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Original Article

Oxytocin receptor variant rs53576 genotype is associated with dysphoric arousal symptoms of DSM-5 posttraumatic stress disorder in Chinese earthquake survivors

Cheng-Qi Cao [a, b], Li Wang [a, b, *], Ruo-Jiao Fang [a, b], Gen Li [a, b], Ping Liu [c], Shu Luo [c], Xiang-Yang Zhang [a, b]

[a] Laboratory for Traumatic Stress Studies, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, 100101, China
[b] Department of Psychology, University of Chinese Academy of Sciences, Beijing, 100049, China
[c] Department of Psychosomatic Medicine, People' s Hospital of Deyang City, Deyang, 618000, Sichuan Province, China

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ABSTRACT

Purpose: Evidence suggests that the oxytocin receptor (*OXTR*) gene may be involved in the psychopathology of posttraumatic stress disorder (PTSD). This study aimed to investigate the effects of *OXTR* rs53576 genotype on PTSD symptoms introduced in the Diagnostic and Statistical Manual, Fifth Edition (DSM-5).

Methods: This study was a cross-sectional study conducted among 1140 adults who had personally experienced the Wenchuan earthquake. PTSD symptoms were measured with the PTSD checklist for DSM-5. A custom-by-design 2 × 48-Plex SNPscan™ Kit were used to determine the *OXTR* rs53576. Multiple regression models were used to analyze the independent and interactive effects of *OXTR* rs53576 genotype and earthquake exposure on the severity of total PTSD symptoms and different dimensions of PTSD symptoms.

Results: The results revealed that the rs53576 genotype could significantly predict PTSD symptoms ($\beta = 0.055$, $p = 0.045$). Further analysis showed that the rs53576 genotype was only significantly associated with dysphoric arousal symptoms of PTSD ($\beta = 0.080$, $p = 0.005$). The rs53576 genotype × earthquake exposure interaction had no significant effect on different symptom clusters ($p > 0.05$).

Conclusion: This study showed that the rs53576 genotype was only associated with the dysphoric arousal symptoms but not with other symptom clusters of PTSD. These findings support the role of the *OXTR* on the psychopathology of PTSD and help us to understand the genetic basis of PTSD.

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder induced by exposure to traumatic events. According to the Diagnostic and Statistical Manual, Fifth Edition (DSM-5),[1] PTSD symptoms include intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity, along with significant functional impairment. More than 70.0% of people have experienced at least one traumatic event, and 30.5% of them have suffered four or more traumas.[2] However, the lifetime prevalence of PTSD is only 5.6% in the population with traumatic experiences.[3] Compared with the high rate of trauma exposure, the low rate of PTSD may indicate the significant individual differences in PTSD. Genetic predisposition is crucial in explaining the individual difference of PTSD after trauma.[4] Recent twin studies further suggest that the heritability of PTSD can be even higher, up to 49%.[5] Further candidate genes have explored association between more than 50 gene variants and PTSD. The most studied genes (e.g., *SLC6A4*, *FKBP5*) may serve as useful biomarkers to further enhance our mechanistic understanding of PTSD.[6] However, compared with other mental illnesses, the number of studies on candidate genes for PTSD is small and findings of these studies remain inconclusive.[7] Accordingly, studies targeting new candidate genes are needed to clarify the genetic basis of PTSD.

* Corresponding author. Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China.
E-mail address: wangli1@psych.ac.cn (L. Wang).
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Oxytocin (OXT) is a widely studied neuropeptide for its critical role in regulating social behaviors and responses to stressors.[8] As PTSD involves the defects of social function and stress regulation,[9] the oxytocinergic system is believed to contribute to the vulnerability to PTSD. The researchers have proposed a possible mechanism for the involvement of oxytocinergic system in PTSD.[9,10] On the one hand, OXT appears to increase the reward sensitivity and further influence social function, which helps to decrease PTSD symptoms after trauma. On the other hand, OXT increases the elimination of fear by affecting the activity of related brain regions and neuroendocrine systems, thereby further reducing PTSD symptoms. OXT has been considered a promising treatment target for PTSD, and some primary studies have been published to explore the therapeutic effect of OXT on PTSD.[11] However, strictly speaking, the exact mechanism of OXT in PTSD is still unclear,[9] and further studies are needed to elucidate how OXT plays its role in the psychopathology of PTSD.

One fundamental way to study the mechanism of OXT in PTSD is to examine the effect of genetic variants of the oxytocinergic system. The rs53576 polymorphism is the most intensively investigated gene variant in the OXT receptor (*OXTR*) gene. The G allele of rs53576 has been linked to several positive characteristics, such as self-esteem and optimism,[12] trust-related behaviors,[13] and sociality.[14] However, the positive impacts of G allele might be reversed when exposed to early-life adversity.[15–17]

To date, two studies were conducted to focus only on the effect of the oxytocinergic system polymorphisms on PTSD, and both of these studies focused on the *OXTR* rs53576 genotype. The first study was conducted among survivors of 9/11 terrorist attacks.[18] They found that among A-allele carriers, negative social environments were positively associated with PTSD symptoms without regard to economic stress. However, among GG carriers, the positive associations between negative social environments and increased PTSD symptoms conditionally existed among participants facing high economic stress. The other study was carried out among U.S. veterans.[19] They found that insecure attachment participants were associated with a greater likelihood of being diagnosed with PTSD if they were rs53576 allele carriers. However, they failed to replicate the findings for rs53576 in the replication sample consisted of 2215 high-risk civilians.

In general, studies focusing on the relationship between rs53576 genotype and PTSD are quite limited. The existing two studies mentioned above considered social environments, different attachment styles, and economic stress as environmental variables in their gene-environment (G × E) interaction models. However, exposure to traumatic events is a prerequisite for diagnosing PTSD, indicating that traumatic exposure may be the most suitable environmental variable in the G × E models of PTSD. Besides, studies have shown that the prevalence and symptom presentations of PTSD may vary across types of trauma.[20] The different symptom patterns across trauma types may impact the associations of PTSD and rs53576 genotype, indicating the need to examine the role of the rs53576 genotype in PTSD in other traumatic samples.

In addition to the above limitations, PTSD with different symptom dimensions is a heterogeneous psychiatric disorder. Using symptom dimensions may increase the chance of finding specific genes associated with PTSD.[21] Recent confirmatory factor analysis studies have found that a seven-factor hybrid model[22] consisting of intrusion, avoidance, negative affect, anhedonia, externalizing behaviors, anxious arousal, and dysphoric arousal symptoms provides a significantly better presentation of PTSD symptoms than other competitive models across samples and countries.[23–26] Some studies have used this model to examine the biological basis of PTSD.[27]

For the above reasons, this study aimed to elucidate the effect of *OXTR* on the development of PTSD and enhance knowledge about the genetic basis of PTSD. We examined the associations between the *OXTR* rs53576 genotype and seven symptom dimensions of PTSD symptoms among Chinese adult earthquake survivors. Given that this is an exploratory study, and there is no research to clarify the effects of the *OXTR* genotype on different symptom dimensions of PTSD, we can only assume that some of these seven-symptom clusters are associated with this genotype.

Methods

Participants and procedures

This study was conducted 5.5 years after 2008 Wenchuan earthquake in Hanwang town, which was severely affected by the earthquake. Household members were randomly selected to participate in this study (see Liu et al.[28] for details). Adult (aged over 16 years) earthquake survivors without any major mental illness and mental retardation were included in this research. First, investigators introduced the research purpose and distributed self-reported questionnaires to the subjects who agreed to participate. After that, the nurses extracted DNA from the subjects' peripheral blood samples and performed genotyping.

Of the 1196 respondents, 24 participants were removed because they refused to draw blood, 26 participants were removed because of DNA extraction failure, and 6 participants were removed due to genotyping failure. Therefore, the final valid sample included 1140 adults, ranging in age from 16 to 73 (mean = 48.1, SD = 10.0) years. In terms of sex, 363 (31.8%) were males, and 777 (68.2%) were females. The majority of individuals were married (86.8%) and relatively less educated, of which 769 (67.5%) had not yet completed high school education. The Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences approved this research.

Measurement

Ten questions (Table 1) commonly used in previous studies were applied to measure earthquake exposures. Each item has two options (yes and no) to reflect if respondents have this experience in the earthquake. Each "yes" answer represents one point awarded, and the total score for these ten items indicates the level of earthquake exposure.

PTSD symptoms were assessed with the PTSD checklist for DSM-5 (PCL-5).[29] The PCL-5 is a measurement from DSM-5 with 20 items. Respondents were instructed to rate their symptoms related to earthquake in the past month from 0 (not at all) to 4 (extremely). Studies in Chinese samples have confirmed the reliability and validity of the Chinese version of PCL-5.[23,24] Cronbach's α was 0.94 in this sample.

Table 1
Features of trauma exposure during the earthquake of the sample.

Trauma exposure during the earthquake	*n* (%)
Were you trapped under rubble? (Yes)	108 (9.5)
Were you injured? (Yes)	151 (13.2)
Were you disabled due to injuries? (Yes)	32 (2.8)
Did you participate in rescue efforts? (Yes)	494 (43.3)
Did you witness a death of someone? (Yes)	803 (70.4)
Did you see mutilated bodies? (Yes)	419 (36.8)
Did any family member die of the disaster? (Yes)	298 (26.1)
Were any family members injuries? (Yes)	383 (33.6)
Did any friend or neighbor die of the disaster? (Yes)	909 (79.7)
Did you lose your livelihood due to the disaster? (Yes)	353 (31.0)

The genotyping for rs53576 was performed with custom-designed 2 × 48-Plex SNPscan™ Kit developed by Genesky Biotechnologies Inc., Shanghai, China. The calling rate of genotypes was more than 98%.

Statistical analysis

Statistical analysis was performed with SPSS 19.0. In this sample, 85 (7.5%), 16 (1.4%), and 7 (0.6%) missed one, two, and three or four PCL-5 items, respectively. The maximum likelihood method was used to estimate and calculate these missing values. In order to avoid multicollinearity, earthquake exposure was concentrated. The allele distribution of rs53576 was tested with the Hardy-Weinberg equilibrium test. The rs53576 genotype was recorded as AA *vs.* any G (GG/GA) to ensure sufficient power for analysis. A multiple regression model was firstly used to analyze the independent and interactive effects of *OXTR* rs53576 genotype and earthquake exposure on the severity of total PTSD symptoms and different dimensions of PTSD symptoms. All analyses were adjusted for sex, age, marital status, and educational level.

Results

The PCL-5 score ranged from 1 to 77 (mean score = 18.8, SD = 13.5). Almost 14% (n = 157) of participants were defined probable PTSD cases based on the DSM-5 diagnosis algorithm. Table 1 presents the features of earthquake exposure. Regarding the earthquake exposure, the score ranged from 0 to 10 (mean score = 3.5, SD = 1.8). The rs53576 genotype distribution was in Hardy-Weinberg equilibrium ($\chi^2 = 3.158$, $p = 0.076$) with 48.1% for AA, 40.9% for GA, and 11.1% for GG.

The regression model for evaluating the effect on PTSD symptoms is presented in Table 2. In Table 2, rs53576 genotype was coded: 0 = AA, 1= GA/GG; sex was coded: 0 = males, 1 = females; marital status was coded: 0 = married, 1 = single/divorced/separated/widowed; education was coded: 0 = less than high school, 1 = high school and above. The rs53576 genotype was significantly associated with the severity of PTSD symptoms. Specifically, G allele carriers had significantly greater PTSD symptoms compared with AA genotype participants. The variance of PTSD symptoms explained by the rs53576 genotype was 0.2%. The earthquake exposure had a significant predictive effect on the PTSD symptoms, while no significant interaction effect was found.

Subsequent analyses were performed to estimate the interaction effects of *OXTR* rs53576 genotype and earthquake exposure on individual symptom clusters of PTSD severity. The rs53576 genotype was only significantly associated with dysphoric arousal symptoms of PTSD (Table 3). The variance of PTSD dysphoric arousal symptoms explained by the rs53576 genotype was 0.6%. The rs53576 genotype × earthquake exposure interaction had no significant effect on different symptom clusters ($p > 0.05$). In order to further verify our key findings, we conducted permutation tests (10,000 times). In each permutation, PTSD symptom clusters were randomly combined among different individuals, and the regression test was re-performed. The estimated p value of each permutation was recorded. The percentile of permutations in which the estimated p statistic did not exceed the original p value was calculated to get the corrected p values. Through the permutation test, the correlation between dysphoric arousal symptoms cluster and rs53576 genotype ($p_{permu} = 0.004$) in the total sample was further determined.

Table 2
Effects of rs53576 genotype and trauma exposure on the severity of PTSD symptoms based on regression analyses.

Predictor	B	SE B	β	t	p
Sex	3.829	0.814	0.133	4.703	<0.001
Age	0.345	0.042	0.255	8.272	<0.001
Marital status	1.423	1.099	0.036	1.295	0.195
Education	−1.721	0.877	−0.060	−1.962	0.050
rs53576	1.480	0.739	0.055	2.003	0.045
Earthquake exposure	2.169	0.280	0.298	7.756	<0.001
rs53576 × trauma exposure	0.151	0.401	0.014	0.378	0.706

Note: rs53576 genotype was coded: 0 = AA, 1 = GA/GG.
Sex was coded: 0 = males, 1 = females.
Marital status was coded: 0 = married, 1 = single/divorced/separated/widowed.
Education was coded: 0 = less than high school, 1 = high school and above.
PTSD: posttraumatic stress disorder, B: regression coefficient, SE: standard error.

Table 3
Individual PTSD symptom clusters as predicted by the rs53576 genotype.

Predictor	B	SE B	β	t	p
Intrusion	0.393	0.240	0.045	1.637	0.102
Avoidance	0.188	0.107	0.050	1.762	0.078
Negative affect	0.148	0.158	0.027	0.941	0.347
Anhedonia	0.198	0.127	0.044	1.560	0.119
Externalizing behaviors	0.137	0.087	0.045	1.572	0.116
Anxious arousal	0.115	0.102	0.032	1.126	0.261
Dysphoric arousal	0.301	0.106	0.080	2.843	0.005

Note: rs53576 genotype was coded: 0 = AA, 1 = GA/GG.
Covariates were controlled as the same as in Table 2.
PTSD: posttraumatic stress disorder, B: regression coefficient, SE: standard error.

Discussion

As far as we know, this is the first study to investigate the role of *OXTR* rs53576 genotype in the psychopathology of PTSD in Chinese epidemiological earthquake exposure samples. Our results showed significant associations between the rs53576 genotype and total PTSD symptoms. Using the contemporary hybrid model of PTSD, we further found that the rs53576 genotype only significantly predicted the severity of dysphoric arousal symptoms of PTSD.

A large amount of evidence has shown the beneficial effect of the G allele on *OXTR* rs53576.[13,14] The study conducted by Sippel et al.[19] found that the GG genotype carriers with secure attachment had a significantly lower risk of PTSD diagnosis in a sample of American veterans. However, some studies have pointed out the harmful effects of this allele under adversity. For example, McQuaid et al.[15] indicated that the G allele was associated with increased depression symptoms when exposed to higher childhood maltreatment levels. Besides, Bradley et al.[16] found that the GG genotype carriers with a higher degree of childhood abuse were more likely to develop emotional dysregulation and disorganized attachment among African Americans. The GG genotype was also associated with internalization symptoms among maltreated adolescents.[17] Furthermore, Lucas-Thompson et al.[18] found that in the sample of 9/11 terrorist attack survivors, GG carriers showed a greater likelihood of developing PTSD symptoms under the influence of negative social environments and economic pressure. Our study found that the G allele was associated with more severe PTSD symptoms, which further indicates the deleterious effects of this allele. The findings of this study, together with the previous evidences, indicate that the G allele may increase the vulnerability of adverse psychological outcomes under adversities.

The exact mechanisms by which the G allele increases the susceptibility to PTSD symptoms, especially dysphoric arousal symptoms, are still unclear. It is suggested that the rs53576 genotype may affect OXT signaling by changing the efficiency of receptors.[30] Dysphoric arousal symptom clusters include sleep disturbances and concentration problems. The rs53576 genotype may alter the

interaction between OXT and other neuropeptides and hormones that play an essential role in regulating sleep and concentration, thereby further affecting these two symptoms. For example, previous studies showed that the rs53576 genotype regulated the OXT–dopamine interaction.[31] It is necessary to further study the exact mechanisms by which the *OXTR* rs53576 G allele may increase the susceptibility to PTSD in adversity. Moreover, the current study was conducted 5.5 years after the earthquake, which assessed the long-term psychological effects of trauma exposure. Further studies conducted at different time points, especially in the early stage after trauma, are needed to clarify the relationship between *OXTR* rs53576 genotype and PTSD.

This study did not find the significant interaction effect of the rs53576 genotype × trauma exposure on PTSD symptoms. Stein has suggested that the G × E interaction may be uncommon, and researchers should not concentrate on fining interactions.[32] Therefore, the non-significant rs53576 genotype × trauma exposure interaction in our study is understandable. On the other hand, we only investigated the level of earthquake exposure as an environment variable and did not take other environment variables (e.g., other exposures) into account. Since other environment variables may interact with the rs53576 genotype to predict PTSD symptoms, further studies are needed to explore G × E interactions.

Previous studies have indicated that different biological processes may be involved in the pathophysiological process of distinct symptom clusters of PTSD.[27] Using the latest seven-factor model of PTSD, this study further analyzed the relationship between different PTSD symptom clusters and the rs53576 genotype. The results revealed a significant association only existed between dysphoric arousal symptoms and the rs53576 genotype. These results provide biological evidence to support that dysphoric arousal cluster is a distinct dimension of PTSD and inspire for constructing a phenotypic model of PTSD. The dysphoric arousal symptoms are not typical fear-related symptoms as anxious arousal symptoms, but were involved in general distress also existing in other psychiatric disorders (e.g., major depression, generalized disorders).[33] Given that *OXTR* has been found to be involved in the etiology of other psychiatric disorders,[34] it may pose a general risk for psychopathology instead of a unique risk gene for PTSD. The current findings may give implications for comorbidities between PTSD and other psychiatric disorders. Since dysphoric arousal symptoms include sleep disturbances and concentration problems, our findings are consistent with previous researches that OXT can promote sleep.[35,36] Considering that dysphoric arousal seems to be the main driving factor of functional impairment associated with PTSD,[37] intervention studies of oxytocinergic system should pay more attention to the dysphoric arousal cluster of PTSD. Further intervention studies on OXT targeted symptom clusters of PTSD are also encouraged to give implications for personalized treatment.[38]

In this study, several limitations are worth considering. Firstly, this study included a medium-sized sample exposed to a specific type of trauma 5.5 years later. The findings should be replicated with a larger sized sample exposed to different traumatic events at different time points after trauma. Secondly, a clinician-administered instead of the self-reported questionnaire should be used in future studies. Thirdly, this study only investigated the level of earthquake exposure as an environmental variable. Further studies should measure more environment variables to detect the G × E interaction.

The current study confirmed the independent role of *OXTR* gene polymorphism on PTSD symptoms, especially on dysphoric arousal symptoms. These findings add to the knowledge about the genetic underpinning of PTSD. Moreover, the current findings further explained individual differences of PTSD from a genetic perspective. Considering therapeutic prospects of oxytocinergic system, this study has certain significance for the prevention and/or treatment of PTSD.

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Ethical statement

This study was approved by the Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences.

Declaration of competing interest

The authors declare that they have no competing interests.

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