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Genotype-controlled analysis of serum dopamine β -hydroxylase activity in civilian Post-traumatic Stress Disorder

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Abstract

Background—Norepinephrine (NE) plays a central role in post-traumatic stress disorder (PTSD). Dopamine β -hydroxylase (D β H) converts dopamine (DA) to NE and its activity varies widely across individuals. Mustapic et al. (2007) reported a PTSD-associated deficit in serum D β H activity (sD β H) in a genotype-controlled analysis of combat veterans. We tested whether such a deficit would occur in a sample of civilians.

Methods—The severity of current adult PTSD symptoms and current DSM-IV diagnosis of PTSD were determined by the PTSD Symptom Scale (PSS). Adulthood trauma exposure was assessed using the Traumatic Experience Inventory (TEI). sD β H was assayed by HPLC with electrochemical detection and genotypes were determined using the Taqman® platform.

Results—Two hundred and twenty seven African American (AA) subjects were enrolled in this study, with a mean age ($\pm$ SD) of 42.9 ($\pm$ 12.9) years. We found a strong association between rs1611115 genotype and sD β H ($p < 0.0001$). After controlling for adulthood trauma exposure, there were no significant differences of sD β H between subjects who met a PTSD diagnosis and those who did not ($p > 0.05$) in any genotype group. No significant correlations were found between sD β H and PTSD severity, but sD β H significantly associated with the status of comorbid depression based on the cutoff of HAMD ($p = 0.014$) in subjects with PTSD.

Conclusions—We have replicated in this sample the prior finding that *DBH* rs1611115 genotype strongly associates with sD β H. No associations between sD β H and PTSD diagnosis or symptom severity in this civilian sample.

Keywords

post-traumatic stress disorder; serum dopamine β -hydroxylase; genotype; depression; civilian trauma; association

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Introduction

Norepinephrine (NE) is one of the principal mediators of central and peripheral autonomic stress responses. Because of its multiple roles in regulating arousal and autonomic stress responses, as well as promoting the encoding of emotional memories, NE has been a central focus of research in studies of the pathophysiology of PTSD (Heim and Nemeroff, 2009). NE has been found to be directly linked to the pathophysiology of posttraumatic stress disorder (PTSD) (Southwick et al., 1999; Yehuda et al., 1992). Cerebrospinal fluid (CSF) concentrations of NE are not only elevated in combat veterans with PTSD, but also correlate with the severity of PTSD symptoms (Geraciotti et al., 2001). Sustained hyperactivity of the sympathetic division of the autonomic nervous system is a prominent feature of PTSD, as evidenced by heart rate, blood pressure, skin conductance level, and other psychophysiological measures. Accordingly, increased urinary excretion of NE and epinephrine, and their metabolites, has been documented in combat veterans (Southwick et al., 1999; Yehuda et al., 1992), abused women (Lemieux and Coe, 1995), and children with PTSD (De Bellis et al., 1994; Delahanty et al., 2005). In addition, patients with PTSD exhibit increased heart rate, blood pressure, and NE responses to challenge, such as traumatic reminders. Decreased platelet α_2 receptor binding further suggests NE hyperactivity in PTSD (Strawn and Geraciotti, 2008; Vermetten and Bremner, 2002). There is also evidence for a role of altered CNS NE function in PTSD. Administration of the α_2 receptor antagonist yohimbine, which increases NE release, induces symptoms of flashbacks and increased autonomic responses in patients with PTSD (Southwick et al., 1999). Serial sampling revealed sustained increases in CSF NE concentrations and increased CSF NE responses to psychological stressors in PTSD (Geraciotti et al., 2001; Geraciotti et al., 2008). Taken together, increased CNS NE activity plausibly contributes to features of PTSD, including hyperarousal, increased startle, and encoded fear memories (Strawn and Geraciotti, 2008).

NE is synthesized from dopamine (DA) by dopamine β -hydroxylase (D β H) in noradrenergic neurons. D β H is localized within vesicles of central noradrenergic and adrenergic neurons as well as peripheral noradrenergic (sympathetic) neurons and adrenomedullary neurosecretory cells (Weinshilboum, 1978). D β H enzyme activity is measurable in the serum (or plasma) and is a highly heritable trait. Abundant evidence indicates that the structural gene encoding the protein, *DBH*, regulates much of the genetic variation in the trait (reviewed by Cubells and Zabetian, 2004). Prior work has shown several polymorphisms at *DBH* to be associated with plasma D β H activity (Cubells et al., 2000; Cubells et al., 2002; Cubells et al., 1998; Tang et al., 2005; Tang et al., 2006; Wei et al., 1997; Zabetian et al., 2001; Zabetian et al., 2003), including the putatively functional polymorphism -1021C $\rightarrow$ T (rs1611115), which has been found to account for 31–52% of the variance in D β H activity in populations from diverse geographic origins (Kohnke et al., 2002; Tang et al., 2007; Zabetian et al., 2001).

So far, the role of D β H and the *DBH* gene in PTSD is not clear. There have been a few reports investigating the role of D β H in PTSD, but the findings are inconsistent. For example, a study of veteran PTSD subjects (N=19) found higher plasma D β H activity in a subset of psychotic PTSD subjects (Hamner and Gold, 1998) and suggested that the finding may reflect individual vulnerabilities to develop psychosis in the context of trauma. However, that study, in addition to being quite small, did not control for genotype at *DBH*, so it is difficult to draw clear conclusions from the data. Recently, Mustapic and colleagues (Mustapic et al., 2007) reported a PTSD-associated deficit in plasma D β H activity in a genotype-controlled analysis of combat veterans. Specifically, although they did not find differences of genotype frequency between combat veterans with (N=133) or without (N=34) PTSD, they found significantly lower plasma D β H activities in veterans with PTSD

carrying the CC genotype as compared to veterans without PTSD carrying the corresponding genotype. They argue that since both groups were exposed to the same trauma, it is possible that a pre-existing trait difference in regulation of NE function contributed to a differential vulnerability to develop PTSD, or that the regulation of DBH expression was different in response to trauma. Their findings suggest the potential role of genotype-controlled measurement of plasma D β H activity as a biological marker of the response to trauma.

Of note, the published studies regarding D β H and PTSD so far have been conducted in military or veteran populations. It is of great interest to see if these findings can be replicated in civilian populations. Therefore the current study aimed to test whether such a deficit would occur in a predominantly African American sample of civilian subjects who had been exposed to a high level of poverty-related stress and trauma.

Methods

1. Subjects and research setting

Subjects in this study were ascertained as part of the Grady Trauma Project, which is an ongoing molecular genetic study with a primary focus on post-traumatic stress disorder (Binder et al., 2008; Bradley et al., 2008; Gillespie et al., 2009). Only a subset of subjects, from whom serum samples were available, was included in this study. Participants were approached while in the waiting rooms of primary care or obstetrical–gynecological clinics of Grady Memorial Hospital in Atlanta, GA. Subject recruitment took place Monday–Friday during regular clinic hours. Subjects were approached while waiting for appointments in the primary care and obstetrical–gynecological by a member of the research team and solicited for study participation. Those subjects who agreed to participate completed a battery of self-report measures which took 45–75 min to complete (dependent in large part on the extent of the participant's trauma history and symptoms). Due to variation between subjects with respect to literacy, all self-report measures were obtained by verbal interview including measures originally designed and normed for paper and pencil response. Non-self-report measures such as the Hamilton Rating Scale for Depression and Hamilton Rating Scale for Anxiety were administered by trained research staff. Each person was paid \$15 for participation. Eligibility requirements included the ability to give informed consent. Written and verbal informed consent was obtained for all subjects. Exclusion criteria included mental retardation or active psychosis. All procedures in this study were approved by the institutional review boards of Emory University School of Medicine and Grady Memorial Hospital.

2. Biochemical, Bioinformatic and Molecular analysis

Venous blood was collected and serum prepared by centrifugation. All samples were stored frozen at -80°C until analyzed. All serum samples were detected in duplicate 5- μL aliquots following the protocol described by Cubells et al. (1998). Our preliminary experiments have demonstrated that D β H activities in plasma and serum samples were identical in the range of enzyme activity values (data not shown). sD β H was determined by the rate of conversion of tyramine to octopamine. Octopamine was measured by a column-switching, reverse phase high performance liquid chromatography (HPLC) system, using coulometric electrochemical detection, and reported as $\mu\text{mol}\cdot\text{min}^{-1}\cdot\text{L}^{-1}$.

Genomic DNA was extracted from whole blood using a Mag-Bind SQ Blood DNA kit (Omega Bio-Tek, Norcross, GA) on a KingFisher Flex Magnetic Particle Processor (Thermo Scientific, Waltham, MA) following the manufacturer's instructions. The 5'-exonuclease (TaqMan®) method was used for genotyping. The assay kit and genotyping reagents were

ordered from Applied Biosystems (Foster City, CA). Genotyping was performed on an ABI 7900HT system, with samples arrayed in 384-well plates. As a routine quality-control measure, all plates included negative controls (wells containing no DNA), duplicate samples, and control DNA samples that reside on all plates processed in the lab. Before uploading for analysis, data were quality checked for absence of signal in negative wells, and consistency of genotype calling for both within- and across-plate duplicate samples.

3. Assessments

All patients who met eligibility criteria and provided consent were asked to complete a battery of self-report assessments, which included a demographic form and other basic data, such as subject age, self-identified race, marital status, education, income, and employment. Basic data included but were not limited to information related to comorbid psychiatric diagnostic status, family history for psychiatric disorders, past and current substance abuse, stress, and legal issues, etc. In addition, subjects also needed to complete the following interviews:

3.1 The PTSD Symptom Scale (PSS) is a 17-item interview used to aid in the detection and diagnosis of PTSD (Foa et al., 1993; Foa and Tolin, 2000). The structure and content of the PSS mirror the DSM-IV criteria for PTSD. The psychometric properties of the PSS indicate that the PSS has satisfactory internal consistency, high test-retest reliability, and good concurrent validity. Consistent with prior literature, we summed the PSS frequency items (“0: not at all” to “3: ≥ 5 times a week”) to obtain a continuous measure of PTSD symptom severity ranging from 0 to 51.

3.2 The Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1997; Bernstein et al., 1994) is a 28-item, self-report inventory assessing five types of maltreatment: sexual, physical and emotional abuse and emotional and physical neglect. Cutoff scores for each category have shown excellent sensitivity and specificity in correctly classifying cases of abuse and neglect in psychiatric patients (Bernstein et al., 1997; Bernstein et al., 2003a). Multiple studies have established the internal consistency, stability over time and criterion validity of both the original 70-item CTQ and the current brief version (see, e.g., Bernstein et al., 2003b). The CTQ yields a total score and subscale scores for each of the 5 types of child abuse and neglect: physical abuse, sexual abuse, emotional abuse, emotional neglect, and physical neglect.

3.3 The Traumatic Events Inventory (TEI) (Schwartz et al., 2005) is a 14-item screening instrument for lifetime history of traumatic events. For each traumatic event, the TEI assesses experiencing and witnessing separately. It also assesses confrontation of traumatic events where appropriate. In addition, the TEI also asks the number of times that each event has occurred; age at self-perceived “worst” instance for a given traumatic event; and feelings of helplessness or horror for each traumatic event.

3.4 In order to assess comorbid symptoms of depression and anxiety, subjects were also assessed with the Hamilton Rating Scale for Depression (HAMD, Hamilton, 1960), and the Hamilton Rating Scale for Anxiety (HAMA, Hamilton, 1959).

4. Statistical analysis

All analyses were performed using SPSS17.0 software. Descriptive statistics on demographics were calculated and expressed in terms of the total number of subjects and percentages of the sample as a function of PTSD diagnosis and particular characteristics. We examined differences with respect to PTSD diagnosis using student t-tests or chi square tests when appropriate.

We used Analyses of Variance (ANOVA) to examine the individual effects of the SNP on sDβH. Prior to analysis; we transformed DβH activity to follow an approximate normal distribution using a square-root transformation (Wilson et al., 1988; Zabetian et al., 2001). Square root sDβH was the dependent variable, and genotypes at the *DBH* SNPs the independent variables. Spearman correlations were used to test the possible correlations between sDβH and PTSD symptoms and other PTSD-related measures. Linear or Logistic regressions were used to adjust for possible confounding factors (age, sex) as appropriate. In addition, we also used a general linear model to examine possible interaction between *DBH* genotype and PTSD diagnosis on serum DβH activity.

Results

1. Sample characteristics

A total of 227 subjects had complete data on the demographic form, the PSS and gave blood for the DβH assay. Table 1 summarizes the demographic characteristics of our sample. The sample was all self-reported African-American. The mean age was 43.9 years (SD = 12.9). The majority of subjects were female (57.8%). There was a significant difference in age by sex (p -value <0.01) with male subjects being older (46.8 years in males v.s. 42.2 years in females). While patients with (N=69) and without (N=158) PTSD did not differ in sex and age, patients with PTSD tended to have more severe childhood trauma exposure (measured by CTQ), especially on emotional abuse. Not surprisingly, patients with PTSD had higher levels of adulthood trauma exposure (measured by the TEI), as well as more severe comorbid anxiety and depressive symptoms (measured by the HAMD and HAMA).

2. Association of DβH activity and DBH genotype

There were no significant effects of age and sex on plasma DβH activities (all p 's >0.05). The genotypic frequency of rs1611115 did not significantly deviate from Hardy-Weinberg equilibrium (p >0.05). The ANOVA showed that *DBH* genotype at rs1611115 significantly associated with sDβH in a co-dominant manner, with genotype CC (N=166) having the highest activity (square root, hereafter, 5.0 ± 1.3), genotype CT the intermediate (N=66, DβH=3.6±1.5), and genotype TT (N=6) the lowest (1.8 ± 1.4) ($F=38.158$, d.f.=2, $p<0.0001$). Regression analysis showed that this genotype alone accounted for approximately 25% of the variance in sDβH.

3. DBH genotype, DβH activity and PTSD diagnosis

The frequencies of CC, CT and TT at rs1611115 in patients who met the current DSM-IV diagnostic criteria of PTSD were 50 (72.5%), 17(24.6%), and 2(2.9%), respectively. For patients who did not meet the diagnosis, the frequencies were 106 (67.1%), 49(31.0%), and 3(1.9%), respectively. There was no significant difference in frequency across diagnosis ($\chi^2= 1.091$, d.f.=2, $p=0.583$). We also compared the sDβH between the two groups and found no significant differences (4.67 ± 1.60 in patients with PTSD vs. 4.46 ± 1.56 in patients without PTSD, $p=0.519$). Significant associations existed between sDβH and genotype within each diagnostic group (both p 's <0.001). Genotype-controlled analysis did show significant association between sDβH and PTSD diagnosis (Figure 1).

Since subjects in the two groups had different levels of trauma exposure, measured by the TEI and the CTQ, we performed a logistic regression using PTSD diagnosis (0=no, 1=yes) as the dependent variable and using sDβH, age, sex, TEI total types of trauma, and total score of CTQ as covariates. Results showed that sDβH did not significantly associate with PTSD diagnosis ($p=0.874$). Not surprisingly, we found that total trauma (in adulthood) significantly associated with PTSD diagnosis ($p<0.0001$, OR=1.383, 95%CI 1.165–1.641), while the total score of the CTQ did not significantly associate with PTSD diagnosis

($p>0.05$) in this regression model. Since the samples reported by Mustapic et al. (2007) were all male veterans, we did the analysis in male and female patients separately, and the results were similar to the entire sample: sDBH did not significantly associate with PTSD diagnosis ($p>0.05$), while adult trauma significantly associated with PTSD diagnosis (both $p<0.01$ in males and females).

We also examined possible interactions between DBH genotype and PTSD diagnosis on sDBH by performing a general linear analysis: sDBH was the dependent variable, rs1611115 genotype and PTSD diagnosis were the fixed factors, and covariates included in the analysis were CTQ total, TEI adulthood trauma, sex, age and total score of HAMD. Consistent with previous ANOVA result, genotype at rs1611115 strongly associated with sDBH ($F=27,286$, $p<0.00001$). The interaction between genotype and PTSD diagnosis was not significant in the model ($F=0.660$, $p=0.518$). A trend-level association ($p=0.061$) was observed between the total score of HAMD and sDBH. Similarly, we assessed the possible impact of traumatic load on sDBH activities in interaction with the genotype and we did not find a significant interaction ($p=0.363$).

4. Correlations between serum DBH activity and severity of different clusters

To further analyze the relationship between sDBH and PTSD symptoms, we performed a series of correlation analyses between sDBH and the total scores of PSS (the overall severity of PTSD), and the scores of different clusters of symptoms (intrusive, avoidance/numbness, and hyperarousal). We did not find significant correlations between sDBH and PTSD-related variables in the entire sample (all p 's >0.05).

We further broke down the samples into patients with and without PTSD diagnosis and analyzed the relationship between sDBH and PTSD-related phenotypes. Analyses using total respective scores of the HAMD or HAMA showed that while sDBH did not associate with depression and anxiety symptoms in subjects without PTSD ($N=158$), it associated significantly with total scores of both the HAMD and HAMA (all $p<0.05$) in subjects with a diagnosis of PTSD ($N=69$). We repeated the analysis categorizing subjects into depressed vs. non-depressed groups using a cutoff of 18 on the HAMD. A logistic regression analysis, accounting age, sex and genotype at rs1611115, showed that sDBH significantly associated with the presence of clinically significant comorbid depression ($p=0.020$), with depressed patients having a significantly lower sDBH ($N=35$, 3.86 ± 1.55) than that in non-depressed patients ($N=44$, 4.93 ± 1.53).

Discussion

In this study, we studied the relationship between sDBH and PTSD diagnosis and PTSD symptoms based on a relatively large sample of civilians who had been exposed to high levels of poverty-related stress and trauma. We found that adulthood trauma exposure significantly associated with the diagnosis of PTSD, but not sDBH. Correlation analysis did not find significant relationships between sDBH and the overall severity of PTSD, or severity of the three PTSD symptom clusters (intrusive, avoidant/numbing, and hyperarousal), but we found that sDBH significantly associated with the status of comorbid depressive symptoms in patients with PTSD diagnosis.

This study did not replicate the finding reported by Mustapic et al. (2007) of a PTSD-associated deficit in sDBH in a genotype-controlled analysis of combat veterans. Before we try to interpret the inconsistency, several differences between the Mustapic study and ours have to be acknowledged: (1) the subjects in the Mustapic study were all combat veterans from one military unit, so had been exposed to a (presumably comparable) level of combat-related trauma exposure; in contrast, our study was of lifetime trauma exposure, and

therefore less likely to find an identically trauma-exposed non-PTSD group, without excluding many subjects, possibly introducing unknown biases in the sample; (2) while lifetime PTSD diagnosis in the Mustapic study was determined by the SCID-I, the diagnosis in our study was for current PTSD, based on scores from PSS; (3) the samples in the Mustapic study were all males, while approximately 60% of our samples were female; (4) while their subjects were medication-free, some of our patients might have been on some psychotropic medications, which might also have affected the results (Markianos et al., 1976); (5) in their study, subjects with a HAMD total score higher than 18 were not included, but the authors did not elaborate their rationale and did not report how many subjects were excluded based on this criterion. Although the exact effects of this criterion are not clear, we would speculate that some subjects with severe PTSD and comorbid depressive symptoms might have been excluded, which would have affected their results. In our analysis, we tried to exclude patients whose HAMD score ≥ 18 and we still did not observe differences in different genotype groups (data not shown here). In addition, we also used the HAMD to group patients into depressed and non-depressed groups using a cutoff score of 18 and found that, after controlling for age, sex and genotype at rs1611115, sD β H significantly associated with the status of Comorbid depression ($p=0.014$), which suggests that while sD β H may not be associated with PTSD diagnosis or its symptomatology, it reflects some of its comorbidities. As already noted, our civilian study population did not share a common exposure to a specific traumatic event as the war veterans studied by Mustapic et al. It is possible that other civilian populations, such as those exposed to natural disasters (earthquakes, floods, etc), or to wartime trauma, would be more comparable to the Mustapic study.

Some authors have suggested that altered D β H expression could in turn affect DA (Sher et al., 2005) or NE-mediated transmission (Southwick et al., 1999). Some studies have reported higher DA levels in plasma (Hamner and Diamond, 1993) and in urine (Glover et al., 2003); other studies reported inconsistent results regarding plasma NE levels (Southwick et al., 1999) or similar 24-hr urine NE and 3-methoxy-4-hydroxyphenylglycol (MHPG) excretion (Mellman et al., 1995; Yehuda et al., 1998) or elevated cerebrospinal fluid levels of MHPG in PTSD compared to control subjects. All of these support a possible role of the NE system, and possibly D β H in PTSD. Further studies are clearly needed and studies in the future should also include measurements of dopamine and NE.

In summary, the current study, based on a large sample of civilians who had a high level of poverty-related stress and trauma exposure, replicated the finding that the level of adult trauma was associated with PTSD diagnosis. We have also replicated in this African American sample the prior finding that *DBH* rs1611115 genotype strongly associates with sD β H in a co-dominant manner. However, after controlling for childhood and adult trauma levels, we found no associations between sD β H and PTSD diagnosis or symptom severity in this civilian sample, but sD β H may associate with comorbid depression in patients with PTSD.

Research highlights

This study tested whether such a previously reported PTSD-associated deficit in serum D β H activity (sD β H) in a sample of civilians. Two hundred and twenty seven African American (AA) subjects were enrolled in this study, and we found:

1. a strong association between rs1611115 genotype and sD β H ($p<0.0001$);
2. After controlling for adulthood trauma exposure, there were no significant differences of sD β H between subjects who met a PTSD diagnosis and those who did not ($p>0.05$) in any genotype group;

3. No significant correlations were found between sDBH and PTSD severity, but sDBH significantly associated with the status of comorbid depression based on the cutoff of HAMD ($p=0.014$) in subjects with PTSD.

We have replicated in this sample the prior finding that *DBH* rs1611115 genotype strongly associates with sDBH. No associations between sDBH and PTSD diagnosis or symptom severity in this civilian sample.

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Fig. 1.

Plasma DβH activity and DBH genotypes at rs1611115 SNP in subjects with and without PTSD diagnosis. Each column represents mean± S.D. While significant associations existed between plasma DβH activity (square root) and genotype regardless of the PTSD diagnosis, no significant differences in plasma DβH activity were observed between subjects with and without PTSD diagnosis. There was no significant interaction between genotype at rs166665 and PTSD diagnosis on plasma DβH activity ($p=0.18$)

Table 1

Demographic characteristics of the samples.

Demographic	Total Sample (N=227)	PTSD+ (N=69)	PTSD- (N=158)	p
Age (mean±S.D.)	43.9±12.8	43.9±12.0	43.9±13.2	0.999
Sex (male)	97/226 (42.9)	27/69 (39.1)	87/157(44.6)	0.445
Currently unemployed	44/225 (19.6)	8/69(11.6)	26/156 (23.1)	0.045
Currently receiving disability	69/224 (30.8)	24/69(34.8)	45/155(29.0)	0.389
Family history of psychiatric disorders	66/221(29.9)	22/67(32.8)	44/154(28.6)	0.524
Current substance abuse problem	21/223(9.4)	12/68(17.6)	9/155(5.8)	0.005*
Past substance abuse	87/221(39.4)	36/68(52.9)	51/153(33.3)	0.006*
Suicide attempt	38/222(17.1)	20/67(29.9)	18/155(11.6)	0.001*
Ever been in jail	130/224(58.0)	43/69(62.3)	87/155(56.1)	0.386
Ever been in prison	37/222(16.7)	10/67(14.9)	27/155(17.4)	0.647
PSS total	12.2±12.2	26.8±9.5	5.8±6.1	<0.0001**
CTQ total score	42.6±17.3	47.1±19.0	40.6±16.1	0.010*
CTQ sexual abuse	7.5±4.7	8.2±5.1	7.2±4.6	0.137
CTQ physical abuse	8.7±4.3	9.6±4.7	8.2±4.1	0.029 ^o
CTQ emotional abuse	9.1±4.4	10.4±4.8	8.6±4.2	0.004*
CTQ emotional neglect	9.6±5.0	10.6±5.5	9.1±4.8	0.051
CTQ physical neglect	7.7±3.6	8.3±3.9	7.5±3.5	0.130
TEI-total types of trauma experienced	3.3±2.4	4.3±2.4	2.9±2.2	<0.0001**
TEI-total types of trauma experienced (non-childhood)	2.7±2.0	3.6±2.1	2.4±1.9	<0.0001**
Total life stress	16.2±6.2	19.5±5.6	14.7±5.9	<0.0001**
HAMD	9.3±9.8	14.3±11.1	7.2±8.4	<0.0001**
HAMA	10.0±8.6	15.0±13.5	7.9±7.7	<0.0001**

^op<0.05 after adjusting for sex and age;

*p<0.01 after adjusting for sex and age;

**p<0.001 after adjusting for age and sex