI.

| Independent variable | β | B | SE | 95% CI for B | P |
|---|---|---|---|---|---|
| **Univariate** | | | | | |
| Age | 0.000 | 0.000 | 0.001 | −0.001 to 0.001 | 0.997 |
| Gender | 0.036 | 0.042 | 0.018 | 0.007 to 0.078 | 0.020 |
| Race ethnicity | 0.007 | 0.001 | 0.003 | −0.004 to 0.007 | 0.637 |
| Depression | 0.532 | 0.043 | 0.001 | 0.041 to 0.045 | 0.000 |
| PTSD | 0.324 | 0.448 | 0.020 | 0.408 to 0.487 | 0.000 |
| Traumatic life events | 0.023 | 0.034 | 0.023 | −0.011 to 0.079 | 0.139 |
| BDNF | 0.080 | 0.012 | 0.002 | 0.007 to 0.017 | 0.000 |
| BDNF x depression | 0.396 | 0.050 | 0.002 | 0.046 to 0.053 | 0.000 |
| BDNF x PTSD | 0.322 | 0.035 | 0.002 | 0.032 to 0.038 | 0.000 |
| **Multiple variate model one** | | | | | |
| Age | −0.004 | 0.000 | 0.001 | −0.002 to 0.001 | 0.773 |
| Gender | 0.029 | 0.034 | 0.018 | 0.000 to 0.069 | 0.053 |
| Race ethnicity | −0.016 | −0.003 | 0.003 | −0.008 to 0.003 | 0.304 |
| Depression | 0.227 | 0.372 | 0.102 | 0.173 to 0.571 | 0.000 |
| PTSD | 0.120 | 0.167 | 0.097 | −0.024 to 0.358 | 0.047 |
| Traumatic life events | −0.036 | −0.003 | 0.001 | −0.006 to −0.001 | 0.021 |
| BDNF | 0.043 | 0.006 | 0.002 | 0.003 to 0.011 | 0.003 |
| BDNF x depression | 0.128 | 0.015 | 0.008 | 0.000 to 0.030 | 0.056 |
| BDNF x PTSD | 0.054 | 0.006 | 0.008 | −0.009 to 0.021 | 0.456 |
| **Multiple variate model two** | | | | | |
| Depression | 0.511 | 0.041 | 0.001 | 0.038 to 0.043 | 0.000 |
| PTSD | 0.034 | 0.047 | 0.023 | 0.001 to 0.093 | 0.044 |
| Traumatic life events | −0.035 | −0.051 | 0.021 | −0.092 to −0.011 | 0.013 |
| BDNF | 0.047 | 0.007 | 0.002 | 0.003 to 0.011 | 0.001 |

suicidal behavior studies (Baud et al., 2007; Roy et al., 2010; Supriyanto et al., 2011). These differences may due to: (a) the difference in the phenotypes examined (suicide attempt vs suicide ideation) as well as (b) the measurement and definition of constructs. Additionally, the previously cited studies focuses on a civilian sample, whereas the current study draws from a military sample. Thus, suicide risk variables may vary between those in a civilian versus a voluntary military population.

Two other findings warrant mention. First, although there was significant difference in the CSI rate between males and females, there was no association between gender and severity of CSI. Second, mental health conditions were identified as possible modifiable predictors for CSI. Met carriers with PTSD or depression were more likely to report CSI than individuals without PTSD or depression. The suicidal ideation risk associated with BDNF was increased by 32% and 59% when PTSD and depression were added, respectively. Therefore, in addition to identifying the subset of subjects with a specific genetic profile, it is important to determine the individual's mental health status to better design diagnostic and therapeutic approaches for suicidal ideation. A combination of these four factors (PTSD, depression, traumatic life events, and the polymorphism of BDNF) explain over 50% of the CSI severity. Both BDNF x depression and BDNF x PTSD were associated with CSI. Although, conversely, multivariate analysis found there was no correlations between CSI and either BDNF x depression, or BDNF x PTSD, those data indicates that, at least in part, G × E interaction played a substantial role in both susceptibility and severity of CSI among soldiers. Mediation analysis showed that BDNF was positive correlated with CSI while BDNF was correlated with depression or

PTSD. In addition, depression or PTSD was correlated with CSI, with controlling for BDNF, and influence of BDNF on CSI remained significant, indicating that depression or PTSD was considered as partial mediator (Baron and Kenny, 1986).

Over the past several years, studies on the role of BDNF in the pathophysiology of suicidal behavior have attracted significant interest from researchers. Multiple lines of researches examining blood levels of BDNF (Park et al., 2014), postmortem brain (Sher, 2011), and genetic association studies (Perroud et al., 2009) link BDNF to suicidal behavior. Polymorphisms in BDNF have been significantly associated with greater suicidal ideation (Perroud et al., 2009). BDNF rs6265 polymorphism has also been associated with suicide in a cohort of subjects with completed suicide (Pregelj et al., 2011). The first meta-analysis of the functional BDNF marker Val66Met (rs6265, 196G > A) in suicide behavior revealed a trend whereby the Met allele and Met-carrying genotypes conferred a risk of suicide (Zai et al., 2012). In addition, the meta-analysis of 16,786 subjects demonstrated an association between Val/Val genotype and suicide attempt. Our findings support these reports from other genetic studies, suggesting a significant relationship between BDNF and suicidal behavior even after adjusting for depression and PTSD (Dwivedi, 2009).

BDNF, which regulates neuronal survival, growth, differentiation and synapse formation, broadly regulates the stress response (Rakofsky et al., 2012). Polymorphism in the BDNF gene (Val66Met) influence hippocampal volume (Frodl et al., 2007), memory (Frielingsdorf et al., 2010) and appears related to susceptibility to a variety of neuropsychiatric disorders, including PTSD (Zhang et al., 2014), bipolar disorder and depression (Costanza et al., 2014; Gonzalez-Castro et al., 2015; Park et al., 2014), in which suicidal behavior is commonly observed (Costanza et al., 2014; Park et al., 2014). Met carriers have a smaller hippocampal volume relative to controls (Frodl et al., 2007). The allelic frequency of Met was two-fold higher in individuals with probable-PTSD than in controls (Zhang et al., 2014). Thus, the pathogenesis of suicidal behavior, PTSD and depression appears to involve BDNF-altered neural plasticity in the inability of the brain to make appropriate adaptive responses to environmental stimuli (Duman et al., 2000; Fossati et al., 2004; Garcia, 2002). Studies have also found that stress or depressive behavior are related to a reduction in cell number, density, and cell body size in frontal cortex or hippocampus, as well as a decrease in parahippocampal cortex and cortical/laminar thickness (Altshuler et al., 1990; Ongur et al., 1998a, 1998b; Rajkowska, 1997).

The relationship between traumatic stress and Val66Met polymorphism in the BDNF gene also has drawn much attention. Data show that the Met allele significantly moderates the relationship between traumatic stress and depression (Hosang et al., 2014). Our data complement these results, showing *BDNF*, traumatic life events, depression and PTSD as independent predictors of CSI severity. We noted that multivariate regression analyses showed a relative smaller size to current levels of depression symptoms. These findings further provided insight towards understanding the relationship between CSI and BDNF.

While the etiology of suicide is unclear, risk factors include psychiatric disorders (especially mood disorders), substance use disorders, chronic illness, and demographic variables (age and sex) (Crump et al., 2014). In addition, gene expression, such as BDNF levels may be associated with suicide risk (Eisen et al., 2015). BDNF is associated with depression, bipolar disorder, and anxiety (Castren, 2014) and It is the most abundant member of the neurotrophin family and implicated in suicidal behaviour (Bozorgmehr et al., 2018; Choi et al., 2018; Kim and Kim, 2018; Park et al., 2018; Pedrotti Moreira et al., 2018; Regue-Guyon et al., 2018; Sonal and Raghavan, 2018; Xia et al., 2018; Youssef et al., 2018). BDNF is expressed in the brain and circulates throughout the body in the bloodstream (Dwivedi, 2009). It triggers a cascade of events that lead to neurogenesis, nerve growth, neuroplasticity, and neurotransmission and plays important roles in morphological plasticity, neurite outgrowth, phenotypic maturation, and protein synthesis for neuron and synaptic functioning (Dwivedi, 2009). Lower expression of BDNF is associated with psychiatric disorders, suicide, vulnerability to depression, and acute depressive status in the general population (Paska et al., 2013; Terracciano et al., 2011, 2013).

Despite the study's strengths, limitations should be noted. First, the present methodology is population-based. Participation was anonymous and follow-up was not possible. Second, CSI was assessed using a single item from the PHQ-9. Assessing CSI with a more comprehensive assessment, such as the Beck Suicidal Ideation Inventory, is preferable to a single item screen. Third, due to the interplay of several factors in the analysis, the relationship between BDNF polymorphisms and CSI, namely whether or not there is a direct relationship or if the interactions are mediated though depression or PTSD, needs to be determined. Fourth, only a limited number of risk alleles were tested for associations with CSI. A comprehensive approach would utilize GWAS machine learning to conduct an unbiased search for polygenetic risk profiles. Future studies should attempt to assess complete gene markers of suicidal ideation using genome-wide association prospective study.

## 5. Conclusions

The Val66Met in BDNF is a predictor of CSI. This finding may have clinical implications particularly for military personnel following an armed conflict. Complementing other findings (Nock et al., 2014), using BDNF as a predictor combined with mental health conditions could improve suicide screening and intervention efforts. In addition, genetic studies of suicidal ideation and BDNF may assist in the understanding of mechanisms underlying vulnerability. This, in turn, may help to find a specific molecular target(s), such as BDNF, to develop novel pharmacological agents to treat this condition. Studies of BDNF genetic effects stratified by PTSD and depression, or *vice versa*, may increase the ability to understand the pathophysiology of suicidal ideation. Overall, our findings suggest that BDNF is associated with CSI and contributes to its severity. Therefore, BDNF may be a genetic predictor of suicidal risk, and warrants developing a laboratory tool for suicide prevention and treatment, which will ultimately benefit both military and civilian populations.

## Contributions

L.Z. designed the studies with the X.Z.H., D.M.B, C.S.F, R.D.F and R.U together, generated most of the data along with X.Z.H and X.X.L, and interpreted all the results. X.Z.H. and L.Z. purified DNA and conducted genotyping. X.Z.H and L.Z provide the data of genetic association study. D.B served as the study's principal investigator during the data collection phases. D.B, R.F and J.N conducted the active duty data collections. D.R coordinated all of the National Guard data collections. Biomarker team, J.A.N, and G.W. provided the information of the demography and PCL data of the subjects. R.U and C.F. participated in the discussion of results and design of variable collection procedure as well as in writing of the manuscript. L.Z. wrote the manuscript, and X.Z.H and R.U. provided the comments on the manuscript and provided the Tables and modification of the Figures. All co-authors read and approved the manuscript. L.Z supervised the study.

## Conflicts of interest

The authors declare no conflict of interests.

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