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Gene-by-social-environment interaction (*GxSE*) between *ADCYAP1R1* genotype and neighborhood crime predicts major depression symptoms in trauma-exposed women

Sarah R. Lowe, Ph.D.^a, John Pothen, B.S.^b, James W. Quinn, M.A.^a, Andrew Rundle, Dr.P.H.^a, Bekh Bradley, Ph.D.^{c,d}, Sandro Galea, M.D., Dr.P.H.^e, Kerry J. Ressler, M.D., Ph.D.^d, and Karestan C. Koenen, Ph.D.^a

^aDepartment of Epidemiology, Columbia University Mailman School of Public Health, New York, NY

^bM.D./Ph.D. Program, Emory University School of Medicine, Atlanta, GA, USA

^cMental Health Service Line, Atlanta Veterans Affairs Medical Center, Decatur, GA

^dDepartment of Psychiatry, Emory University School of Medicine, Atlanta, GA, USA

^eDepartment of Epidemiology, Boston University School of Public Health, Boston, MA, USA

Abstract

Background—Few studies have explored interactions between genes and social environmental exposures (*GxSEs*) for trauma-related psychopathology, including symptoms of posttraumatic stress (PTS) and major depression (MD). The extant literature suggests the possibility of a *GxSE* between the rs2267735 variant of the *ADCYAP1R1* gene and neighborhood crime. The current study aimed to explore this possibility among a predominantly African American sample of trauma-exposed women.

Methods—Female participants ($N = 1361$) were recruited from a public hospital, and completed measures of PTS and MD symptoms and provided DNA samples. Participants' home addresses were mapped onto 300 neighborhoods (2010 census tracts), and data on crime within neighborhoods was collected.

Results—Multilevel models detected a significant *GxSE* between rs2267735 and neighborhood crime for MD symptoms ($p = .01$). Having two copies of the risk (C) allele was associated with higher MD symptoms for participants living in high-crime neighborhoods.

Limitations—At least six limitations are noteworthy: (1) low statistical power; (2) use of self-report symptom inventories; (3) lack of information on symptom onset; (4) homogeneous sample

Correspondence, Sarah R. Lowe, Ph.D., Department of Epidemiology, Columbia University Mailman School of Public Health, 722 West 168th Street, Room 720-F, New York, NY 10032, USA; Phone: (212) 305-6706; Fax: (212) 305-9413; srl2143@cumc.columbia.edu.

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from a single metropolitan area; (5) non-specific index of crime; and (6) use of census tracts to define neighborhoods.

Conclusions—The results provide further evidence of *GxSEs* for psychiatric outcomes among trauma-exposed populations. Further investigations of genetic factors for trauma-related psychopathology should include careful assessments of the social environment.

Keywords

Posttraumatic stress; major depression; genetic risk; social environment; gene-by-social-environment interactions; neighborhood crime; multilevel modeling

Introduction

Exposure to traumatic events is associated with a range of adverse psychiatric consequences, including symptoms of posttraumatic stress (PTS) and major depression (MD) (Lowe et al., 2015). Several risk factors for higher PTS and MD symptoms have been identified, including genetic variants (*G*; Dunn et al., 2015; Skelton et al., 2012), individual environmental exposures (*E*; e.g., child abuse; Carr et al., 2013), and social environmental exposures (*SE*; e.g., neighborhood segregation; Lee, 2009). A growing body of literature has investigated interactions between genes and individual environmental exposures (*GxEs*) as predictors of both outcomes (e.g., Dunn et al., 2015; Skelton et al., 2012). Comparatively fewer studies have explored the joint influence of genes and social environmental exposures (*GxSEs*; e.g., Uddin et al., 2010, 2011).

One gene that might be involved in *GxSEs* for PTS and MD symptoms is *ADCYAP1R1*. *ADCYAP1R1* encodes PAC1, the receptor for pituitary adenylate cyclase-activating polypeptide (PACAP), which has been implicated in stress response processes (Hashimoto et al., 2006) and PTS symptoms in females (Ressler et al., 2011). Two prior studies found that, controlling for comorbid symptoms, the risk for higher PTS associated with the rs2267735 variant of *ADCYAP1R1* was enhanced among women with more extensive trauma histories, whereas this *GxE* was non-significant for MD symptoms (Almli et al., 2013; Uddin et al., 2013). Another study suggested that *GxSEs* with *ADCYAP1R1* might have broader effects on trauma-related psychopathology (Roman et al., 2014). In this study, signaling of PACAP in a stress-related limbic structure through PAC1 receptors was associated with increased anxious behaviors and weight loss, and decreased food intake among rodents in a chronic stress, versus control, condition.

Living in a high-crime neighborhood represents a chronic stressor for human populations, and has been found to increase risk for mood and anxiety disorders (Stockdale et al., 2007). A previous study documented a significant *GxSE* with neighborhood crime among a predominantly White sample of natural disaster survivors, such that the risk for PTSD associated with the serotonin protein gene promoter variant was enhanced for participants living in high-crime neighborhoods (Koenen et al., 2009). Yet, it remains unclear whether this relationship extends to *ADCYAP1R1*, survivors of a broader range of traumatic events, and ethnic minority samples.

In summary, the extant literature suggests the possibility of a $G \times SE$ between the rs2267735 variant of *ADCYAP1R1* and neighborhood crime for PTS and MD symptoms. In the current study, we tested this possibility among a predominantly African American sample of trauma-exposed women.

Methods

Participants and Procedures

Participants were recruited from the primary care and obstetrics gynecology clinics at a public hospital in Atlanta, Georgia. Participants completed a survey that included measures of PTS and MD symptoms, administered verbally due to the relatively high rates of impaired literacy in the community served at the hospital. The battery took 30–90 minutes to complete, and participants were offered \$15 for their participation. The appropriate Institutional Review Boards approved the study, and participants provided written informed consent.

The current study included 1361 trauma-exposed female participants who provided complete data on all study variables. The sample was majority African American (94.1%). On average, participants were 37.47-years old ($SD = 13.30$; Range: 18–74).

Measures

Lifetime Trauma Exposure—Participants completed a screener of lifetime trauma exposure, the Traumatic Events Inventory (TEI; Schwartz et al., 2005). Participants indicated whether they had ever experienced 14 potentially traumatic events (e.g., child physical abuse, serious accident or injury), and feelings of terror, horror, or helplessness during such events.

PTS symptoms—PTS symptoms were assessed via the Posttraumatic Symptom Scale-Interview Version (PSS-I; Foa et al., 1993). The PSS consists of 17 items corresponding PTSD symptoms as specified in the Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision; *DSM-IV-TR* (American Psychiatric Association, 2000). Participants rated the extent to which they experienced each symptom (e.g., “Have you been having recurrent bad dreams or nightmares about the trauma?”) over the prior two weeks from 0 (*not at all*) to 3 (*5 or more times per week*), and a symptom severity score was computed as the sum of all ratings. The PSS-I has been shown to have high internal consistency, inter-rater reliability, and validity (Foa and Tolin, 2000) ($M = 13.12$, $SD = 12.40$, Range: 0–51; $\alpha = .92$).

MD symptoms—The Beck Depression Inventory-II (BDI; Beck et al., 1996) assessed MD symptoms. The BDI consists of 21 items corresponding to *DSM-IV-TR* symptoms of major depressive disorder. For each item, participants indicate which of four statements best describes the way they have been feeling over the past two weeks. Each statement has a corresponding score, ranging from 0 (e.g., “I do not feel sad”) to 3 (e.g., “I am so sad or unhappy that I can’t stand it”). A symptom severity score was computed as the sum of all ratings. The BDI-II has had evidence of reliability, internal consistency, and validity across

a wide variety of samples, including primary care medical patients (Arnau et al., 2001) ($M = 14.91$, $SD = 12.36$, Range: 0–58; $\alpha = .93$).

Neighborhood crime—Participants' geocoded home addresses were mapped onto 2010 census tracts ($n = 300$) and data on crime within tracts were collected from the CrimeRisk 2010 (Applied Geographic Solutions, 2010). Values are relative to the national average, which is set at 100. For example, a value of 200 would mean that the tract had twice the amount of crime as the national average, and a value of 50 would mean that the tract had half the amount of crime as the national average. Crimes included within this index are murder, rape, assault, robbery, burglary, larceny, and motor vehicle theft. The crime variable was divided by its interquartile range at the community-level ($IQR = 344$) prior to entry into the analysis to facilitate interpretation. In the analysis, each unit increase in crime is therefore equivalent to the difference between the 25th percentile neighborhood and the 75th percentile neighborhood ($M = 267.53$, $SD = 234.54$, Range: 5–892).

Genotyping—Participants provided DNA samples from blood or saliva samples. Further details on DNA collection have been published previously (*masked for blind review*). Briefly, samples were genotyped using both Sequenom (Sequenom Inc., San Diego, CA) and Taqman (Applied Biosystems Inc., Foster City, CA). The rs2267735 SNP passed quality control filters (call rate > 95%, minor allele frequency > 0.01, Hardy-Weinberg disequilibrium $P > 1 \times 10^{-6}$). Genotypic frequencies were as follows: G/G: 11.7% ($n = 159$); G/C: 46.1% ($n = 627$); C/C: 42.2% ($n = 575$). To be consistent with the two prior studies documenting *GxEs* with rs2267735 (Almli et al., 2013; Uddin et al., 2013), we assumed an additive genetic effect, such that the number of risk (C) alleles was included in statistical models.

Data Analysis

Analyses were conducted in Mplus 7.1 (Muthén & Muthén, 1998–2012). Prior to analyses fulfilling study aims, we estimated the bivariate association between rs2267735 and crime, which could potentially undermine the interpretation of a significant *GxSE* (Dick, 2011). The association was non-significant ($Coeff. = .01$, $SE = .03$, $p = .69$).

Subsequently, multilevel models predicting PTS and MD symptoms, with participants nested in census tracts, were conducted. Model 1 for each outcome included the main effects of the number of rs2267735 C alleles, demographics (age, self-reported African American ethnicity) and comorbid symptoms at the individual-level, and crime at the neighborhood-level. Comorbid symptoms were MD symptoms in the model predicting PTS symptoms, and PTS symptoms in the model predicting MD symptoms. Model 2 for each outcome included the addition of a cross-level interaction between the number of risk alleles and crime. We present nominally significant results ($p < .05$) and note whether they held with a Bonferroni correction for the number of outcomes being analyzed ($\alpha/2$; $p < .025$). Unstandardized results are listed, as standardized coefficients are unavailable in multilevel modeling in Mplus 7.1.

Results

Table 1 shows the results of the multilevel analyses. For PTS, having more copies of the rs2267735 C allele was a nominally significant predictor of higher PTS ($p = .04$), and higher MD symptoms a significant predictor of higher PTS symptoms after Bonferroni correction ($p < .001$) in Model 1. In Model 2, the cross-level association between rs2267735 and neighborhood crime was non-significant ($p = .44$).

For MD symptoms, older age and higher PTS were significant predictors of higher MD symptoms after Bonferroni correction (both $p < .001$) in Model 1. In Model 2, the cross-level interaction between rs2267735 and crime was statistically significant after Bonferroni correction ($p = .01$). To illustrate the interaction, mean levels of MD symptoms were computed in the individual-level data file for participants 0, 1, and 2 copies of the rs2267735 C allele, living in neighborhoods with high- versus low-levels of crime (defined as one standard deviation or more above or below the mean, respectively). As shown in Fig. 1, having two copies of the C allele was associated with risk for higher MD symptoms for participants living in high-crime neighborhoods.

Discussion

We found a significant *GxSE* between the rs2267735 variant of the *ADCYAP1R1* gene and neighborhood crime for MD symptoms among trauma-exposed women. Higher MD symptoms were observed among women carrying two copies of the C allele who were living in high-crime neighborhoods.

The results aligned with prior research showing *GxEs* including this variant for trauma-related psychopathology (Almli et al., 2013; Uddin et al., 2013). They extend this research by using a social environmental exposure, showing a significant *GxSE* for MD symptoms. The pattern of results was inconsistent with the previous study showing a *GxSE* with neighbourhood crime to be predictive of PTS symptoms (Koenen et al., 2009). The discrepancy is likely due to differences between the two samples (e.g., in demographic characteristics, trauma histories), as well as in the genetic variants included.

Future research is needed to replicate the results and provide an understanding of the biological mechanisms that underlie them. For example, prior research has implicated reactivity of the hippocampus and amygdala, and functional connectivity between these structures, as mediating the relationship between *ADCYAP1R1* and women's trauma-related psychopathology (Stevens et al., 2014). Future investigations could explore these processes among women living in high- and low-crime neighborhoods. Additionally, further analyses could explore *GxSEs* with other social environmental exposures that have been shown to influence trauma-related psychopathology in African Americans, including neighborhood racial composition and poverty (e.g., Dallaire et al., 2008; Wright et al., 2005). Taken together, these lines of research could help identify African American women most likely to experience trauma-related psychopathology based on the combined presence of genetic and social environmental risks, and inform efforts to prevent and reduce trauma-related symptoms through biological and psychosocial interventions.

At least six limitations of the study are worth noting. First, the sample was relatively small, limiting statistical power. Second, symptoms were assessed using self-report inventories, which are not substitutable for clinician assessments. Third, we did not have information on symptom onset, for example whether onset occurred preceded or followed participants' residence in their current neighborhoods. Fourth, the study was conducted in a homogeneous sample. However, this sample has high rates of trauma-related psychopathology, increasing the public health relevance of the research (Gillespie et al., 2009). Ethnic homogeneity was also advantageous in the current study, given that genetic variants have been associated with different patterns of risk among different ethnic groups and that population stratification can lead to spurious GxE findings (Nugent et al., 2011). Fourth, the index of crime included a range of personal and property crimes, and it is unknown whether one or more of these drove the significant cross-level interaction. Lastly, neighborhoods were defined by census tracts, which perhaps do not reflect participants' perceived neighborhoods.

Despite these limitations, these findings contribute to research on genetic and environmental risk for trauma related psychopathology. To date very few genetic studies examine social environment, despite its importance in risk for trauma related psychopathology. The results provide further evidence that social environmental exposures can shape genetic risk for psychiatric outcomes among trauma-exposed populations. Further investigations of genetic factors for trauma-related psychopathology should therefore include careful assessments of the social environment.

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Research Highlights

- Genes and the social environment shape risk for trauma-related psychopathology.
- Few studies have explored gene-by-social-environment interactions (*GxSEs*).
- Female participants ($N = 1361$) completed surveys and provided DNA samples.
- A significant *GxSE* between the *ADCYAP1R1* gene and neighborhood crime was found.
- Genetic risk for depression was enhanced for women in high-crime neighborhoods.

Figure 1. Decomposition of cross-level interaction between neighborhood crime and rs2267735 in predicting major depression symptoms

N = 1361 female participants living in 300 neighborhoods (2010 census tracts). MD = major depression. High and low crime neighborhoods are defined as one standard deviation or more above or below the mean, respectively.

Table 1

Results of Multilevel Level Models Predicting Posttraumatic Stress and Major Depression Symptoms

	PTS Symptoms		MD Symptoms	
	Model 1	Model 2	Model 1	Model 2
	<i>Coeff. (SE)</i>	<i>Coeff. (SE)</i>	<i>Coeff. (SE)</i>	<i>Coeff. (SE)</i>
<i>Individual-level</i>				
Age	−02 (.02)	−02 (.02)	.06 (.02)***	.05 (.03)
African American	−1.78 (1.17)	−1.84 (1.17)	−46 (1.08)	−1.37 (2.73)
Comorbid symptoms	.71 (.02)***	.71 (.02)***	.70 (.02)***	.69 (.03)***
rs2267735	.74 (.36)*	1.15 (.63)	−38 (.32)	−1.46 (1.45)
<i>Community-level</i>				
Crime	.10 (.38)	.10 (.38)	−06 (.35)	−09 (.73)
<i>Cross-level</i>				
rs2267735×crime	--	−42 (.54)	--	1.20 (.48)*

Note. *N* = 1361 female participants nested in 300 neighborhoods (2010 census tracts). PTS = Posttraumatic Stress, MD = Major Depression, *Coeff.* = Coefficient, *SE* = Standard Error.

Results in boldface held after a Bonferroni-correction of $\alpha/2$ ($p < .025$).

*
 $p < .05$,

**
 $p < .01$,

 $p < .001$