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Preliminary communication

Examining the relation between the serotonin transporter 5-HTTPLR genotype x trauma exposure interaction on a contemporary phenotypic model of posttraumatic stress symptomatology: A pilot study

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ABSTRACT

Background: Little is known about the specificity of the interaction of serotonin transporter 5-HTTLPR genotype x trauma exposure in relation to contemporary structural models of PTSD symptomatology, which suggest that 4- or 5-factor models provide a better representation of the phenotypic expression of this disorder.

Methods: One hundred forty-nine respondents of a representative sample of adults affected by Hurricane Ike were interviewed 2–5 months after this 2008 disaster.

Results: After adjustment for age, sex, and ancestral proportion scores, the interaction of 5-HTTPLR genotype x trauma exposure was significantly associated with both severity ($\beta = .40$, $p < .001$) and probable diagnosis (*Wald* = 4.55, $p = .033$; odds ratio = 3.81, 95% *CI* = 1.11–13.03) of Ike-related PTSD. Respondents with the low-expression variant of the 5-HTTPLR polymorphism (S allele carriers) who were highly exposed to Hurricane Ike reported significantly greater severity of PTSD symptoms and were more likely to screen positive for PTSD than respondents homozygous for the L allele who were highly exposed to Hurricane Ike. Confirmatory factor analyses revealed that a 5-factor model of intercorrelated re-experiencing, avoidance, numbing, dysphoric arousal, and anxious arousal symptoms provided the best structural representation of PTSD symptomatology. The 5-HTTPLR genotype x exposure interaction was significant only for anxious arousal ($\beta = .44$, $p < .001$) and re-experiencing ($\beta = .35$, $p < .001$) symptoms, but not avoidance, numbing, or dysphoric arousal symptoms (all βs $\leq .20$, all ps $> .13$).

Limitations: The small sample size and employment of self-report measures may limit generalizability of these findings.

Conclusions: Results of this pilot study suggest that the low-expression variant of the 5-HTTLPR polymorphism modifies risk for PTSD, but that this effect may be specific to anxious arousal and re-experiencing symptoms.

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1. Introduction

Posttraumatic stress disorder (PTSD) is one of the most prevalent and disabling psychiatric disorders associated with exposure to disasters (Galea et al., 2005; Norris et al., 2002a, 2002b). The 5-HTTPLR variant mapped to the promoter region of the serotonin transporter (5-HTT) gene *SLC6A4* has received considerable attention as a possible genetic risk factor for PTSD, with several studies demonstrating that the genotypes at this locus that are associated with lower gene expression (i.e., those containing one or more copies of the S allele) may moderate the relation between severity of trauma and stressful life event exposures and risk for PTSD (e.g., Kilpatrick et al., 2007; Koenen et al., 2009; Xie et al., 2009, 2012); however, some studies have found that the high expression allele may moderate this association (e.g., Grabe et al., 2009; Thakur et al., 2009).

One notable gap in the literature on the role of the 5-HTTLPR genotype in moderating the relation between trauma exposure and risk for PTSD is that little is known about the specificity of the 5-HTTLPR x trauma exposure interaction in relation to the clinical phenomenology of PTSD. PTSD is a heterogeneous disorder characterized by symptoms of re-experiencing, avoidance/numbing, and

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hyperarousal symptoms. Recent confirmatory factor analytic (CFA) studies have consistently demonstrated that more refined 4- or 5-factor models provide a significantly better representation of the structure of PTSD symptoms than the DSM-IV model (Elhai et al., 2011; Elhai and Palmieri, 2011; Yufik and Simms, 2010). These models include the 4-factor dysphoria model, which is comprised of separate clusters of re-experiencing, avoidance, dysphoria, and hyperarousal symptoms; and the 4-factor emotional numbing model, which is comprised of re-experiencing, avoidance, numbing, and hyperarousal symptoms. Given that the only difference between these two 4-factor models is the assignment of three symptoms (i.e., sleep disturbance, anger/irritability, and concentration difficulties), Elhai et al. (2011) recently evaluated and found support for a novel, 5-factor model that separates the DSM-IV hyperarousal symptom clusters into dysphoric arousal (i.e., sleep difficulties, anger/irritability, and concentration problems) and anxious arousal (i.e., hyperviligance, exaggerated startle response). This separation of the hyperarousal cluster is based on a theoretical model proposed by Watson (2005), which describes arousal symptoms characterized by restlessness and agitation (e.g., irritability) as distinct from those characterized by fear-based, panic-like symptoms (e.g., exaggerated startle response).

A growing number of CFA studies has since demonstrated that this 5-factor model provides a significantly better representation of PTSD symptom dimensions than the DSM-IV or 4-factor models in a broad range of trauma-exposed samples (Armour et al., 2012; Elhai et al., 2011; Pietrzak et al., 2012a, 2012b; Wang et al., 2011a, 2011b, 2011c, 2012a, 2012b). However, no study of which we are aware has evaluated whether the 5-HTTLPR x trauma exposure interaction may be differentially related to these dimensions of PTSD symptomatology. Several neuroimaging studies have found that the 5-HTTLPR S allele is associated with amygdala hyperreactivity (e.g., Hariri et al., 2002) and dysregulation of amygdala–cingulate circuitry (e.g., Pezawas et al., 2005). Thus, it is reasonable to expect that individuals with the low expression variant of the 5-HTTLPR polymorphism who are highly exposed to trauma may experience greater severity of PTSD symptoms characterized by hyperreactivity and/or emotion dysregulation, such as anxious arousal. Further, in light of neuropsychological data suggesting that the low expression variant of the 5-HTTLPR polymorphism is associated with an attentional bias toward negative stimuli (Beevers et al., 2009; Pergamin-Hight et al., 2012), it is also reasonable to expect that these individuals may experience greater severity of re-experiencing symptoms.

The purpose of this pilot study was to evaluate whether the 5-HTTLPR x trauma exposure interaction is differentially related to the expression of CFA-derived PTSD symptom dimensions in a sample of individuals who were recently exposed to a large-magnitude natural disaster. Based on prior research (Kilpatrick et al., 2007; Koenen et al., 2009; Xie et al., 2009, 2012), we hypothesized that the low expression 5-HTTPLR genotype would moderate the association between disaster exposure and PTSD such that individuals with one or two copies of the S allele would have greater severity of and likelihood of developing PTSD than individuals homozygous for the L allele. We further expected that this interaction would be differentially associated with PTSD symptoms characterized by hyperreactivity and negative attentional bias, such as anxious arousal and re-experiencing symptoms.

2. Methods and materials

2.1. Sample

Adults aged 18 or older who had been living in Galveston County or Chambers County, Texas, for at least one month before September 13, 2008, when Hurricane Ike made landfall, participated in this study. Details regarding sampling and recruitment procedures are available elsewhere (Norris et al., 2010). Briefly, a disproportionate stratified cluster sampling was employed to acquire samples in areas that experienced more damage from Hurricane Ike and that were more likely to be exposed to hurricane-related traumas. Interviews were conducted by experienced interviewers at the University of Michigan Institute for Social Research using a computer-assisted interview system. Within 1 week of completing an interview, each respondent was mailed a packet that included an invitation to participate in an additional component of the study; this packet included consent documents, a brief questionnaire, and a saliva collection kit that was labeled with an anonymous ID unique to the respondent. Standard protocols were employed to obtain saliva samples (e.g., Kilpatrick et al., 2007). Of the 658 individuals who completed an interview, 163 (24.8%) returned a saliva sample. Compared to respondents who did not return a sample, respondents who did return a sample were more likely to be older, White/non-Hispanic, and more highly educated; they did not differ with respect to sex, marital status, or household income. For the current study, complete data were available for 149 respondents; missing data were due to no consent card being included with the sample ($n=9$); and/or leaking of or too little sample returned ($n=5$). This study was approved by institutional review boards of each of the participating academic institutions.

2.2. Genotyping

DNA was extracted from saliva OriGene kits (DNA Genotek). The functional polymorphism in the 5′ flanking regulatory/promoter region of the gene (*SLC6A4*) coding for the serotonin transporter protein was studied. This polymorphism (5-HTTLPR) has two common alleles: long (16 repeats) and short (14 repeats); other alleles have also been identified (Gelernter et al., 1997). Genotyping was performed with polymerase chain reaction followed by size fractionation (Gelernter et al., 1997) with prior *Mspl* restriction endonuclease digestion for triallelic classification (Stein et al., 2006), which allowed classification of long alleles into L_A and L_G. Thirty four additional short tandem repeat markers were genotyped to provide ancestry information (Yang et al., 2005).

Genotype frequencies for the 5-HTTLPR polymorphism, which were classified triallelically, were reclassified based on their transcriptional efficiency: L_A/L_A were classified as L′/L′. L_A/S and L_A/L_G were classified as L′/S′. L_G/L_G, L_G/S, and S/S were classified as S′/S′. Based on this classification, 30 (20.5%) of the full sample had the L′/L′ genotype, 68 (46.6%) had the L′/S′ genotype, and 48 (32.9%) had the S′/S′ genotype; three subjects had an extra long allele and were excluded from this study. L′/L′, L′/S′, and S′/S′ genotype frequencies did not differ from the Hardy–Weinberg equilibrium, $\chi^2=.43$, $p=.51$. Among European Americans, these frequencies were 22.1%, 45.2%, and 32.7%; among Non-European Americans, these frequencies were 20.0%, 54.3%, and 25.7%. In both groups, these frequencies did not differ from the Hardy Weinberg equilibrium, $\chi^2=.77$, $p=.38$ and $\chi^2=.27$, $p=.60$, respectively. Genotype frequencies did not differ by race in this small sample, $\chi^2=.92$, $p=.63$. We also genotyped an STR panel of ancestry informative markers and computed ancestry proportion scores by means of STRUCTURE (Pritchard and Rosenberg, 1999). Ancestral proportions did not differ between respondents with and without PTSD ($t=1.66$, $p=.12$).

2.3. Hurricane Ike exposure

Respondents were asked about their experiences during and after Hurricane Ike. These experiences included: (1) threat to