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Modification of the risk of post-traumatic stress disorder (PTSD) by the 5-HTTLPR polymorphisms after Lorca's earthquakes (Murcia, Spain).

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ABSTRACT

Information of the modulation effect of the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*) on post-traumatic stress disorder (PTSD) after earthquakes is scarce and contradictory. A cross-sectional face-to-face interview survey of a representative sample of the adults was carried out after the Lorca (Spain) earthquakes (May 11, 2011). Socio-demographic variables, DSM-IV diagnostic assessment and earthquake-related stressors were obtained from the Composite International Diagnostic Interview (CIDI). The triallelic and biallelic classification of the *5-HTTLPR* polymorphism were genotyped from buccal swabs.

Multivariate logistic regression models were used to predict PTSD, including interaction terms to explore gene-environment (G x E) interactions. The vast majority (83%, $n = 341$) of the Lorca survey respondents ($n = 412$, 71% response rate) were genotyped. Both classifications of the *5-HTTLPR* genotype were in Hardy-Weinberg equilibrium. Prior lifetime PTSD was the only variable that remained a significant predictor after adjustments. There were no significant main effects of earthquake related stressors or *5-HTTLPR*. However, G x E interactions of *5-HTTLPR* with high emotional impact and prior lifetime anxiety disorders were statistically significant. These results provide new evidence of the modulation effect of the *5-HTTLPR* polymorphisms on PTSD risk. This information might characterize people at higher risk of developing PTSD after an earthquake exposure.

1. Introduction

Although the vast majority of people in the general populations of most countries report lifetime exposure to one or more traumatic events (Benjet et al., 2015), only a relatively small minority of those exposed to trauma (estimated as averaging 5.6% across studies) develop posttraumatic stress disorder (PTSD) (Koenen et al., 2017). PTSD is a mental disorder characterized by symptoms of re-experiencing, avoidance, dulling of the senses and hyperarousal that occurs following exposure to a potentially traumatic life event (Yehuda et al., 2015). PTSD risk is known to vary by type of trauma (Kessler et al., 2017, 2014). Earthquakes and other natural disasters are commonly-occurring types

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of trauma that have huge and varying impacts on the general population, many sorts (e.g., destruction of infrastructure, personal injury, injury-death of loved ones, geographic displacement, financial adversity) in the general population (Bartholdson and von Schreeb, 2018; Silove and Steel, 2006). PTSD is considered the most frequent psychopathological response to earthquake exposure (Anwar et al., 2013; Cheng et al., 2014; Galea et al., 2005; Neria et al., 2008; Norris et al., 2002a, 2002b). The post-earthquake risk of PTSD and other mental disorders is reported as influenced by experiences that occur during and in the aftermath of the earthquake, pre-disaster characteristics of the exposed individuals and their communities, and interactions between the two broad classes of risk factors (Bromet et al., 2017; Galea et al., 2005; Kessler et al., 2017, 2014).

PTSD is a complex and multifactorial mental disorder (Koenen et al., 2009b). Environmental factors clearly contribute to its development and there is a general consensus on the importance of genetics in its etiology (C.R. Brewin et al., 2000; Dai et al., 2016; Duncan et al., 2018). Several candidate genes related to the current understanding of the neurobiology of the disorder have been studied (Koenen, 2007). One of the most frequently researched genetic variants is the human serotonin transporter (*5-hydroxytryptamine transporter, 5-HTT*) gene (*SLC6A4*), through polymorphisms in its promoter region (*5-HTTLPR*) (Caspi et al., 2010). The less frequent short allele (*S*) in the *5-HTTLPR* has been associated with a lower transcriptional efficiency compared to the more frequent long (*L*) allele (Lesch et al., 1996). It has been related to different mental outcomes or disorders (Hu et al., 2005; Lesch et al., 1996; Li and He, 2007; Lotrich and Pollock, 2004; Takano et al., 2007). A triallelic model has also been studied, since a third functional allele, L_G, was described (Nakamura et al., 2000) with an equivalent expression to the *S* allele (Hu et al., 2005). Thus, *5-HTTLPR* might be considered as a triallelic locus with alleles designated as L_G, L_A, and S, allowing a functional re-arrangement of genotypes (or re-classification) on the basis of lower and higher levels of expression (Parsey et al., 2006; Zalsman et al., 2006).

Three meta-analyses have analysed the association of the *5-HTTLPR* polymorphisms and PTSD. The first suggested that current evidence would not support a direct effect of the *5-HTTLPR* polymorphisms on PTSD, with neither the biallelic nor the triallelic approach (Fernando Navarro-Mateu et al., 2013). The second also found no direct association, but in a sensitivity analysis, being a carrier of the *SS* genotype seemed to represent a risk factor for PTSD among those exposed to higher levels of trauma (Gressier et al., 2013). The possibility of a modulation effect of the *5-HTTLPR* in PTSD through a gene-environment interaction (Koenen et al., 2009b) has been recently explored in the third meta-analyses and its results suggested a modulation effect of the 5-HTTLPR polymorphisms on the association between stress and PTSD (Zhao et al., 2017). Gene-environment (G x E) interactions imply that the effect of a genetic variant is modified by an environmental exposure or vice versa (Koenen et al., 2008, 2009b). Only one of the 14 studies in the latest meta-analysis focused on earthquakes and it found significant interaction between the S allele with the exposure on the risk of PTSD after the exposure to the 2008 Winchuan earthquake in China (Tian et al., 2015). Since then, only two more studies have analysed this G x E interaction in survivors of the same Chinese earthquake (Li et al., 2019; Liu et al., 2017). One did not find an association of the biallelic classification of the genotype on total PTSD symptoms (Liu et al., 2017) but the most recent one showed that those child and adolescent carriers with *S'S'* alleles had higher initial PTSD symptoms as well as faster recovery rate in a longitudinal study design of 5.5 years of follow-up (Li et al., 2019). Only one of the three latest studies analysed the triallelic classification of the polymorphism (Li et al., 2019) and none controlled for prior history of mental disorders, considered to be one of the most important factors influencing the risk of mental disorders after a natural disaster (C. R. Brewin et al., 2000; Kessler et al., 2014).

On May 11, 2011 a moderate magnitude earthquake (5.1 Mw) occurred in Lorca (Murcia, Spain) preceded by a smaller one (4.5 Mw) and followed by almost 50 minor aftershocks on following days. This was during a European financial crisis and while an epidemiological survey was being performed in a representative sample of the general population in the region of Murcia, the PEGASUS-Murcia ("Psychiatric Enquiry to General Population in Southeast Spain-Murcia") project (Fernando Navarro-Mateu et al., 2013; Navarro-Mateu et al., 2015). Significant differences in the 12-month prevalence of PTSD were found comparing the exposed area of Lorca with the rest of Murcia (3.6% vs 0.5%) (Navarro-Mateu et al., 2017). The aims of the current study were to evaluate *5-HTTLPR* polymorphism as a risk factor for PTSD among people exposed to the earthquakes in Lorca, 2011 (Murcia, Spain) and to explore G x E interactions with earthquake-related stressors and lifetime mental disorders prior to the earthquakes.

2. Methods

2.1. Study design and participants

Details of the PEGASUS-Murcia project protocol, sampling frame, selection and weighting procedures are described elsewhere (F. Navarro-Mateu et al., 2013). Briefly, the study uses a cross-sectional survey design to carry out face-to-face interviews with a representative sample of the adult and non-institutionalized general population of the Region of Murcia, in south-eastern Spain. The eligible population was defined as any person aged 18 or older residing in the household population of Lorca, not living in institutions and registered in PERSAN, a periodically up-dated regional registry of all residents covered by the public health system, with virtually universal coverage. A stratified, multistage, clustered by health area, probability random sampling design was used. Fieldwork in Lorca was done by trained lay interviewers between January and April 2012, 8–11 months after the earthquake.

2.2. Diagnostic assessment and socio-demographic variables

The structured interview schedule used in the study was a revised version of the WHO Composite International Diagnostic Interview (CIDI 3.0, hereafter referred to as CIDI) adapted for use in Spain (Navarro-Mateu et al., 2012). The CIDI is a fully structured interview designed by the World Health Organization (WHO) to ascertain diagnoses of mental illnesses for comparative research of the community epidemiology of mental illnesses throughout the world (Kessler and Ustun, 2004). Different mental disorders according to DSM-IV have been considered (i.e. Mood Disorders -including major depression, bipolar and dysthymia-, post-traumatic stress disorder (PTSD), other Anxiety Disorders -generalized anxiety disorder, social phobia, specific phobia, agoraphobia without panic, panic disorder, obsessive compulsive disorder and adult separation anxiety disorder- and Substance Disorders –alcohol and drug abuse and/or dependence-). All diagnoses included organic exclusions and without diagnostic hierarchy rules except for major depressive disorder, dysthymia and general anxiety disorder. For substance use disorders, abuse was defined with or without dependence recognizing that abuse is a stage in progression to dependence. PTSD prevalence estimates were determined by whether respondents' symptomatology met the 12-month DSM-IV diagnostic criteria for the mental disorder. Lifetime prevalence of mental disorders prior to the earthquakes was determined by whether respondents had a history of mental disorder with an age-of-onset (AOO) a year prior the interview. Retrospective AOO reports were obtained in the CIDI using a series of questions designed to avoid the implausible response patterns obtained when using the standard CIDI age-of-onset questions (Kessler et al., 2005).

Socio-demographic variables evaluated in this study were: age at interview, sex, completed years of education (grouped in 2 categories: None, primary or lower: 0–11 years; Secondary or higher: 12 or more years of education); marital status (grouped in 2 categories: living with a partner (married-cohabiting) and not living with a partner (separated-

widowed-divorced-never married)). Employment status was categorized in 2 categories (working and not working (student, homemaker, retired/disabled, unemployed and others). Referred ethnicity also had 2 categories (White/Caucasian and Others).

2.3. Earthquake-related stressors

The questionnaire used in the survey, the WHO Composite International Diagnostic Interview (CIDI 3.0) (Navarro-Mateu et al., 2012) was expanded to include questions examining respondent involvement and severity of individual exposure to the catastrophe shortly after the earthquake and the psychopathological effects of this exposure. As previously described in detail (Navarro-Mateu et al., 2017), this included 22 structured questions exploring exposure to different earthquake-related stressors. Each were categorized in 10 different categories of stressors coded as dichotomous variables (yes/no): (1) Life-threatening experience for you or for close people; (2) death of family members, friends or neighbours; (3) seriously personally injured; (4) seriously family members, friends of close neighbours injured; (5) buried or trapped in rubble; (6) financial loss; (7) property (home) seriously damaged or destroyed; (8) more family or household duties or living with relatives, friends, neighbours or strangers; (9) neighbourhood destroyed or seriously damaged; and (10) job affected or loss. Full text of the interview schedule that includes the complete set of stressor questions is available elsewhere (The World Mental Health Survey Initiative, 2015). Two scores were then calculated to evaluate the impact of the earthquake on individuals: a Global Earthquake Stressor Score (GESS) (range: 0–10), by adding the individual score of each of the 10 categories, and the Earthquake's Experienced Stress (EES), based on a specific question ("*On a scale between 0 and 10 where 0 means "no stress at all" and 10 means "the most stress you can imagine a person having", what number describes how much stress you experienced as a result of the earthquake?*"). Finally, for this study, these scores were dichotomized into binary variables (yes/no) if the scores were above the sample mean. These new variables were named 'High Earthquake Exposure' (HEE) and 'High Emotional Impact' (HEI), respectively. This particular section, including lifetime and post-earthquake PTSD evaluation, was asked of all Lorca respondents, regardless of the long-short path itinerary used in other areas of Murcia (F. Navarro-Mateu et al., 2013).

2.4. Genotyping

On completion of the interview, interviewees were asked to provide a biological sample of the buccal mucosal epithelium for genetic analyses. Samples were collected in sterile 1.5 ml tubes and registered and stored at BIOBANC-HCUVA (the biobank for biomedical research network of the Region of Murcia, University Clinical Hospital Virgen de la Arrixaca –TD09/0076/00065) (http://www.imib.es/portal/plataformas/biobanco.jsf?subentrada_actual_web=259&padre=241). Genomic DNA was isolated from participants' buccal swabs using QIAamp DNA Blood Mini Kit (QIAGEN) and performed automatically in a QIAcube system (QIAGEN) to minimize variability due to manual handling. The SLC6A4 gene presents a 44 bp variable number of tandem repeats (VNTR) polymorphism in its promoter region, which is located approximately 1 kb upstream from the transcription start site, known as 5-HTTLPR polymorphism. Three variants (alleles) of the 5-HTTLPR polymorphism were genotyped in two steps, involving a polymerase chain reaction (PCR) amplification step, followed by digestion with HpaII. The primers used to perform the PCR were previously described (Mellman et al., 2009): sense-ATCGCTCCTGCATCC CCCATTAT and antisense- GAGGTGCAGGGGGATGCTGGAA. Briefly, 25 µl reaction included 50 ng genomic DNA, 1X amplification buffer, 0.2 mM dNTPs, 1.5 mM MgSO4, 0.2 µM of each primer, 1 unit Platinum Taq PCRx polymerase (Invitrogen) and 1X PCR enhancer owing to the high GC content in the polymorphism region. The reaction was initially heated to 95 °C (5 min), followed by 35 cycles of 95 °C (35 s), 60 °C (30 s) and 68 °C (30 s) and a final elongation step of 72 °C (5 min). To distinguish between S (103 bp) and L (146 bp) alleles, PCR product reactions were analysed by size determination on a QIAxcel Advanced System (QIAGEN) by high-resolution capillary electrophoresis. As a result of biallelic genotyping, individuals were genotyped as S/S, S/L or L/L. Afterwards and according to the manufacturer's instructions, fast HpaII restriction enzyme digestion (Thermoscientific) was carried out for SNP rs25531. This SNP involved the presence of adenine (A) or guanine (G), being digested in the last position. Final digested products were visualized on a QIAexcel, and individuals were genotyped as *S/S, S/L_A, S/L_G, L_A/L_A, L_A/L_G* and *L_G/ L_G*. The "triallelic" approach (*S, L_A, L_G*) allows the functional re-classification of *S/L_G* and *L_G/ L_G* as *S´S´, L_A/L_G* as *S´L´* and *L_A/L_A* as *L´L´*. The products' sizes after digestion were: *S* (103 bp), *L_A* (146 bp) and *L_G* (83 bp, 63 bp). All genetic analyses were done blinded to the diagnostic status of participants by the same geneticist.

2.5. Statistical methods

Calculations for deviation from the Hardy–Weinberg equilibrium were performed using chi-square tests for biallelic and triallelic genotype frequencies. Differences between participants who either provided or did not provide genetic samples by socio-demographic variables and diagnostic categories were calculated by chi-square or student's t tests. Bivariate analyses were initially used to explore differences by the presence (no/yes) of 12-month PTSD and each demographic characteristic (female sex, age, marital status, education level and employment status), prior mental disorders (PTSD, other anxiety, mood and substance disorders), exposure-related variables (HEE and HEI) and the genotype frequencies measured as the number of *L* alleles.

Hierarchical logistic regression models were estimated to predict 12-month PTSD. Logits were exponentiated to create Odds Ratios (OR) and their 95% Confidence Intervals (95%CI). Model 1 (M1) was implemented as a simple logistic regression with each previous relevant independent variables. Model 2 (M2) included all sociodemographic variables and lifetime disorders prior to exposure. Model 3 (M3) added the *5-HTTLPR* polymorphism to M2. As there is no consensus on the inheritance model of the 5-HTTLPR polymorphisms, three different approaches for each classification (biallelic or triallelic genotypes) were used to explore their relationship with 12-month PTSD: a codominant model (*SS, SL* or *LL* and *S'S', S'L'* or *L'L'*), a *S* or *S'* dominant model (*LL* vs *SS* + *SL* or *L'L'* vs *S'S'* + *S'L'*) and a *S* or *S'* recessive model (*LL* + *SL* vs *SS* or *L'L'* + *S'L'* vs *S'S'*) were analysed in model M2. Finally, to test for gene-environment interactions, another hierarchical series of multivariate logistic regression models was performed with the sequential inclusion of the different previously defined interaction terms formed by the combination of the 5-HTTLPR genotype (both, with triallelic and biallelic approaches) with earthquake-related measures (HEE and HEI) and the four prior lifetime mental disorders (PTSD, other anxiety, mood and substance disorders). All statistics used two-sided tests with alpha level of 0.05. No correction for multiple testing was performed. In exploratory analyses of a genetically complex trait in which the relationship between genotype and phenotype has not been yet established (Fernando Navarro-Mateu et al., 2013), multiple test adjustment is not strictly required (Bender and Lange, 2001) as it could increase the likelihood that real effects be missed (type II error rates) (Rothman, 1990).

The Clinical Research Ethics Committee of the University Hospital Virgen de la Arrixaca of Murcia approved the protocol. Written informed consent was obtained from all participants before interview. The study was carried out in accordance with the STREGA (Strengthening The Reporting of Genetic Association Studies) guidelines, an extension of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, for candidate gene studies (Little et al., 2009).

Table 1
Demographic, prior lifetime history of mental disorders, earthquake-related variables and triallelic and biallelic genotypes frequencies of study participants by 12-month Post-traumatic stress disorder (PTSD) status.

Variables	No 12 PTSD N (%)	12 m PTSD N (%)	*p*-value[#]
Sex			
Male	154 (47.5)	4 (23.5)	
Female	170 (52.5)	13 (76.5)	0.053
Age (Mean, SD)	47.22 (16.332)	48.00 (14.794)	0.85
Ethnicity			
White/Caucasic	293 (90.4)	12 (70.6)	
Not white/caucasic	31 (9.6)	5 (29.4)	**0.02**[&]
Marital status			
Living with a partner	244 (75.3)	12 (70.6)	
Not living with a partner	80 (24.7)	5 (29.4)	0.66
Education			
Secondary or higher	123 (38.0)	3 (17.6)	
Primary or lower	201 (62.0)	14 (82.4)	0.09
Employment			
Working	172 (53.1)	4 (23.5)	
Not working	152 (46.9)	13 (76.54)	**0.02**
Any prior lifetime PTSD	4 (1.2)	8 (47.1)	< **0.005**
Number of any prior lifetime other anxiety disorders (Mean, SD)	0.10 (0.350)	0.53 (0.800)	**0.04**
Number of Any prior lifetime mood disorder (Mean, SD)	0.12 (0.341)	0.47 (0.514)	**0.01**
Number of any prior substance disorder (Mean, SD)	0.05 (0.274)	0.18 (0.529)	0.33
Number of any prior lifetime mental disorders (Mean, SD)	0.27 (0.677)	1.18 (1.334)	**0.01**
High Earthquake Exposure (HEE)[†]	154 (59.5)	13 (81.2)	**0.01**
High Emotional Impact (HEI)[‡]	189 (57.1)	14 (87.5)	**0.02**
Triallelic classification			
S'S'	108 (33.3)	5 (29.4)	
S'L'	154 (47.5)	7 (41.2)	
L'L'	62 (19.1)	5 (29.4)	0.58
Biallelic classification			
SS	96 (29.6)	5 (29.4)	
SL	160 (49.4)	7 (41.2)	
LL	68 (21.0)	5 (29.4)	0.68

[#] Chi-squared or Student-T test for categoric or continuous measures respectively.

[±] **Include:** student, homemaker, retired/disabled, unemployed and others different from working.

[†] **High Earthquake Exposure (HEE):** defined as those with an exposure score above the mean rate of the total sample.

[‡] **High Emotional Impact (HEI):** defined as those with an emotional impact above the mean rate of the total sample.

[&] **Fisher's exact test**.

3. Results

The vast majority (83.5%, $n = 344$) of the Lorca survey participants ($n = 412$, 71.0% response rate) provided a biological sample to facilitate genetic analyses. The remaining survey respondents (16.5%, $n = 68$) declined. The socio-demographic variables for the entire sample comparing both groups are presented in Supplementary table S1. The groups differed only in mean age and employment status, with those providing biological samples being younger and more likely to be employed than those who declined. DNA from three biological samples could not be genotyped due to very low DNA concentration levels. Thus, the final sample used in this study comprises the 341 people interviewed following the Lorca earthquakes for whom we had complete *5-HTTLPR* genotype data.

Description of socio-demographic variables, lifetime mental disorders prior to exposure, earthquake exposure description, and triallelic and the biallelic genotype frequencies are presented in Table 1. The global allele frequencies of the different alleles were: $S = 369$ (54.1%), $L_A = 18$ (2.6%) and $L_G = 295$ (43.3%). Both genotype classifications did not deviate from Hardy-Weinberg equilibrium ("triallelic" approach: *S'S'* = 113 (33.1%), *S'L'* = 161 (47.2%), *L'L'* = 67 (19.6%), $\chi^2_{,1\ df.} = 0.498$, p-value = 0.48; "biallelic" approach: *SS* = 101(29.6%), *SL* = 167 (49.0%), *LL* = 73 (21.4%), $\chi^2_{,1\ df.} = 0.066$, p-value = 0.80). Participants who had 12-month PTSD more often had another employment status (student, homemaker, retired/disabled and unemployed among others) different to working, had more lifetime PTSD antecedents, other anxiety, mood and substance disorders prior to the earthquakes and were more affected by exposure to the natural catastrophes, both regarding the number of stress-related events and the emotional impact secondary to exposure, than people without 12-month PTSD. No differences were found between either group as regards distributions of the "triallelic" and the "biallelic" *5-HTTLPR* genotype classification between both groups.

Table 2 summarizes the association between the variables with PTSD status with the "triallelic" approach in a bivariate model (M1) and multivariate model (M2). The only variable that remained significant following adjustment for socio-demographic, prior mental disorders and earthquake-related variables was lifetime history of PTSD prior to the earthquake's exposure. There was no significant main effect for earthquake exposure-related variables and *5-HTTLPR* "triallelic" genotype. A similar pattern was found with the "biallelic" genotype (supplementary Table 2).

Different gene-environment interaction models were analysed with the sequential inclusion of different interaction terms formed with the combination of *5-HTTLPR* genotype with earthquakes exposure-related measures (HEE and HEI) and the four prior lifetime mental disorders (PTSD, other anxiety, mood and substance disorders). Interaction terms were significant only in two models, specifically: the number of *L'* alleles x HEI (p-value = 0.027), and the number of *L'* alleles and other prior anxiety disorders (p-value = 0.027) (see Table 2). The same interaction pattern was found with the "biallelic" approach (number of *L* alleles x HEI, p-value = 0.026, and number of *L* alleles and other prior anxiety disorders, p-value = 0.027) (see supplementary Table 2).

Analysis of the association between the three different inheritance models of the *5-HTTLPR* genotype in the "triallelic" (per *L'* allele: adjusted OR (95%CI) = 1.81 (0.65; 5.02); *S' > L'*: 0.25 (0.06; 1.13) and *L' > S'*: 0.94 (0.20; 4.37) and the "biallelic" (per *L* allele: 1.73 (0.62; 4.78); *S > L*: 0.28 (0.06; 1.22) and *L > S*: 1.00 (0.21; 4.69) approach found no significant effect for any of the above.

Stratified analyses with a multivariate logistic regression adjusted for variables included in model 2 (M2) showed that the number of *L´* alleles does not influence the PTSD risk among persons who suffered low emotional impact (adjusted OR = 0.29; 95%CI: 0.02, 4.05) but did increase the risk among those suffering high emotional impact (adjusted OR = 4.84; 95%CI: 1.26, 18.64) and predicted an increased PTSD risk among those with no history of any anxiety disorder except for prior lifetime PTSD (3.74, 1.14; 12.07). A similar pattern was found with the number of L alleles. Stratified analyses with a multivariate logistic regression adjusted for variables included in model 2 (M2) showed a similar pattern among persons who suffered low emotional impact (aOR = 0.27; 95%CI: 0.02, 3.83) but increased PTSD risk among those suffering high emotional impact (aOR = 4.55; 95%CI: 1.19, 17.46) and an increased PTSD risk among those with no history of anxiety disorder except for prior lifetime PTSD (3.43, 1.07; 11.02). Limitations of the sample size did not allow for calculating the risk associated with two or more anxiety disorders.

4. Discussion

The aims of this study were to evaluate the association of the *5-HTTLPR* polymorphism and PTSD and to explore the moderation effect of this genotype on the PTSD risk associated to earthquake-related stressors and lifetime mental disorders prior to exposure in a representative sample of the general population exposed to the earthquakes of Lorca, 2011 (Murcia, Spain). The results suggest that the *5-*

Table 2
Association between risk factors and analyses of gene-environment interactions on the risk of 12-month Post-traumatic stress disorder (PTSD) status after the exposure to Lorca's earthquakes, 2011 with a triallelic *5-HTTLPR* genotype approach.

	Model M1 OR (95%CI)	Model M2 OR (95%CI)	Model M3 OR (95%CI)	Model M4 interaction 1 OR (95%CI)	Model M5 interaction 2 OR (95%CI)
High earthquake exposure (HEE)[†]	**4.42 (1.23; 15.81)***	5.11 (0.86; 30.24)	4.59 (0.76; 27.42)	6.06 (0.85; 43.02)	3.61 (0.62; 21.01)
High emotional impact (HEI)[‡]	**4.67 (1.04; 20.88)***	3.07 (0.49; 19.21)	3.28 (0.48; 22.20)	0.17 (0.01; 2.43)	3.62 (0.48; 27.32)
Any prior lifetime PTSD	**71.11 (18.05; 280.10)***	**70.38 (9.50; 521.58)***	**62.67 (8.60; 456.70)***	**176.49 (13.44; 2317.89)***	**71.50 (7.41; 690.09)***
Number of any prior lifetime other anxiety disorders	**3.74 (1.81; 7.76) ***	1.29 (0.26; 6.35)	1.21 (0.28; 5.27)	1.20 (0.26; 5.44)	0.01 (0.00; 1.37)
Number of any prior lifetime mood disorder	**4.97 (2.01; 12.28)***	1.47 (0.35; 6.14)	1.65 (0.38; 7.15)	1.65 (0.41; 6.65)	1.81 (0.35; 9.42)
Number of any prior substance disorder	2.27 (0.85; 6.06)	0.80 (0.14; 4.67)	0.98 (0.17; 5.71)	0.82 (0.12; 5.51)	0.78 (0.09; 6.70)
Number of *L´* alleles	1.32 (0.67; 2.60)	–	1.81 (0.65; 5.02)	0.12 (0.01; 1.42)	3.20 (0.91; 11.18)
Interaction: high emotional impact (HEI)-by-number of *L´* alleles	–	–	–	**33.83 (1.74; 657.86)***	–
Interaction: other anxiety-by-number of *L´* alleles	–	–	–	–	**45.69 (1.737; 1202.04)***

Model M1: each row represents a simple logistic regression model with 12-month PTSD as the dependent variable.
Model M2: M1 adjusted by sociodemographic variables (student, homemaker, retired/disabled, unemployed and others different from working) and prior mental disorders.
Model M3: the number of *L´* alleles is included in M2.
Model M4 Interaction 1: M3 including the interaction term created with the product of HEI and the number of *L´* alleles**.**
Model M5 Interaction 2: M3 including the interaction term between the number of *L´* alleles and the number of any prior lifetime other anxiety disorders.
[†] **High Earthquake Exposure (HEE):** defined as those with an exposure score above the mean rate of the total sample.
[‡] **High Emotional Impact (HEI):** defined as those with an emotional impact above the mean rate of the total sample.
* p-value < 0.05.

HTTLPR polymorphism had no main effect in predicting PTSD which is consistent with previous meta-analytic research where no direct association is described (Gressier et al., 2013; Fernando Navarro-Mateu et al., 2013). To analyse the impact of the earthquake exposure, two scores were measured: severity (HEE) and emotional impact (HEI) of the exposure. Contrary to our expectations and despite finding significant differences between participants who developed 12-month PTSD and those who did not in terms of high exposure and high emotional impact in the bivariate analyses, neither score remained significant in multivariate analyses. Unfortunately, we did not have data on previous emotion regulation skills or cognitive biases of participants that could confound the effect (Woud et al., 2017). The most consistent and strongest risk factor predicting PTSD is consistent with a recent cross-national epidemiological analysis of PTSD risk factors among people exposed to trauma in the context of the WHO World Mental Health (WMH) Surveys (Kessler et al., 2018), where only prior anxiety disorders significantly predicted PTSD in a multivariate model.

The *5-HTTLPR* genotype modulated the effect of the emotional impact of the earthquakes' exposure and of the history of previous anxiety disorders on the risk of PTSD, both with the tri- and biallelic functional classification of the polymorphism. L'L' and LL allele carriers were at higher PTSD risk. Three papers have analysed the *5-HTTLPR* x earthquake exposure (Li et al., 2019; Liu et al., 2017; Tian et al., 2015) and only one found a statistically significant G x E interaction with bialellic genotype (Tian et al., 2015). These interactions are broadly consistent with previous studies finding the *L* or *L'* alleles to be involved in the risk of PTSD instead of the *S* or *S'* alleles. A risk-reducing effect of the *SS* genotype has previously been described regarding chronic PTSD in motor-vehicle accident victims (Thakur et al., 2009) and in the development of re-experiencing and arousal symptoms of PTSD in two independent African American samples exposed to childhood emotional abuse (Walsh et al., 2014). Moreover, two other studies implicated *L'* or *L* alleles in G x E interactions predicting PTSD. The *L'* allele was found to interact with the number of trauma events in PTSD with a stronger effect in homozygous (Grabe et al., 2009). In the second study, the likehood of developing lifetime PTSD was dependent on genotype (Kolassa et al., 2010). While *SS* homozygous were at higher risk for developing PTSD regardless of the number of traumatic events, *SL* or *LL* carriers showed an S-shaped dose-response relationship with the increased number of traumas. However, only a trend towards an interaction between genotype polymorphisms and number of traumatic events experienced was found. It is possible that participants with those antecedents were more prone to higher emotional impact after such exposure, though this possibility could not be confirmed in an exploratory bivariate analysis in our sample (results not presented). The risk of developing PTSD following stressful exposure has previously been described as being mediated by pre-existing psychopathology, including panic or generalized anxiety disorder (Koenen et al., 2002).

PTSD offers unique opportunities to study G x E interactions in psychiatry (Koenen et al., 2008, 2009b) but also brings enormous challenges. This mental disorder has been considered a complex and heterogeneous phenotype comprising a combination of symptom dimensions potentially influenced by different G x G, G x E and/or E x E interactions (Smoller, 2016; Yehuda et al., 2015), and by even more complex interaction models (e.g. G x G x E or G x E x E interactions) (Mehta and Binder, 2012). An important limitation of PTSD studies is the great heterogeneity in the index trauma analysed as this influences the consequent PTSD conditional risk (Kessler et al., 2018, 2014). The study of PTSD after exposure to an earthquake has at least, two advantages: i) it limits variability in the index trauma exposure, and ii) reduces the possibility of a gene-by-environment correlation (rGE), where genetic variants influencing the disorder risk may act through the effect of exposure to index traumas (Koenen et al., 2008; Mehta and Binder, 2012). Research on psychological consequences following an earthquake is extremely complicated because of the specific difficulties involved in complex logistic organization required to begin a survey after an unpredicted disaster (Kessler et al., 2008). In addition, high heterogeneity has been found in published literature related to characteristics: (i) of the disaster exposure, such as type of trauma, timing, intensity and/or duration of the trauma; (ii) of the exposed population, including the region/country affected and group-level environmental factors, such as social support or crime and unemployment rates; and (iii) different methodological issues, such as study design, power and sample size and diagnostic instruments selected (Bromet and Dew, 1995; Galea et al., 2008; Kilpatrick et al., 2007; Koenen et al., 2009a, 2008).

Several strengths of the study should be highlighted. First, it was performed in a representative sample of the general population from

Lorca (F. Navarro-Mateu et al., 2013; Navarro-Mateu et al., 2017). The target population was selected before the earthquake occurred in Lorca with a response rate of 71% of participants, above the 60% conventionally considered as a minimum standard in general population surveys (Johnson and Wislar, 2012). There were only slight differences (mean age and employment status) between those who provided biological samples (85%) and those who declined (16.5%), and these were apparently unrelated to genotype or disease status. Thus, the data seems to have a good external validity. Second, a careful evaluation of the prior history of mental disorders together with other sociodemographic variables allowed a comprehensive control for potential confounders. This is more important in the context of shared genetic effects between PTSD and other disorders (Duncan et al., 2018). Finally, both, the "triallelic" and "biallelic" approaches were considered in the analyses. Nevertheless, some limitations deserve careful consideration. First, DSM-IV diagnoses of PTSD and prior lifetime mental disorders were based on a fully structured lay-administered interview, the CIDI 3.0, rather than semi-structured clinical interviews. However, this has been evaluated with a moderate-to-excellent concordance with diagnosis of most mental disorders (Haro et al., 2006; Kessler et al., 2004) and the instrument has been widely used in epidemiologic surveys of general populations all over the world (Kessler and Ustun, 2004). Second, some concerns about population stratification could be raised as the method used to evaluate ethnicity was not based on genetic markers but on declared ethnicity. All statistical analyses were adjusted to control for differences found in declared ethnicity. Third, other environment variables might have obscured other potential interactions, such as the history of childhood adversities (Kessler et al., 2010; Walsh et al., 2014; Zhao et al., 2017), previous stressful life events (Kessler et al., 2018), specific personality traits (e.g. neuroticism and/or resilience) (Aburn et al., 2016; Munafo et al., 2006) or epigenetic mechanisms such as the level of methylation (Koenen et al., 2011). Future studies should explore their modulation effect as this is the first genetic analysis in our sample. Fourth, the cross-sectional design limits the interpretation of the associations found being causal and might explain the heterogeneity of results. More longitudinal designs (Li et al., 2019) are needed. Finally, the relatively small sample size and the investigation of a number of interactions raise the possibility that the observed significant interactions might fail to replicate in future studies, although the broad consistency of these with the results of other studies suggests that they might be stable. Future research would be needed to investigate this issue.

The risk of developing PTSD after the exposure to the earthquakes of Lorca is influenced by the previous PTSD history and the emotional impact of the experience and the previous history of anxiety disorders are modulated by the *5-HTTLPR* genotype. Therapeutic interventions to prevent mental disorders after exposure to earthquakes should focus on people at higher risk and our study shows that this should particularly include those with a higher direct exposure to the natural disaster and those with a prior history of mental disorders. Nowadays, to identify genetic biomarkers that would enable distinguishing between persons at high or low risk of developing PTSD after trauma exposure, more independent replicative studies with larger samples, future up-date or new meta-analyses with the *5-HTTLPR* or other candidate genes, and large genome-wide association (GWAS) studies are needed to improve our knowledge of the etio-pathogenesis of the PTSD phenotype (Koenen et al., 2008; Logue et al., 2015).

5. Role of the funding source

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6. Data sharing statement

The de-identified minimal dataset needed for only monitoring purposes will be made available on request due to ethical restrictions in the signed agreements with the WHO WMH Survey Initiative.

Declaration of Competing Interest

Dr. Kessler has served on advisory boards for Mensante Corporation, Plus One Health Management, Lake Nona Institute, and U.S. Preventive Medicine, is a co-owner of DataStat, Inc. In the past three years, Dr. Kessler has been a consultant for Hoffman- La Roche, Inc., Johnson & Johnson Wellness and Prevention, and Sonofi-Aventis Groupe. There are no patents, products in development or marketed products to declare. Preliminary results of this study were presented as a poster at the XVI World Congress of the World Psychiatry in Madrid, Spain, in September 2014; at XIX National Congress of Psychiatry in Palma de Mallorca, in October 2016; and at XVII SESPAS Congress ("Ciencia para la Acción") in Barcelona, Septembre 2017.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112640.

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