Received: 28 April 2019 | Revised: 15 August 2019 | Accepted: 29 August 2019

DOI: 10.1002/mgg3.974

ORIGINAL ARTICLE

Molecular Genetics & Genomic Medicine Open Access WILEY

Effects of early trauma and corticotropin-releasing factor receptor 1 gene polymorphism on adult visual spatial memory

Fei-Fei Sun | **Ran Wang** | **Na Li** | **Xiao-Chuan Zhao** | **Lan Wang** | **Mei Song** | **Lu-Lu Yu** | **Ya-Nan Chen** | **Cui-Xia An** | **Xue-Yi Wang**

Institute of Mental Health, The First Hospital of Hebei Medical University, Shijiazhuang, China

Correspondence
Xue-Yi Wang and Cui-Xia An, Institute of Mental Health, The First Hospital of Hebei Medical University, No. 89 Donggang Road, Shijiazhuang, 050031, China.
Email: ydyywxy@163.com (X.-Y. W.) and acxsunny@sina.com (C.-X. A.)

Funding information
Natural Science Foundation Project of Hebei Province, Grant/Award Number: H2014206280; Major medical research projects from Health Commission of Hebei Province, Grant/Award Number: zd2013085; Government Sponsored Provincial Clinical Medicine Talents Program, Grant/Award Number: LS201605; National Natural Science Foundation of China, Grant/Award Number: 81271489; Science and Technology Research and Development Program of Hebei Province, Grant/Award Number: 09276103D

Abstract

Background: The study sought to determine the effects of earthquake on the working memory of adults who experienced earthquake either as infants or fetuses and also investigates whether earthquake exposure and corticotropin-releasing factor receptor 1 (*CRHR1*) variants rs242924 and rs7209436 interacted with each other in modulating working memory.

Methods: We enrolled subjects who experienced the Tangshan Earthquake as fetuses (group I) or infants (group II), as well as those who did not experience the earthquake (group III). Their working memory was measured using Brief Visuospatial Memory Test-Revised (BVMT-R) and Hopkins Verbal Learning Test-Revised (HVLT-R). Two single-nucleotide polymorphisms (SNPs) of *CRHR1* rs242924 and rs7209436 were analyzed by fluorescence quantitative polymerase chain reaction (PCR).

Results: The study enrolled 535 subjects, including 172 subjects in group I, 176 subjects group II, and 187 subjects in group III. Both group I and II had significantly lower BVMT-R scores than group III ($p < .05$). Moreover, no difference was observed in HVLT-R scores among the three groups ($p > .05$). The allele frequency was 84.7% for AA, 82.8% for TT, 13.6% for AC, and 15.9% for TC. C gene carriers in group II ($t = -4.231$, $p < .01$) and group I ($t = -3.201$, $p < .05$) had significantly lower visual spatial memory scores than group III. Furthermore, AT gene carriers had significantly lower visual spatial memory scores than C gene carriers in group III ($t = 2.215$, $p < .05$). Moreover, there was significant interaction between earthquake exposure and *CRHR1* genotype in their effects on visual spatial memory ($F = 4.028$, $p < .05$).

Conclusions: Our cross-sectional study has demonstrated that infant or fetus exposure to earthquake impairs visual spatial memory during adulthood and *CRHR1* polymorphisms and earthquake exposure may interact with each other to accentuate this impairment.

KEYWORDS
corticotropin-releasing factor receptor 1, earthquake, polymorphism, rs242924, rs7209436, spatial memory, stress

1 | INTRODUCTION

Childhood stress and trauma significantly influence the risk of adult psychopathology and can have lasting effects on the hypothalamic-pituitary-adrenal (HPA) axis (McEwen, 2003). Corticotropin-releasing hormone (CRH) is the main mediator of stress response and mainly exerts its biological actions by binding to CRH receptor 1 (CRHR1; Yang et al., 2010), a G protein-coupled receptor localized in the frontal cortical areas, forebrain, brainstem, amygdala, cerebellum, and the anterior pituitary (Steckler & Holsboer, 1999). CRHR1 plays a key role in the regulation of the HPA axis in response to stressful events. *CRHR1* single-nucleotide polymorphism (SNP) has been shown to be associated with posttraumatic stress symptoms in disaster adult victims (White et al., 2013) and with longitudinal trajectory of trauma symptoms over time in pediatric injury patients (Amstadter et al., 2011).

The brain processes and temporarily stores information necessary for language comprehension, visual image manipulation, reasoning, learning, and information integration, and uses the information as working memory. Working memory consists of a central execution system, a voice loop system, and a visual space storage system. The visual space storage system, also called visual space memory, is an important part of working memory, and mainly handles some visual spatial information (Aben, Stapert, & Blokland, 2012). *CRHR1* variants, including rs242924 and rs7209436, also have effects on working memory (Bradley et al., 2008; Grimm et al., 2015), and interact with childhood trauma in modulating working memory function (Fuge et al., 2014). Our previous study has revealed that fetal exposure to cataclysmic earthquake reduces abstract thinking ability subsequently in life (Nelson et al., 2007); other investigators have also found that fetal exposure to earthquake impairs executive function and working memory during adulthood (Gao, Wang, & Wang, 2016; Li, Zhao, & Wang, 2015; Wang, Zhang, & Zhang, 2001). However, no study is yet available on the effect of early experience of cataclysmic earthquake on the working memory of adults as well as the role of, if any, *CRHR1* variants in the process.

The Tangshan Earthquake struck the city of Tangshan, Hebei province, China on 28 July 1976 with a magnitude of 7.8 and killed approximately a quarter million people and severely injured 160,000 people. In the current cross-sectional study, we sought to determine the effects of earthquake on the working memory of adults who experienced the traumatic event either as infants or fetuses and also investigate whether earthquake exposure and *CRHR1* variants rs242924 and rs7209436 interacted with each other in modulating working memory.

2 | SUBJECTS AND METHODS

2.1 | Subjects

The study protocol was approved by the ethics committee of the First Affiliated Hospital of Hebei Medical University, Shijiazhuang, Hebei, China (No. 2,014,005). Written informed consent was provided by all the study participants.

The current study was carried out between January and December 2014 and enrolled subjects who experienced the earthquake as infants (born between 29 July 1975 and 28 April 1976) or fetuses (born between 29 July 1976 and 28 April 1977), and those who did not experience the earthquake (born between 29 July 1977 and 28 April 1978). We included those who had resided in Tangshan since birth. Furthermore, only subjects whose genomic DNA was available for *CRHR1* genotyping were included. We excluded pregnant or lactating women, subjects with active infection, hypertension, epilepsy or convulsions, diabetes, thyroid disease, alcohol use, and history of trauma other than earthquakes. We also excluded subjects with a recent or previous diagnosis of mental illness or neurological diseases and other diseases affecting cognitive function. Persons with incomplete data or who did not understand instructions or were not cooperative were also excluded.

2.2 | Subject assessment

The study participants were asked to complete a questionnaire that elicited data on sociodemographic variables, pregnancy history including experiences by the mothers during the earthquake, birth history, previous history of the subjects, and their family history. Furthermore, mental illness was evaluated using DSM-IV Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (SCID-I/P; Li, Zhou, & Hu, 2004).

Childhood Trauma Questionnaire (CTQ; Fu, Yao, & Yu, 2005) was used to assess the trauma experience of subjects before the age of 16 years. The CTQ has been validated for use in the Chinese population and consists of 28 items (Jiang et al., 2018); there are five items for each of five domains: emotional neglect, physical neglect, emotional abuse, physical abuse, and sex abuse, and three items for the tendency to minimize/deny. Each item assesses the frequency of trauma experience by using a 5-point Likert-type response, ranging from 1 = never to 5 = very often. The total score of each domain ranges from 5 to 25. The Life Event Scale (LES; Zhang, Fan, & Cai, 1987) was used to assess traumatic events after subjects turned 16 years of age. The LES has been validated for use in the Chinese population and was used to measure the scale of stressful events, including loss of family members and houses during the earthquake.

Sleep was evaluated using the Pittsburgh Sleep Quality Index (PSQI; Liu, Tang, & Hu, 1996), which has been validated in Chinese subjects (Tsai et al., 2005). The PSQI has seven domains, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. Answers in each domain are scored using a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert scale and the range of the global sum is 0 to 21. The PSQI score above 7 is defined as sleep disturbance. Furthermore, the Hamilton Anxiety Scale (HAMA; Zhang & He, 2015) was used to assess anxiety and a HAMA score above 7 indicates probable/definite anxiety. In addition, the Hamilton Depression Scale (HAMD; Zhang & He, 2015) was used to assess depression and a HAMD score above 7 indicates probable/definite depression.

2.3 | Working memory tests

Hopkins Verbal Learning Test-Revised (HVLT-R) was used to test the ability to learn, instantly recall word information, and maintain recognition. Higher HVLT-R scores indicated better memory retention. Furthermore, Brief Visuospatial Memory Test-Revised (BVMT-R) was used to test instantaneous recall, learning rate, and retention ability of the visual space (Zou, Cui, & Wang, 2009).

2.4 | Genotyping

Five milliliter peripheral blood was taken of each subject after an overnight fast. Genomic DNA (10 ng) was extracted using a commercially available kit (Tiangen Biotech) as instructed by the manufacturer. The Chinese Han population typing data were downloaded from the HapMap (http://www.hapmap.org) database and selected according to the principle of minimum allele frequency (MAF) >0.05 and linkage disequilibrium coefficient (r^2) > 0.8. Two SNPs, rs242924 and rs7209436, of *CRHR1* were selected and analyzed by fluorescence quantitative polymerase chain reaction (PCR) as instructed by the manufacturer (Tiangen Biotech). Subjects with the rs242924 AA and rs7209436 TT alleles were classified as AT allele carriers and subjects with homozygous and heterozygous C alleles were classified as C allele carriers (Fuge et al., 2014).

2.5 | Statistical analysis

SPSS 22.0 software (SPSS Inc.) was used for statistical analysis. Data were represented by mean ± *SD*. Non-normally distributed data were expressed by median (interquartile range, IQR). One-way ANOVA was used for comparison among multiple groups. Countable data were compared by Chi-squared test and $p < .05$ was considered statistically different; gender was used as a covariate; using a two-factor factorial design, we carried out variance analysis to analyze whether the determinants of working memory (seismic stress and genotyping) interacted with each other.

3 | RESULTS

3.1 | Sociodemographic and baseline characteristics of the study population

The study flowchart is shown in Figure 1. The current study enrolled 1,534 subjects. Totally 1,328 (86.6%) questionnaires were effective. About 728 subjects were excluded because their genomic DNA was not available for analysis.

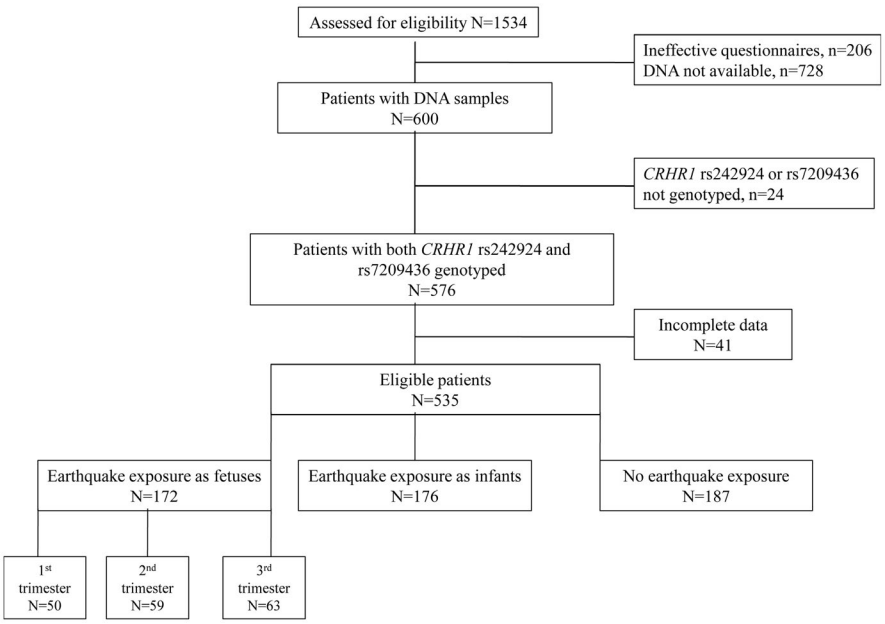

FIGURE 1 The study flowchart

TABLE 1 Sociodemographic and baseline characteristics of the study subjects

	Earthquake exposure when infants	Earthquake exposure when foetuses	Control group/Earthquake exposure when one years old	*p*
N	176	172	187	
Male gender, *n* (%)	149 (84.7)	151 (87.8)	155 (82.9)	.422
Mean age, years ± *SD*	40.0 ± 1.0	39.0 ± 1.0	38.0 ± 1.0	.000
Years of education, *n* (%)				
<6	2 (1.1)	1 (0.6)	4 (2.1)	.310
6–12	137 (77.8)	131 (76.2)	130 (69.5)	
>12	37 (21.0)	40 (23.3)	53 (28.3)	
Mean CTQ score ± *SD*	33.3 ± 7.9	33.5 ± 7.9	33.8 ± 7.5	.832
Mean LES score (IQR)	17 (3,37)	19 (5,34)	18 (2,41)	.977
Sleep problems, *n* (%)				
Yes	25 (14.2)	25 (14.5)	22 (13.4)	.947
Anxiety symptoms, *n* (%)				
Yes	9 (5.2)	7 (4.0)	13 (7.0)	.453
Depressive symptoms, *n* (%)				
Yes	1 (0.6)	1 (0.6)	2 (1.1)	.818
Property loss, *n* (%)				
Yes	59 (33.5)	63 (36.6)	67 (35.8)	.819
Mother buried under rubles, *n* (%)				
Yes	17 (9.7)	11 (6.4)	21 (11.2)	.273
Casualties among relatives of the mothers, *n* (%)				
Yes	39 (22.2)	34 (19.8)	36 (19.3)	.767

Abbreviations: CTQ, child trauma questionnaire; LES, life event scale.

Twenty-four subjects were not included because *CRHR1* rs242924 orrs7209436 was not genotyped and 41 subjects with incomplete data were also excluded. Finally, 535 subjects were included in the current study. They included 172 subjects who experienced the earthquake as fetuses (50 fetuses experienced the earthquake in the first trimester, 59 in the second trimester, and 63 in the third trimester), 176 subjects who experienced the earthquake as infants, and 187 subjects who did not experience the earthquake. The majority (85.05%) of the study subjects were male. Moreover, 13.46% of the subjects had sleep problems, 5.42% of them had anxiety, and 0.75% of them had depressive symptoms. The mean CTQ score was 33.5 ± 7.7 and the median LES score was 18 (IQR: 3, 36) for the study population. The three groups were comparable in the sociodemographic and baseline variables ($p > .05$) except age ($Z = 397.404$, $p < .01$; Table 1).

3.2 | BVMT-R and HVLT-R scores

Subjects who experienced the earthquake as infants had significantly lower BVMT-R scores versus the control group ($t = -2.517$, $p = .012$; Figure 2a). Subjects who experienced the earthquake as fetuses also had significantly lower BVMT-R scores versus the control group ($t = -1.982$, $p = .048$). There was no significant difference in BVMT-R scores between subjects who experienced the earthquake as infants and those who experienced the earthquake as fetuses ($p > .05$). Furthermore, subjects who experienced the earthquake as fetuses in the second trimester had significantly lower BVMT-R scores versus the control group ($p < .05$) while there was no statistical difference in BVMT-R scores between those who experienced the earthquake in the first or third trimester and the control group ($p > .05$; Figure 2a).

Moreover, there was no difference in HVLT-R scores among subjects who experienced the earthquake as fetuses or infants and the control group ($p > .05$; Figure 2b). There was also no significant difference in HVLT-R scores among subjects who experienced the earthquake as fetuses in the first, second, and third trimester ($p > .05$; Figure 2b).

3.3 | CRHR1 polymorphisms and visual spatial memory

Totally 535 subjects were analyzed for *CRHR1* polymorphism at rs242924 and rs7209436. The distribution of both

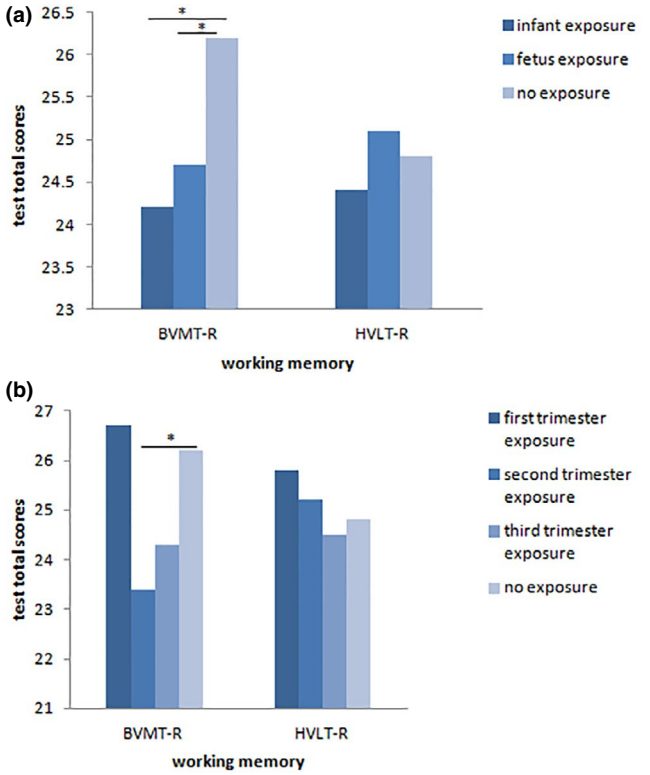

FIGURE 2 Brief Visuospatial Memory Test-Revised (BVMT-R) and HVLT-R scores. (a) BVMT-R and HVLT-R scores in the three groups. (b) BVMT-R and HVLT-R scores stratified by trimester of subjects who experienced the earthquake as fetuses. *$P < 0.05$

SNPs in the study population was in Hardy–Weinberg equilibrium. The allele frequency was 84.7% for AA, 82.8% for TT, 13.6% for AC, and 15.9% for TC (Table 2). Moreover, 80.4% subjects were AT gene carriers and 19.6% subjects were C gene carriers. According to high linkage disequilibrium, occurrence of the C allele in these two SNPs was associated. The combined allele frequency was 80.4% for AA/TT and 11.0% for AC/TC (Table 3). C gene carriers who experienced the earthquake as infants ($t = -4.231$, $p < .01$) and those who experienced the earthquake as fetuses ($t = -3.201$, $p < .05$) had significantly lower visual spatial memory scores than those who did not experience the earthquake (Figure 3). Furthermore, AT gene carriers had significantly lower visual spatial memory scores than C gene carriers who did not experience the earthquake ($t = 2.215$, $p < .05$).

TABLE 2 Hardy–Weinberg equilibrium of *CRHR1* rs242924 and rs7209436 ($n = 535$)

SNP	Minor Allele/ Major Allele	MAF	HWE, *P* Value	Genotypes	*N* (%)
rs242924	C/A	0.09	0.91	AA	453 (84.7)
				AC	73 (13.6)
				CC	9 (1.7)
rs7209436	C/T	0.10	0.90	TT	443 (82.8)
				TC	85 (15.9)
				CC	7 (1.3)

Abbreviations: HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

TABLE 3 Combined frequencies of *CRHR1* rs242924 and rs7209436 alleles

	rs242924, *n* (%)		
	AA	AC	CC
rs7209436, *n* (%)			
TT	430 (80.4)	12 (2.2)	1 (0.2)
TC	21 (3.9)	59 (11.0)	5 (0.9)
CC	2 (0.4)	2 (0.4)	3 (0.6)

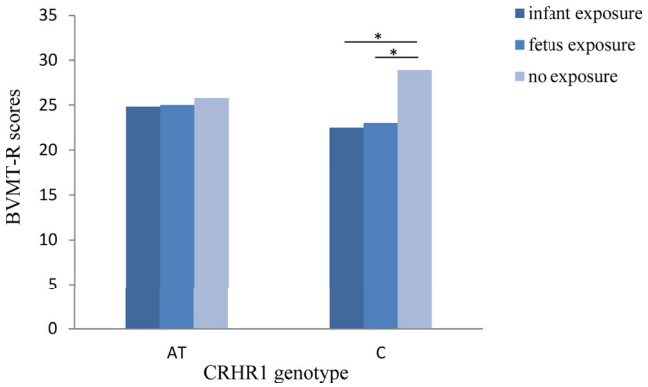

FIGURE 3 *CRHR1* polymorphisms and visual spatial memory. *$P < 0.05$

3.4 | Interactive effects of earthquake exposure and CRHR1 genotypes on visual spatial memory

We found significant interaction between earthquake exposure and *CRHR1* genotype in their effects on visual spatial memory ($F = 4.028$, $p < .05$; Table 4). Gender was a covariate but showed no significant effect on visual spatial memory ($p > .05$). The effects of different levels of *CRHR1* genotypes were further analyzed. At the level of C allele, subjects who experienced the earthquake as infants or fetuses had significantly lower BVMT-R scores than those who did not experience the earthquake ($p < .01$). Meanwhile, at the level of AT allele, no statistical difference was observed in BVMT-R scores among the three groups ($p > .05$; Table 5).

4 | DISCUSSION

Our study showed that people who experienced earthquake as fetuses and infants had significantly lower BVMT-R scores

TABLE 4 Interactive effects of earthquake exposure and CRHR1 genotypes on visual spatial memory[a]

Sources	Type III sum of squares	Degree of freedom	Mean square	*F*	*p*
Corrected model	965.685	6	160.947	2.690	.014
Cutoff	27,762.602	1	27,762.602	464.097	.000
Sex	38.975	1	38.975	0.652	.420
Genotype	848.742	2	424.371	7.094	.001
Earthquake exposure	32.061	1	32.061	0.536	.464
Genotype * earthquake exposure	481.944	2	240.972	4.028	.018

[a]BVMT-RT is used as a dependent variable.
*Interaction of two factors.

TABLE 5 Effects of different levels of *CRHR1* genotypes on visual spatial memory[a]

Genotype 1 = AT, 2 = C	(I) 1 = infant exposure; 2 = fetus exposure, 3 = no exposure	(J) 1 = infant exposure; 2 = fetus exposure, 3 = no exposure	Difference in mean (I-J)	SME	*p*	95% CI	
						Lower limit	Upper limit
1	1	2	−0.229	0.924	.993	−2.443	1.985
		3	−1.209	0.920	.467	−3.413	0.995
	2	3	−0.980	0.900	.622	−3.136	1.176
2	1	2	−0.426	1.867	.994	−4.897	4.045
	3	1	6.425	1.721	.001	2.303	10.548
		2	5.999	1.943	.006	1.346	10.652

[a]BVMT-RT is used as a dependent variable.

than those who did not experience the earthquake. Subgroup analysis further revealed that exposure to earthquake in the second trimester significantly lowered the BVMT-R scores, which were not observed in those experiencing the earthquake in the first or third trimester. By contrast, we observed no difference in HVLT-R scores among the three groups. In addition, significant interaction was present between earthquake exposure and *CRHR1* genotype in their effects on visual spatial memory. Our study indicates that traumatic experience in the fetal period, particularly in the second trimester, may selectively compromise visual spatial memory of adults.

The cataclysmic 1976 Tangshan Earthquake caused indelible mental trauma to the residents of Tangshan, and had a long-lasting impact on the mental state of people residing in the disaster area at the time and compromised the development of the nervous system of the offspring (Wang et al., 2001). In the present study, working memory tests were performed 38 years after the traumatic event. The tests revealed that exposure to earthquake at infancy and during the fetal period significantly impaired visual spatial memory of adults approximately 40 years after the seismic event, suggesting that earthquake exposure may lead to a subsequent loss of immediate recall and learning in visual spatial memory. Earthquake stress may increase the level of stress hormones in the pregnant mother, which pass through the placenta and affect the development of the fetal HPA axis and/or cortisol receptors. In infancy, the traumatic event may overwhelm the stress response of the maturing brain; besides, the activation or inhibition pathway of the paraventricular nucleus of the hypothalamus and the feedback mechanism of glucocorticoids in infants are still in a delicate state and vulnerable to excessive stress. Our previous study found that subjects who were exposed to earthquake during the fetal period had markedly lower abstract thinking ability on Raven's test performed 18 years later (Wang et al., 2001), indicating that early trauma experience may impact on subsequent cognitive function. We found that subjects who experienced earthquake in the second trimester had the greatest decline in visual spatial memory compared with those experiencing the earthquake in the other two trimesters, suggesting that there might be a critical sensitive period in the fetus. The second trimester is an active period in the fetal brain, and the myelin sheath of the fetus forms at this stage and continues to form until 1 year after birth.

Early trauma is one of the risk factors for working memory deficits in adulthood (Hsu et al., 2012). However, only some adults who have experienced early trauma have cognitive impairment, and genetic factors may be the basis of cognitive impairment. A previous study analyzed the effects of *CRHR1* SNPs rs110402 and rs242924 on working memory of 451 healthy subjects. It was found that homozygous GG genotype was a high risk for working memory in childhood trauma subjects, while AT allele carriage can affect

working memory only upon exposure to severe childhood trauma (Fuge et al., 2014). Our results showed that *CRHR1* C genotype carriers who experienced earthquake as infants or fetuses had significantly lower visual spatial memory levels than those who did not experience earthquake, suggesting that *CRHR1* C genotype confers a risk of future visual spatial memory impairment, which is consistent with the study by Fuge et al. (2014). The mechanism whereby rs242924 and rs7209436 affect CRHR1 function is still unclear. *CRHR1* SNPs may affect the metabolic activities of the cortical limb system and CRHR1 regulation, resulting in impaired working memory of C genotype carriers, increased sensitivity to neuroendocrine changes, and reduced oxygen dependence in the dorsolateral cortex of the prefrontal cortex and cingulate gyrus (Grimm et al., 2015; Vijayakumari, Thomas, Menon, & Kesavadas, 2018). These findings together suggest that *CRHR1* SNPs may be markers of subsequent working memory impairment in early trauma victims.

The study showed that the visual spatial memory of C gene carriers in the fetal- and infancy-exposed groups was lower than that in the control group. The interaction between early traumatic and susceptible genotypes had significant effects on visual spatial memory, suggesting that early earthquake trauma and *CRHR1* vulnerable genotype interaction may be the main reason for subsequent impairment of visual spatial memory. Our findings indicate that not all individuals experiencing early trauma are at increased risk of subsequent impairment of working memory in adulthood, as both genetic and environmental factors may work together to impact on self-regulation and cumulative life events.

The study has several limitations. The majority of the study population was male because most of our subjects were miners. Furthermore, we need to further expand the sample size to explore the genetic and neurobiological pathways of impaired working memory by combining with neuroimaging techniques or other biological indicators such as brain-derived factors, and cortisol, and further explore the mechanisms of early traumatic regulation of brain neural activity.

In conclusion, our cross-sectional study has demonstrated that infant or fetus exposure to earthquake impairs visual spatial memory during adulthood and *CRHR1* polymorphisms and earthquake exposure may interact with each other to accentuate this impairment.

CONFLICT OF INTEREST

None declared.

ORCID

Cui-Xia An https://orcid.org/0000-0001-9061-6922
Xue-Yi Wang https://orcid.org/0000-0003-1796-5258

REFERENCES

Aben, B., Stapert, S., & Blokland, A. (2012). About the distinction between working memory and short-term memory. *Front Psychol*, *3*, 301. https://doi.org/10.3389/fpsyg.2012.00301

Amstadter, A. B., Nugent, N. R., Yang, B. Z., Miller, A., Siburian, R., Moorjani, P., … Koenen, K. C. (2011). Corticotrophin-releasing hormone type 1 receptor gene (CRHR1) variants predict posttraumatic stress disorder onset and course in pediatric injury patients. *Disease Markers*, *30*(2–3), 89–99. https://doi.org/10.3233/DMA-2011-0761

Bradley, R. G., Binder, E. B., Epstein, M. P., Tang, Y., Nair, H. P., Liu, W., … Ressler, K. J. (2008). Influence of child abuse on adult depression: Moderation by the corticotropin-releasing hormone receptor gene. *Archives of General Psychiatry*, *65*(2), 190–200. https://doi.org/10.1001/archgenpsychiatry.2007.26

Fu, W., Yao, S., & Yu, H. (2005). Study on the reliability and validity of the childhood trauma questionnaire in Chinese college students. *Chinese Journal of Clinical Psychology*, *13*(1), 40–42.

Fuge, P., Aust, S., Fan, Y., Weigand, A., Gartner, M., Feeser, M., … Grimm, S. (2014). Interaction of early life stress and corticotropin-releasing hormone receptor gene: Effects on working memory. *Biological Psychiatry*, *76*(11), 888–894. https://doi.org/10.1016/j.biopsych.2014.04.016

Gao, Y., Wang, Y., & Wang, X. (2016). The effect of earthquake stress on the executive and memory function of adult offspring. *China Journal of Neuropsychiatric Disorders*, *42*(5), 277–281.

Grimm, S., Gartner, M., Fuge, P., Fan, Y., Weigand, A., Feeser, M., … Bajbouj, M. (2015). Variation in the corticotropin-releasing hormone receptor 1 (CRHR1) gene modulates age effects on working memory. *Journal of Psychiatric Research*, *61*, 57–63. https://doi.org/10.1016/j.jpsychires.2014.12.001

Hsu, D. T., Mickey, B. J., Langenecker, S. A., Heitzeg, M. M., Love, T. M., Wang, H., … Zubieta, J. K. (2012). Variation in the corticotropin-releasing hormone receptor 1 (CRHR1) gene influences fMRI signal responses during emotional stimulus processing. *Journal of Neuroscience*, *32*(9), 3253–3260. https://doi.org/10.1523/JNEUROSCI.5533-11.2012

Jiang, W. J., Zhong, B. L., Liu, L. Z., Zhou, Y. J., Hu, X. H., & Li, Y. (2018). Reliability and validity of the Chinese version of the childhood trauma questionnaire-short form for inpatients with schizophrenia. *PLoS ONE*, *13*(12), e0208779. https://doi.org/10.1371/journal.pone.0208779

Li, N., Zhao, X., & Wang, X. (2015). Research on working memory after infancy and fetal life experienced by earthquake stressful people. *Chinese Journal of Psychiatry*, *48*(6), 360–364.

Li, T., Zhou, R., & Hu, J. (2004). DSM-IV-TR axis I disorder clinical trial patient edition (SCID-I/P). 1-219.

Liu, X., Tang, M., & Hu, L. (1996). Reliability and validity of the Pittsburgh Sleep Quality Index. *Chinese Journal of Psychiatry*, *29*(2), 29103–29107.

McEwen, B. S. (2003). Early life influences on life-long patterns of behavior and health. *Mental Retardation and Developmental Disabilities Research Reviews*, *9*(3), 149–154. https://doi.org/10.1002/mrdd.10074

Nelson, C. A. 3rd, Zeanah, C. H., Fox, N. A., Marshall, P. J., Smyke, A. T., & Guthrie, D. (2007). Cognitive recovery in socially deprived young children: The Bucharest Early Intervention Project. *Science*, *318*(5858), 1937–1940. https://doi.org/10.1126/science.1143921

Steckler, T., & Holsboer, F. (1999). Corticotropin-releasing hormone receptor subtypes and emotion. *Biological Psychiatry*, *46*(11), 1480–1508.

Tsai, P. S., Wang, S. Y., Wang, M. Y., Su, C. T., Yang, T. T., Huang, C. J., & Fang, S. C. (2005). Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. *Quality of Life Research*, *14*(8), 1943–1952. https://doi.org/10.1007/s11136-005-4346-x

Vijayakumari, A. A., Thomas, B., Menon, R. N., & Kesavadas, C. (2018). Association between glutamate/glutamine and blood oxygen level dependent signal in the left dorsolateral prefrontal region during verbal working memory. *NeuroReport*, *29*(6), 478–482. https://doi.org/10.1097/WNR.0000000000001000

Wang, X., Zhang, B., & Zhang, B. (2001). A forward study on cognitive function of young people experiencing the great earthquake in Tangshan. *Chinese Journal of Mental Health*, *15*(1), 42–43.

White, S., Acierno, R., Ruggiero, K. J., Koenen, K. C., Kilpatrick, D. G., Galea, S., … Amstadter, A. B. (2013). Association of CRHR1 variants and posttraumatic stress symptoms in hurricane exposed adults. *Journal of Anxiety Disorders*, *27*(7), 678–683. https://doi.org/10.1016/j.janxdis.2013.08.003

Yang, L. Z., Tovote, P., Rayner, M., Kockskamper, J., Pieske, B., & Spiess, J. (2010). Corticotropin-releasing factor receptors and urocortins, links between the brain and the heart. *European Journal of Pharmacology*, *632*(1–3), 1–6. https://doi.org/10.1016/j.ejphar.2010.01.027

Zhang, M., Fan, B., & Cai, G. (1987). Life events scale: Norm results. *Chinese Journal of Neuropsychiatric Diseases*, *2*, 70–73.

Zhang, M., & He, Y. (2015). *Handbook of Psychiatric Rating Scale*. Changsha: Hunan Science and Technology Press.

Zou, Y., Cui, J., & Wang, J. (2009). Clinical reliability and validity of the Chinese version of the cognitive function test for schizophrenia. *Chinese Journal of Psychiatry*, *28* (1), 40–44.

How to cite this article: Sun F-F, Wang R, Li N, et al. Effects of early trauma and corticotropin-releasing factor receptor 1 gene polymorphism on adult visual spatial memory. *Mol Genet Genomic Med*. 2019;7:e974. https://doi.org/10.1002/mgg3.974