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THE RELATIONSHIP BETWEEN COMBAT-RELATED POSTTRAUMATIC STRESS DISORDER AND THE 5-HTTLPR/rs25531 POLYMORPHISM

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Abstract

Background—Empirical evidence suggests that there is a significant genetic influence in the development of posttraumatic stress disorder (PTSD). The serotonin transporter (5-HTT) gene (SLC6A4) has been identified as a prime candidate for the development of the disorder, as 5-HTT is a working target for selective serotonin reuptake inhibitors (SSRIs), first line treatment agents for PTSD. Several studies have reported associations between 5-HTT-linked promoter region (5-HTTLPR) polymorphism variants and increased rates of PTSD in civilian samples. This study investigated the role of the 5-HTTLPR polymorphism, triallelically classified, in a sample of combat veterans with and without PTSD.

Methods—Rates of PTSD were examined across three genotypes in a sample of 388 combat veterans. The short/long polymorphism of 5-HTTLPR and the A-G polymorphism within the 5-HTTLPR (rs25531) were genotyped, and statistical analyses were conducted.

Results—There were significant intergroup (PTSD versus non-PTSD) differences in the genotype frequencies of 5-HTTLPR/rs25531 ($\chi^2[1, n=388]=16.23, P=5.62 \times 10^{-5}$). The 5-HTTLPR S'/S' (low transcriptionally efficient) genotype was also associated with the PTSD severity score in the 228 participants who had combat severity data ($r=.15, P=0.03$).

Conclusions—The findings are consistent with previous research among civilian populations that have indicated that the low transcriptionally efficient S'/S' genotype of 5-HTTLPR is a risk factor for the development of PTSD after trauma exposure. Our findings are the first to examine this polymorphism and PTSD in a military sample. Additional large-scale investigations are needed to replicate these findings.

Keywords

post traumatic stress disorder; 5-HTTLPR; combat trauma; genetic risk; 5-HTTLPR genotypes; combat veteran

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a disabling condition that develops following exposure to life-threatening events, such as combat exposure.^[1] The classic symptoms include re-experiencing the trauma through nightmares or flashbacks, persistent avoidance of associated stimuli, and increased arousal manifested as insomnia and exaggerated startle. PTSD is highly prevalent, especially among military personnel and veterans due to increased risk of exposure to combat-related trauma.^[2] Trauma exposure is a required risk factor for the development of PTSD, but this alone does not cause PTSD. Although the exact mechanism is unclear, family and twin studies support the role of genetic predisposition in the development of PTSD and comorbid symptoms.

The development of PTSD is a complex process, most likely involving both environmental and genetic contributions. Twin and family studies support the influence of genetics in the development of PTSD symptoms. True et al.^[3] examined the prevalence of PTSD in monozygotic and dizygotic Vietnam veteran twins, and found that after controlling for trauma exposure, there was a 30% genetic contribution to PTSD susceptibility. Sack et al.^[4] found that the off-spring of Cambodian refugees had a PTSD rate of 12.9% when neither parent had PTSD; the rate increased to 23.3% when one parent was diagnosed with PTSD, and the rate further increased (41.2%) when both parents had PTSD. Another study by Yehuda et al.^[5] indicated that Holocaust survivors with PTSD are more likely to have children with PTSD compared to those without PTSD. These studies suggest that further molecular genetic investigation of the disorder is warranted.

Recently, research efforts have turned to identifying candidate genes that may be associated with risk for PTSD. Neurobiological research over the past two decades has indicated that PTSD is a heterogeneous phenotype involving multiple neurotransmission and neuro-hormonal systems, including the hypothalamic-pituitary-adrenal (HPA) axis, catecholamines, serotonin, γ aminobutyric acid (GABA), glutamate, and other neuropeptides systems.^[6] However, the exact mechanism by which PTSD develops is still unknown. Research on the role of genetic variation in these neurobiologic systems may provide a deeper understanding of the pathophysiology of this condition. The majority of the molecular genetic studies have focused on the HPA axis (*GCCR*, *CRH1R*, *FKBP5*, *CNR1*), dopamine (*DAT1*, *DRD4*, *DRD2*), and serotonin (*SLC6A4*, *5-HT2A*) systems. Although all the selected genes were based on their hypothesized relationship with neurobiological process involved in PTSD development, the serotonin transporter (5-HTT) gene (*SLC6A4*, promoter region referred to as the *5-HTTLPR*)^[7] has received particular attention in PTSD genetic research. Serotonin is a neurotransmitter that is widely distributed in the central nervous system. It is a potent modulator of emotional behavior^[8] and a modulator of stress-responsive hormones in the amygdala, such as corticotropin-releasing hormone (CRH).^[9] Within the serotonin neurotransmission system, the *SLC6A4* gene is particularly important because it regulates the magnitude of synaptic 5-HT level. Additionally, selective serotonin reuptake inhibitors (SSRIs) attenuate the symptoms of PTSD and depression by inhibiting 5-HTT molecules, which provides further evidence for *SLC6A4* as a candidate gene for PTSD.^[10]

The serotonin transporter (5-HTT), a 12 membrane-spanning protein, is encoded by a single gene (*SLC6A4*), mapped to chromosome 17q12. Two potentially functional VNTR polymorphisms have been found in the *SLC6A4* gene. The most frequently studied polymorphism, the *5-HTTLPR*, is located in the promoter region and is a functional polymorphism containing two alleles, l and s, that differ in length by 44 bp.^[11] The *5-HTTLPR* polymorphism alters *SLC6A4* transcription in lymphoblast cells, with the cells containing the s allele having decreased 5-HTT expression and reduced serotonin uptake.^[11] Recently, a third single nucleotide polymorphism (SNP, *A/G, rs25531*) has been identified within the *5-HTTLPR*. Therefore, the *5-HTTLPR* alleles can further be labeled *L_A*, *L_G*, *S_A*. The *L_G* allele has shown similar effect in 5-HTT expression level as the s allele.^[12]

The functional effect on serotonin availability has encouraged clinical studies of association between *5-HTTLPR* genotype and various anxiety- and depression- related phenotypes, including PTSD.^[13–18] The *5-HTTLPR* polymorphism was first reported in a Korean sample, in which investigators found excess homozygous s/s genotypes in individuals with PTSD compared with healthy controls.^[13] Although several recent studies of this variant reported an association with the *S'* allele (or *S'/S'* genotype) and PTSD, the majority of them have reported a gene–environment interaction.^[13–18] Additionally, some studies have not replicated the initial association. Furthermore, none of the studies to date have examined a noncivilian population. It is well documented that combat exposed veterans are at increased risk for PTSD compared to the general population,^[1] making a military populations important for genetic investigations of PTSD. Therefore, this study examined the *5-HTTLPR* in a cohort of combat veterans in order to test the association between genotype and PTSD. It was hypothesized that the *S'/S'* genotype would be associated with increased rates and severity of PTSD.

MATERIALS AND METHODS

PARTICIPANTS

A total of 388 combat veterans were enrolled. Of the 388 participants in the study, 54.6% (*n*=212) met criteria for PTSD. The majority of the participants were male, and 70% were Caucasian. Demographics and genotypes for those diagnosed with PTSD and control participants are presented in Table 1. All participants were combat veterans recruited through two Veterans Affairs Medical Centers (VAMC): Cincinnati VAMC, Cincinnati, OH and Charleston VAMC, Charleston, SC. The research protocol was approved by the Institutional Review Boards (IRB) of both the University of Cincinnati and Medical University of South Carolina. Subjects were recruited using similar methods at the two sites. The brief description and voluntary nature of this study were explained to participants by a trained research assistant, and interested participants were screened to determine eligibility. Written informed consent was obtained from all the participants before the formal interview.

PROCEDURE

After collecting the demographic and deployment information, the participants were assessed by a trained research assistant for the presence of PTSD or other psychiatric disorders with either Structured Clinical Interview for DSM-IV (SCID)^[19] or Mini-International Neuropsychiatric Interview (MINI).^[20] Both the SCID and MINI are valid and reliable structured diagnostic instruments that assess the presence of DSM-IV diagnoses. A board-certified psychiatrist (Z.W., D.B.) interviewed participants for combat exposure history and PTSD status, as well as other major psychiatric illnesses that would be exclusionary (see inclusion/exclusion section below). Therefore, full diagnostic level data and demographic data are available for all 388 participants. All participants provided a peripheral blood sample via standard methods for the isolation of genomic material.

Mid-way through the study additional interview and self-report measures were implemented as part of the study design to measure severity of combat exposure and severity of PTSD symptoms, and therefore, for a subset of participants ($n=228$ of the total 388), information on these measures was available.

These 228 participants completed the Combat Exposure Scale (CES),^[21] a seven-item self-report measure, used to obtain information regarding exposure to wartime stressor events. The measure has total scores ranging from 1 to 41, with a higher number reflecting a higher severity of combat exposure. These participants were also interviewed using the Clinician Administered PTSD Scale (CAPS),^[22] a diagnostic interview for current and lifetime PTSD. The CAPS has been used in over 200 studies and has excellent psychometric properties.^[23] The CAPS demonstrated high inter-rater reliability (i.e., above .86) and internal consistency on each of the three PTSD symptom clusters (range .63 to .89), and correlates strongly (i.e., above .61) with other measures of PTSD.^[23,24] When tested in conjunction with the SCID, the CAPS provided a PTSD diagnosis with specificity ranging from 94%^[25] to 95%,^[26] and sensitivity ranging from 84%^[25] to 90%.^[26] Further, each of the core 17 items on the CAPS, with the exception of amnesia, discriminates individuals with PTSD from those without PTSD,^[22] which suggests adequate discriminant validity. Developed by researchers at the National Center of PTSD, this structured interview assesses all 17 symptoms of PTSD for frequency (scored on a 0 [never] to 4 [daily or almost every day]) and intensity (0 [none] to 4 [extreme, incapacitating distress]). This measure also assesses subjective distress, functional impairment, and onset and duration of symptoms, and includes response validity items.

INCLUSION/EXCLUSION CRITERIA

To be eligible for this study, participating veterans were required to have a history of combat exposure, as evidenced by a DD214, and report of combat exposure during the interview with a psychiatrist. In order to match the trauma-exposure severity between the PTSD subjects and controls, majority of the participants in the second half of this study were required to have CES score of 10 or above. Combat veterans with comorbid major depression and anxiety disorders other than PTSD were included. Individuals with a past history of substance abuse and dependence were also included if the last use of the substance was over 6 months prior to the enrollment. For those with PTSD, 61%, $n=129$ met criteria for comorbid major depressive disorder and 30%, $n=64$ met criteria for comorbid substance abuse. Subjects with current or lifetime DSM-IV schizophrenia, other psychotic disorders, bipolar disorder, and active substance abuse or dependence in the past six months were excluded. Control subjects were free of Axis I psychiatric disorders.

Laboratory procedure—Genomic DNA was isolated from venous blood using the Puregene kit (Gentra Systems Inc., Minneapolis, MN) according to the manufacturer's protocol. The three potentially functional polymorphisms of the *SLC6A4* were genotyped using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) method. The PCR for *5-HTTLPR* was carried out in a 15 μ l reaction containing: 50 ng DNA, 10pmol of each primer, forward 5'-ATGCC-AGCACCTAACCCCTAATGT-3' and 5'-GGACCGCAAGGTGGGCGGGA-3',^[27] 200 μ M dNTP mixed with 1:1 7-deaza-dGTP, 0.1 unit of Pfx DNA polymerase, 1 $\times$ PCR buffer with enhancer (Invitrogen). Due to the high GC content in the polymorphism region, we used Pfx DNA polymerase, and mixed 7-deaza-dGTP with other dNTP and 1 $\times$ PCR buffer with enhancer (Roche). The reaction was initially heated to 95°C for 5 min, and followed by 35 cycles of 30 sec for each 94°C, 62°C, 68°C. The final cycle is 72°C for 7 min. The Pfx DNA polymerase, and 7-deaza-dGTP were used to detect functional SNP *rs25531*, the PCR products were digested with 0.5 units of restriction endonuclease MspI. The final product was analyzed in 3% agarose gel

with ethidium bromide. The product sizes after digestion were: $L_A=325+62+33$, $L_G=174+150+62+33$, and $S_A=281+62+33$. The gels were read by experienced laboratory assistant, and confirmed by the first author (Z.W.), and both were blind to the diagnoses.

Analytic plan—Bivariate associations between the PTSD diagnosis and demographics were conducted via χ^2 tests for dichotomous variables and t -tests were conducted for continuous variables. Calculations for deviation from the Hardy–Weinberg equilibrium were performed using the χ^2 test. Given that diagnostic information was available on all subjects ($n=388$) but the PTSD severity score based on the CAPS and combat severity score (CES) was only available on a subset of participants ($n=228$), one main outcome analysis and one exploratory analysis was conducted; given that we examined two related outcomes (one diagnostic and one quantitative phenotype) we elected to employ a Bonferroni correction to adjust for multiple testing, and our P -value for the determination of significance is $P<0.025$. Prior to the main outcome or exploratory analyses, we examined the correlation between diagnosis of PTSD and the CAPS score to determine the correspondence between the two outcomes. For the main outcome analysis, we examined the relation between 5-*HTTLPR* genotype and PTSD diagnosis via the χ^2 test in the full sample. To test whether the associations between the polymorphism and PTSD status remained significant after controlling for demographic factors (i.e., sex, age, racial/ethnic status) a logistic regression analysis was conducted. In our secondary, exploratory analysis, in the subset of the sample ($n=228$) that had combat severity and PTSD severity data, a linear regression was conducted to determine whether the 5-*HTTLPR* was associated to CAPS total score, after controlling for relevant demographics. Finally, as the 5-*HTTLPR* genotype distribution differs by racial/ethnic status, we also ran both the diagnostic and the PTSD severity analyses (primary and secondary/exploratory, respectively) in the subset of participants who were European American (EA).

RESULTS

DESCRIPTIVE STATISTICS ($N=388$ UNLESS OTHERWISE NOTED)

Genotype frequencies for the 5-*HTTLPR*/rs25531 polymorphism, classified triallelically, were reclassified based on the transcriptional efficiency. L_A/L_A were classified as L'/L' . L_A/S and L_A/L_G were classified as L'/S' . L_G/L_G , L_G/S , and S/S were classified as S'/S' . According to the new classification, 22.2% ($n=86$) had the L'/L' genotype, 46.1% ($n=179$) had the L'/S' genotype, and 31.7% ($n=123$) had the S'/S' genotype; these frequencies did not deviate significantly from the Hardy–Weinberg equilibrium. Among EAs, 19.9% ($n=54$) had the L'/L' genotype, 47.6% ($n=129$) had the L'/S' genotype, and 32.5% ($n=88$) had the s/s genotype. Among non-EAs, 27.4% ($n=32$) had the L'/L' genotype, 42.7% ($n=50$) had the L'/S' genotype, and 29.9% ($n=35$) had the S'/S' genotype. Table 1 presents genotype frequencies by PTSD status, which are also shown in Figure 1.

Self-reported race/ethnicity was not associated with PTSD status ($\chi^2[1, n=388]=0.47$, $P=0.50$). Self-reported race/ethnicity was also not associated with genotype frequencies for the 5-*HTTLPR* polymorphism ($\chi^2[2, n=388]=2.62$, $P=0.27$); therefore, population stratification was not a potential cause of false-positive findings. Average age was also not significantly different between those without PTSD ($M=49.50$, $SD=13.85$) versus those with PTSD ($M=48.62$, $SD=14.46$), $t(386)=0.61$, $P=0.55$. Additionally, among participants with data for the CES ($n=228$), the level of combat trauma was not significantly different between those without PTSD ($M=20.43$, $SD=8.45$) versus those with PTSD ($M=21.95$, $SD=7.92$), $t(226)=-1.32$, $P=0.19$.

ASSOCIATION BETWEEN THE PTSD DIAGNOSIS AND PTSD SEVERITY SCORE

Given that for 42% of participants, complete data were not available, analyses were conducted to determine the correspondence between the PTSD diagnosis made by a psychiatrist, and the PTSD severity score yielded from the CAPS to ensure that analyses in the full sample and the subset of the sample were comparable to each other (i.e., the data in the primary outcome would be comparable to that of the secondary outcome). The point biserial correlation between the PTSD diagnosis and the CAPS score was $r=.76$, $P=1.63\times 10^{-43}$, suggesting a high correspondence between the diagnosis of PTSD made by the psychiatrist and the CAPS score.

PRIMARY ANALYSIS: ASSOCIATION BETWEEN THE 5-HTTLPR AND PTSD DIAGNOSIS (N=388)

The χ^2 linear-by-linear association test revealed a significant association between the 5-HTTLPR polymorphism and PTSD status ($\chi^2[1, n=388]=16.23$, $P=5.62\times 10^{-5}$; see Fig. 1), reflecting the higher prevalence of the S'/S' genotype in cases (45%) versus controls (17%). To test whether the associations between the polymorphism and PTSD status remained significant after using demographic factors as covariates (i.e., sex, age, racial/ethnic status) a logistic regression analysis was conducted. As shown in Table 2, the S' allele of the 5-HTTLPR remained significantly associated with increased likelihood of having PTSD (OR=1.77) after controlling for demographic variables. When selecting the subset of participants who were Caucasian ($n=271$), results were similar to those of the full sample, with the S' allele being associated with PTSD (OR=1.92).

SECONDARY ANALYSIS: ASSOCIATION BETWEEN THE 5-HTTLPR AND PTSD SEVERITY SCORE (N=228)

The correlation between the 5-HTTLPR and the CAPS score was significant ($r=.15$, $P=0.03$). To determine whether the association remained significant after adjusting for other variables (combat severity score, demographic variables), a regression analysis was conducted. As shown in Table 3, the 5-HTTLPR was significantly associated with the PTSD severity score. Additionally, combat severity was also associated with the PTSD severity score. Findings were similar when selecting just Caucasian participants; both the S' allele and the combat exposure scale score predicted the PTSD severity score.

DISCUSSION

This study examined the relationship between the triallelically classified 5-HTTLPR polymorphism and PTSD diagnostic status, as well as PTSD severity, among a combat exposed sample of veterans. Our hypothesis that the low transcriptionally efficient variant (S') of the 5-HTTLPR would be associated with PTSD were supported, in that each copy of the S' allele was associated with a 1.77-fold increased risk of being in the PTSD group. This finding was highly significant and it remained so after correction for multiple testing. Additionally, among the subset of participants with PTSD severity scores from the CAPS interview, the S'/S' genotype was associated with greater PTSD severity compared to the L'/L' genotype, and this finding also remained significant after Bonferroni correction. Given that the 5-HTTLPR genotype distribution differs by racial/ethnic status, we also ran both the diagnostic and the PTSD severity analyses in the subset of participants who were EA, with consistent results to those found in the full sample. To our knowledge, this is the first examination of this polymorphism in a sample of combat veterans. Our results are consistent with previous studies showing an association between the S'/S' genotype and a diagnosis of PTSD in other traumatic stress populations.^[13,14,23] These results are inconsistent with one study reporting the L'/L' genotype to be associated with chronic PTSD.^[17] A greater proportion of those diagnosed with PTSD had an S' allele such that the S'/S' genotype were

most common in the PTSD sample, those with S'/L' were second, and those with L'/L' were least common. This pattern of genotypes among those diagnosed with PTSD has been shown in prior studies with civilian samples.^[12,17] This pattern differs from that of control participants in this study, as well as other studies, which have shown that the S'/L' genotype as most common genotype.^[10] Taken together, this provides further evidence as to the increased risk of PTSD with the presence of the S' allele of the *5-HTTLPR* polymorphism. Our results are also consistent with research relating the S'/S' genotype to PTSD severity.^[28] Notably, numerous studies did not find a main effect of the *5-HTTLPR*, but reported a gene by environment interaction.^[15,16,29] Given that cumulative traumatic life events were not assessed, and combat severity was only assessed in a subset of participants, examination of gene by environment interactions was not possible in this study.

Quantitative genetic research suggests that both exposure to traumatic events and the development of PTSD are partially influenced by genetic factors.^[3,30] However, molecular genetic research in psychiatric illnesses lags behind other medical conditions with regards to molecular discoveries. Further, PTSD molecular research is in its infancy compared to that of other psychiatric conditions, perhaps due to the inherent challenges in conducting research on this phenotype (e.g., the need for a trauma-exposed control group). Surprisingly, of the investigations in the literature on this frequently studied polymorphism, none to date have been in combat-exposed samples, a population with high rates of PTSD.^[1] Therefore, use of a combat-exposed cohort in the current studies, with and without PTSD, represents a significant addition to the growing literature in this important line of research. Our findings provide further support that the low expression *5-HTTLPR* variant may be a significant genetic risk factor for the development of PTSD trauma exposure, extending to combat trauma.

This study also supported a positive relationship between the PTSD severity and combat exposure in a subsample of 228 participants. This finding is consistent with other reports in the literature that severity of trauma is related to PTSD.^[31] Notably, both the genotype and combat exposure were positively related to PTSD severity, underscoring the need for assessment of both biologic and environmental risk factors in PTSD research. However, combat exposure was not associated with diagnostic category, providing further evidence for the importance of the interaction between trauma exposure and genetic risk factors. Veterans exposed to high levels of combat who also carry a genetic liability are likely to develop more significant PTSD symptoms than those exposed to comparable levels of combat but without such inherited liability. Understanding the complex way in which genes and environment can confer risk or resilience of stress-related conditions, such as PTSD, in a military population is a vitally important task that will help inform prevention and intervention efforts.

This study, although unique in numerous ways, is not without its limitations that may affect the generalizability of the results. First, we did not have ancestral informative markers in our genotyping panel, and therefore, we had to control for the possibility of population stratification based on using self-report as a covariate in the analyses. Although it would be optimal to use an AIMs panel, we attempted to mitigate the effect of this limitation in the following ways: (1) we determined that self-reported race/ethnicity was not related to PTSD status or to genotype frequency; (2) we covaried self-reported race/ethnicity in all analyses; and (3) we repeated the diagnostic level analysis and the PTSD severity analysis in the subsample of participants who were EA (and as stated in the results section, the pattern of findings did not differ from those in the full sample). Additionally, it is well known that PTSD is highly comorbid with other psychiatric conditions. Data were not recorded on these conditions, and therefore, it is not known if cases and controls differ on these key variables. Another key limitation of our study is that full data were not available on all participants. As

noted throughout our methods and results section, the PTSD severity score and combat exposure scale severity score were only available on a subset of participants. Notably, the correspondence between the psychiatrist's diagnosis and the CAPS score was quite high ($r=.76$), which provides confidence in the diagnostic level data. However, given the missing data in roughly 41% of the sample, gene–environment interactions were not conducted. Additionally, other descriptive data on the participants were unavailable including information about cumulative exposure to traumatic events, social support, and other constructs related to PTSD. Furthermore, the 5-HTTLPR polymorphism has received a great deal of attention in the PTSD and broader psychiatric literature. We encourage researchers to examine additional variation within other candidate genes, such as *CRHR1*^[32] and *RGS2*^[33] in future studies to expand our knowledge of the genetic antecedents of PTSD. Furthermore, we were unable to compare rates of other comorbid mental health conditions in those with and without PTSD across the genotypes as control participants did not have any diagnoses. Additional work should further assess the extent that genetic liability is associated with a range of comorbid conditions. Finally, we feel it is important to acknowledge that our sample size is relatively small compared with other association studies; therefore, the results from this study should be considered preliminary. Other large-scale studies are needed to validate our findings.

CONCLUSION

In summary, this study showed a significant association between the specific *5-HTTLPR/rs25531* genotype and PTSD. The triallelic polymorphism was highly correlated with PTSD severity. Despite the limitations of this study, our data do suggest that the low expressing 5-HTTLPR variant is a significant genetic risk factor for PTSD development after severe trauma exposure. The findings will contribute to the growing literature.

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Figure 1.
Proportion of participants classified by triallelic genotype with PTSD and without PTSD (Controls).

TABLE 1

Demographic and genotyping characteristics

Variable	PTSD (N=212)	Control (N=176)
Age (years)	<i>M</i> =48.7, <i>SD</i> =14.47	<i>M</i> =49.5, <i>SD</i> =13.85
CES	<i>M</i> =20.43, <i>SD</i> =8.45	<i>M</i> =21.95, <i>SD</i> =7.92
Gender		
Male	185 (87%)	154 (88%)
Female	27 (13%)	22 (12%)
Race		
European American	149 (70%)	131 (74%)
AA	50 (24%)	41 (23%)
Others	13 (6%)	4 (3%)
5-HTTLPR Genotypes		
<i>L'</i> / <i>L'</i>	45 (21%)	41 (23%)
<i>S'</i> / <i>L'</i>	73 (34%)	106 (60%)
<i>S'</i> / <i>S'</i>	94 (44%)	29 (17%)

CES, Combat Exposure Scale; *M*, mean; *SD*, standard deviation.

TABLE 2Final logistic regression analysis of the association between *5-HTTLPR* genotype and PTSD

Variable	PTSD diagnostic status		
	Adjusted odds ratio	95% CI	<i>P</i>
Age	1.00	0.98–1.01	0.64
Male sex (versus female)	0.91	0.48–1.71	0.77
Caucasian ethnicity (vs. non-Caucasian)	0.88	0.62–1.25	0.47
<i>5-HTTLPR</i> (<i>S'</i> is risk allele)	1.77	1.33–2.35	1.02×10^{-4}

TABLE 3Linear regression analysis of the association between *5-HTTLPR* genotype and PTSD severity score

	β	<i>b</i>	<i>t</i>	<i>P</i>
Age	0.08	0.16	1.11	0.27
Male sex (versus female)	0.11	10.73	1.43	0.16
Caucasian ethnicity (versus non-Caucasian)	0.03	1.57	0.41	0.68
Combat severity score (CES)	0.28	-1.00	3.65	3.42×10^{-4}
<i>5-HTTLPR</i> (<i>S'</i> is risk allele)	0.21	8.00	2.87	0.005