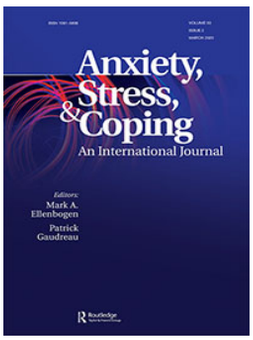

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BRIEF REPORT

Association between the OXTR rs53576 genotype and latent profiles of post-traumatic stress disorder and depression symptoms in a representative sample of earthquake survivors

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ABSTRACT

Background and Objectives: Post-traumatic stress disorder (PTSD) and major depressive disorder are commonly experienced mental disorders among psychological trauma victims. Few studies have investigated the genetic basis for population heterogeneity of trauma-related psychopathology, including PTSD and depression. This study examined the main and interaction effects of the *OXTR* rs53576 genotype in distinguishing four subgroups identified by symptom profiles of PTSD and depression symptoms using latent profile analysis.

Design: A cross-sectional design with a gene-environment interaction approach was adopted in the current study.

Methods: This study was a secondary data analysis conducted on a sample of 1196 adult earthquake survivors. Participants completed assessments of earthquake exposure, PTSD symptoms, and depression symptoms. The rs53576 polymorphism of *OXTR* was genotyped using a custom-by-design 2×48-Plex SNPscan™Kit.

Results: Multinomial logistic regression analyses revealed the main effects of the rs53576 genotype on symptom profiles. Specifically, G allele carriers were more likely in the combined PTSD-depression group than in the low symptom, predominantly depression, and predominantly PTSD groups. No significant interaction effects between this genotype and earthquake exposure on symptom profiles were found.

Conclusions: Our findings support a genetic basis for trauma-related psychopathology heterogeneity. Furthermore, results provide preliminary evidence for the role of *OXTR* in PTSD/depression comorbidity.

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PTSD; depression; population heterogeneity; *OXTR* rs53576; association study

A majority of individuals experience at least one traumatic event in their lifetime. Traumatic events can lead to adverse psychological-emotional outcomes. Although post-traumatic stress disorder (PTSD) is the most common trauma-related mental disorder, major depressive disorder (MDD) is also common among trauma victims, and is frequently concurrent with PTSD. According to a recent meta-analysis of 57 studies, over a half (52%) of individuals with PTSD had co-existing MDD (Rytwinski, Scur, Feeny, & Youngstrom, 2013).

Considering that co-occurring PTSD and MDD are generally associated with greater impairment and poorer quality of life (e.g., Haagsma et al., 2015), clarifying the relationship between these

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disorders has important implications for both research and practice. A number of comorbidity studies based on traditional variable-centered analyses have been conducted, but overlook differences in heterogeneous groups of trauma-exposed individuals (e.g., Contractor et al., 2015). Therefore, person-centered analyses such as latent class analysis (LCA; examining categorical outcome variables) or latent profile analysis (LPA; examining continuous outcome indicators of symptom severity) that account for population heterogeneity are recommended and have been increasingly used in comorbidity studies of PTSD and MDD in recent years. A previous LPA study identified four groups of trauma-exposed individuals based on co-existing patterns of PTSD and MDD (Cao et al., 2015). The four groups were low symptoms (characterized with the lowest symptom severity of PTSD and MDD symptoms), predominantly depression (characterized with relatively low PTSD and relatively high MDD symptom severity), predominantly PTSD (characterized with relatively low MDD and relatively high PTSD symptom severity) and combined PTSD-depression (characterized with the highest symptom severity of PTSD and MDD symptoms). However, psychological and biological factors related to individual differences in co-occurring patterns of PTSD and MDD need to be further clarified.

A substantial amount of variance in comorbidity between PTSD and MDD is explained by genetic factors (Koenen et al., 2008). In the context of comorbidity, exploring the genetic overlap between PTSD and other psychiatric disorders is also an important research direction for the Psychiatric Genomics Consortium Posttraumatic Stress Disorder Workgroup (PCG-PTSD) Workgroup (Logue et al., 2015). Regarding PTSD and MDD, molecular genetics studies have identified common genes associated with both disorders (e.g., Wang, Shelton, & Dwivedi, 2018). Twin studies found significant genetic correlations (r ranges from 0.77 to 1.0) between PTSD and MDD (Koenen et al., 2008; Sartor et al., 2012). Because genetic factors are associated with the comorbidity of PTSD and MDD, it is additionally important to examine how different symptom profiles of these two disorders related to genetic factors.

Oxytocin (OXT) is a neuropeptide predominantly in neurons of the paraventricular and supraoptic nuclei of the hypothalamus. The oxytocinergic system plays a critical role not only in shaping social behaviors (e.g., trust, social support) but also in regulating responses to stressors (e.g., Olff et al., 2013). As both PTSD and depression involve deficits in social functioning and stress regulation, the oxytocinergic system is implicated in the pathophysiology of PTSD and depression. In fact, animal studies have revealed that oxytocin could reduce PTSD-like (Cohen et al., 2010) and depression-like symptoms (Arletti & Bertolini, 1987). Oxytocin has been identified as a promising target for PTSD treatment and several recent pilot studies have explored treatment effects of OXT on PTSD (e.g., Frijling, 2017). Therefore, the gene coding for OXT and its receptor could be a good candidate for genetic analysis of PTSD and depression. One of the most studied polymorphisms of the oxytocinergic system is a single nucleotide polymorphism (SNP) (rs53576) in the OXT receptor gene (*OXTR*). G allele carriers tend to be more optimistic (Saphirebernstein, Way, Kim, Sherman, & Taylor, 2011), trusting (Krueger et al., 2012) and social (Li et al., 2015) than A-carriers. However, recent studies suggest detrimental effects of the G allele under adversity. For example, studies show that the G allele was associated with less resilient coping style under early life adversity (Bradley et al., 2011) and more sensitivity to social exclusion (McQuaid, McInnis, Matheson, & Anisman, 2015). Regarding the relation between the rs53576 genotype and mental disorders, several molecular genetics studies have verified the role of the rs53576 genotype in the pathophysiology of PTSD (e.g., Lucas-Thompson & Holman, 2013; Sippel et al., 2017) and MDD (e.g., Mcquaid, Mcinnis, Stead, Matheson, & Anisman, 2013; Thompson, Hammen, Starr, & Najman, 2014). Therefore, further study is needed to clarify whether empirically based subgroups differ by the rs53576 genotype.

For the above reasons, we conducted secondary data analysis with a sample of Chinese earthquake survivors to investigate whether differential symptom profile membership could be predicted by the rs53576 genotype. Four groups including low symptoms, predominantly depressive symptoms, predominantly PTSD symptoms, and combined PTSD-depression symptoms were identified by our previous LPA study (Cao et al., 2015). Given that this is an exploratory study and no prior

papers have explored relationships between the *OXTR* genotype and co-occurring patterns of PTSD and MDD, we could only hypothesize the main effect of the rs53576 genotype or interaction effect between the rs53576 genotype and earthquake exposure may impact different symptom profiles of these two disorders.

Methods

Participants

A secondary analysis was conducted on a dataset of Chinese earthquake survivors (Cao et al., 2015). The sample consisted of 1196 participants who personally experienced the 2008 Wenchuan earthquake in Sichuan Province, China. Fifty-six participants were excluded from the study for blood draw refusal (24 participants), DNA extraction failure (26 participants) and DNA genotyping failure (6 participants). The final sample included 1140 adults ranging from 16 to 73 years old ($M = 48.1$, $SD = 10.0$). The majority of participants were female (68.2%) and married (86.8%). Regarding education, 769 (67.5%) did not complete high school.

Procedure

The data used in this study were acquired from an epidemiological sample of adult Chinese earthquake survivors. Participants were recruited from one of the largest rebuilt communities in Hanwang Town, Mianzhu City, Sichuan Province, China. This town was almost completely destroyed by the 2008 Wenchuan Earthquake. Our study was conducted five and a half years after the earthquake. Household was treated as the basic sampling unit, and only one adult member in each household was randomly selected as a participant. Participants without mental retardation or major psychosis (e.g., schizophrenia and organic mental disorders) were included in this study. Trained investigators provided a detailed introduction of the study aim, and first administered self-report questionnaires (administered in Mandarin Chinese) to consenting participants. Subsequently, experienced nurses drew peripheral blood samples from subjects for DNA extraction and genotyping. This study was approved by the Institutional Review Board of our Institute.

Measures

Earthquake exposure was assessed by 10 questions (e.g., Cao et al., 2015). Respondents were asked to answer yes (1) or no (0) regarding whether they experienced during or secondary to the earthquake: (1) being trapped under rubble; (2) being injured; (3) being disabled due to injuries; (4) participating in rescue efforts; (5) witnessing a death of someone; (6) exposure to mutilated bodies; (7) traumatic death of a family member; (8) traumatic injury of a family member; (9) traumatic death of a friend or neighbor; and (10) losing livelihood due to the disaster. The total score of these 10 items was used to reflect the level of earthquake exposure.

PTSD symptoms were measured with the PTSD Checklist for *DSM-5* (PCL-5; Blevins, Weathers, Davis, Witte, & Domino, 2015). The 20 items of PCL-5 are rated on a five-point Likert-scale (0 = *not at all*; 4 = *extremely*) to reflect the severity of DSM-5 PTSD symptoms specifically in relation to the earthquake during the past month. Cronbach's α for PCL-5 was 0.94 in this sample.

Depression symptoms were assessed with the Center for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977). The 20 items of CES-D are rated on a four-point Likert-scale reflecting the severity of depression symptoms from 0 (*none of the time*) to 3 (*5–7 days or more per week*) during the past month. In this study, Cronbach's α of CES-D was 0.87.

Genotyping

DNA was extracted from peripheral blood samples using standard methodology. Genotyping of the rs53576 genotype was performed with a custom-by-design 2 × 48-Plex SNPscanTM Kit (Genesky Biotechnologies Inc., Shanghai, China) based on double ligation and multiplex fluorescence PCR. Raw data were analyzed according to fragment size of the allele-specific ligation-PCR product. The genotype call rate was more than 98%.

Statistical analyses

The detailed process of the LPA analysis was described in previous work (albeit, not exploring genetic research questions) (Cao et al., 2015). Based on summed observed subscale scores for four PTSD factors and four depression factors, a 4-class solution yielded the best fit to the data in 1-class to 5-class solutions with LPA analysis using Mplus 7.0. The four groups were low symptoms (53.9%), predominantly depression (18.2%), predominantly PTSD (18.9%) and combined PTSD-depression (9.0%). The mean scores of PCL-5 were 9.6 (*SD* = 5.1), 20.9 (*SD* = 6.7), 28.6 (*SD* = 6.5) and 48.6 (*SD* = 9.0) for low symptoms, predominantly depression, predominantly PTSD and combined PTSD-depression, respectively. The mean scores of CES-D were 24.1 (*SD*=4.0), 35.1 (*SD* = 4.0), 26.7 (*SD* = 3.7) and 37.5 (*SD* = 5.7) or low symptoms, predominantly depression, predominantly PTSD and combined PTSD-depression, respectively.

Based on the results of LPA analysis, in the present paper, we used multinomial logistic regression analyses to examine prediction functions for the main effect of the rs53576 genotype and interaction effect between the rs53576 genotype and earthquake exposure on PTSD and MDD symptoms profiles with SPSS 20.0. The groups identified in LPA analysis served as the dependent variables, while the predictors included earthquake exposure, the rs53576 genotype (AA vs G+) and rs53576 X earthquake exposure. Demographic characteristics including age, sex marital status and educational level were controlled as covariates. In our analysis, earthquake exposure was centered to avoid multicollinearity. The GG and GA individuals were grouped into a G+ group to compare with an AA group to ensure sufficient power for analyses, as the G allele was the minor allele in this sample. A *p*-value less than 0.05 was considered statistically significant, and between 0.05 and 0.10 was considered marginally significant.

Results

The mean score was 18.8 (*SD* = 13.5; range: 1–77) for the PCL-5 and 17.0 (*SD* = 8.6; range: 0–48) for the CES-D, respectively. Regarding earthquake exposure, the mean score 3.5 (*SD* = 1.8; range: 0–10) in this sample. Frequencies of the rs53576 genotype were 548 (48.1%) for AA, 466 (40.9%) for GA, and 126 (11.1%) for GG. The genotype distribution was in Hardy-Weinberg equilibrium ($\chi 2 = 3.158$, $p = .076$).

Results of multinomial logistic regression analyses to examine predictors of latent classes are shown in Table 1. Individuals in the combined PTSD-depression group were older and exposed to higher levels of earthquake exposure than individuals from the three other groups. Individuals in the combined PTSD-depression group were less likely to be males and married than those in the low symptom group. The main effect for the rs53576 genotype on symptom profile was found. Specifically, individuals in the combined PTSD-depression were less AA allele carriers than individuals in the other three groups. The interaction between rs53576 genotype and earthquake exposure was not a robust predictor of latent class membership.

Discussion

To the best of our knowledge, this study was the first to explore the *OXTR* rs53576 genotype in distinguishing co-existing patterns of PTSD and MDD in Chinese earthquake survivors. Results revealed

Table 1. Predictors of different symptom profiles.

	Combined PTSD-depression profile											
	Low symptoms profile(reference group)				Predominantly PTSD profile(reference group)				Predominantly depression profile(reference group)			
	RRR	*d*	95% CI	*p*	RRR	*d*	95% CI	*p*	RRR	*d*	95% CI	*p*
Age	1.093**	0.049	[1.062, 1.124]	<.001	1.034*	0.018	[1.003, 1.066]	.029	1.064**	0.032	[1.032, 1.097]	<.001
Sex												
Female (reference)				-				-				-
Male	0.486*	−0.398	[0.292, 0.808]	.005	0.943	−0.032	[0.541, 1.634]	.836	0.842	−0.095	[0.479, 1.478]	.548
Marital status												
Unmarried (reference)				-				-				-
Married	0.588†	−0.293	[0.315, 1.099]	.096	0.574	−0.306	[0.290, 1.136]	.111	0.797	−0.125	[0.407, 1.560]	.508
Education												
High school or above (reference)				-				-				-
Less than high school	1.066	0.035	[0.619, 1.834]	.818	0.721	−0.180	[0.395, 1.317]	.287	1.061	0.033	[0.586, 1.921]	.845
Earthquake Exposure	1.887**	0.350	[1.552, 2.295]	<.001	1.388*	0.181	[1.133, 1.701]	.002	1.396*	0.184	[1.138, 1.712]	.001
rs53576 genotype												
GA/GG (reference)				-				-				-
AA	0.481*	−0.404	[0.283, 0.818]	.007	0.616†	−0.267	[0.349, 1.085]	.093	0.488*	−0.396	[0.274, 0.867]	.014
rs53576×Earthquake Exposure	0.923	−0.044	[0.716, 1.191]	.539	1.014	0.008	[0.775, 1.327]	.920	0.985	−0.008	[0.749, 1.296]	.914

Note. RRR, relative risk ratio; CI, confidence interval; d = Cohen's d.
**$p < .001$; *$p < .05$; †$p < .10$.

the independent effect of the rs53576 genotype on symptom profiles of PTSD and depression, as participants with the G allele at rs53576 of *OXTR* were more likely to develop both PTSD and depression symptoms.

This study confirmed that the *OXTR* rs53576 genotype was associated with PTSD/depression comorbidity. These findings together with previous studies (e.g., Koenen et al., 2008; Sartor et al., 2012) support the genetic basis of PTSD/depression comorbidity. We found that rs53576 G allele carriers were at higher risk to develop both PTSD and depression symptoms. These findings generally accord with previous studies (Bradley et al., 2011; McQuaid et al., 2015) showing detrimental effects of the G allele. However, some studies also reported that beneficial traits associated were with G allele (e.g., Chen et al., 2011). The diverse effect of the G allele may be due to different cultures as previous studies have shown the culture-dependent effect of alleles (e.g., Sasaki et al., 2013; Sasaki & Kim, 2017).

Unlike previous studies, we failed to find significant interaction effects of the rs53576 genotype and trauma exposure. Stein (2018) proposed that gene-environment interactions may be rare. Therefore, it is understandable that we did not discover a rs53576 genotype by trauma exposure interaction. Moreover, lack of an interaction between the rs53576 genotype and trauma exposure may have resulted from the long-time interval of five and a half years since the earthquake.

The exact mechanism of the *OXTR* rs53576 variant on PTSD/depression comorbidity is still unknown. Previous work indicated that the rs53576 genotype might impact psychopathology through changing the efficiency of receptors and further affecting OXT signaling (Feldman, Monakhov, Pratt, & Ebstein, 2016). Moreover, the rs53576 genotype may contribute to PTSD/depression comorbidity through changing how amygdala activities respond to stressors, as previous work (Dannlowski et al., 2016) demonstrated that GG carriers revealed stronger amygdala responsiveness to emotional cues. Further studies focusing on the exact mechanism and intermediate phenotypes would help to provide a better understanding of the *OXTR* rs53576 genotype on trauma-related psychopathology.

Limitations

The main limitations of this study include a moderate sample size of trauma-exposed participants to a specific type of trauma, and self-report methodology to measure PTSD symptoms. Therefore, further studies using clinician-administered questionnaires with larger samples exposed to various traumatic events are clearly needed. Moreover, other environment variables after the earthquake, which may potentially affect PTSD and depression symptoms, were not measured or included in analysis.

Conclusion

Despite the aforementioned limitations, this study provides preliminary evidence for the role of *OXTR* in PTSD/depression comorbidity, and adds to knowledge in the genetic underpinnings of this comorbidity. This study also provides implications for clinical practice on which clinicians can identify high-risk individuals and provide early intervention.

Disclosure statement

No potential conflict of interest was reported by the authors.

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