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The Role of Social Environment and Gene Interactions on Development of Posttraumatic Stress Disorder

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Among 590 hurricane-exposed Floridians, the serotonin transporter genotype, 5-HTTLPR, was associated with decreased risk of posttraumatic stress disorder (PTSD) in county-level low-risk environments (low crime/unemployment rates) but increased PTSD in county-level high-risk environments (Koenen et al., 2009). These results suggest genetic vulnerability to PTSD may be affected by environmental settings. The current study replicates Koenen's by examining if genetic vulnerability is affected by recovery environment among 55 female sexual assault survivors. It was hypothesized that the s' allele of the 5-HTTLPR polymorphism would evidence fewer PTSD symptoms among those in low-risk environments, and, conversely, increased PTSD symptoms among those in high-risk environments. The D2 dopamine receptor gene DRD2 (rs6277 and rs6279) and the FKBP5 (rs3800373 and rs1360780) gene regions were also explored. Hierarchical regression analyses revealed that while none of the five gene regions yielded statistically significant results predictive of PTSD, trends for the interaction between the 5-HTTLPR region of SLC6A and environment in predicting probable PTSD were inconsistent with results observed in previous studies. It is unclear to what extent genetic characteristics of the 5-HTTLPR region of SLC6A4 influence PTSD outcomes when considering social environment. Future studies should consider alternative group-level settings among other trauma-exposed populations.

Koenen and colleagues (2009) implemented a unique approach to analyzing how gene-environment interactions influence posttraumatic stress disorder (PTSD). Instead of investigating the effect of individual-level characteristics (e.g., social support), group-level, social community characteristics were examined (i.e., zip code level crime and unemployment rates). This study found that genetic characteristics may influence PTSD vulnerability among a hurricane-exposed sample. The results of this study suggest that group-level characteristics should be further evaluated among other trauma survivors to determine if this association is unique to community based events, or if individual traumatic events culminating in posttraumatic symptoms demonstrate the same pattern.

An association between the serotonin transporter gene (SLC6A4) and PTSD has been noted in numerous studies (Bryant et al., 2010; Grabe et al., 2009; Kilpatrick et al., 2007; Morey et al., 2011; Thakur, Joober, & Brunet, 2009; Xie et al., 2009). Various other genes related to the stress response system have been linked to PTSD stemming from both collective and individualized events, too. For example, Voisey et al. (2009) reported that the D2 dopamine receptor (DRD2) was associated with PTSD among war veterans, while Binder et al. (2008) demonstrated that four single nucleotide polymorphisms (SNP's) of FKPB5 interacted with severity of child abuse as a predictor of adult PTSD symptoms. Additionally, the risk or resilience of particular genotypes has been investigated and is undetermined. For example, although there is evidence that the 's' allele of the 5-HTTLPR polymorphism in SLC6A4 is often associated with affective disorders (Bryant et al., 2010; Kilpatrick et al., 2007; Koenen et al, 2009), results are inconsistent (Thakur et al., 2009).

At the time of the current study's data collection, the strongest candidate genes for PTSD included D2 dopamine receptor (DRD2 rs6277 and rs6279), four single nucleotide polymorphisms (SNP's) of FKBP5 (rs3800373 and rs1360780), and the 5-HTTLPR region of SLC6A4. Given the dearth of data examining gene-social environment interactions in studies of PTSD, the aim of this investigation was to determine if the impact of genes on PTSD symptoms among rape survivors is affected by social environments. It is hypothesized that social environment will modify the relationship between genetics and PTSD symptoms, assessed two months after a sexual assault, such that low-risk environments (i.e., low crime/unemployment rates) will be less indicative of probable PTSD than high-risk environments (i.e., high crime/unemployment rates).

Method

Participants

Data are drawn from a larger study examining the effectiveness of a brief video intervention on symptoms post sexual assault. One hundred seventy-nine female sexual assault survivors were recruited within 120 hours of the assault during a physical evaluation by a Sexual Assault Nurse Examiner (SANE) at a local hospital. Prospective participants were excluded if they were not at least 18 years of age, were not English speakers (i.e., video intervention available in English only) and/or if their mental capacity was diminished (e.g., by the use of drugs or alcohol). At two months, the current study retained 105 of the initial 179 participants, but ultimately only 55 provided all the data needed for the analyses. Participants were dropped from analyses if they were missing all genetic data (n = 9), failed to provide zip codes (n = 20), and/or if information about the zip code

was not usable or accessible through the online resource (n = 21). Those retained in the analyses did not differ in any systematic way from those suspended from the analyses with respect to baseline symptoms [i.e., anxiety symptoms measured with the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushenen, Vaggs, & Jacobs, 1983) and the Posttraumatic Stress Disorder Symptom Scale-Self Report (PSS-SR; described later)] and demographic characteristics (e.g., age and race). The retained participants ranged in age from 18-70 years (M = 29, SD = 10.7). The majority of participants (64%) identified themselves as Caucasian, followed by African American (24%), Native American (7%), Hispanic (2%), Asian American (2%), and Other (1%).

Procedure

Data for this project focus on crime and unemployment statistics derived from zip code information obtained in the demographic questionnaire, genetic samples gathered during the pre-exam session, and PTSD symptoms assessment two months following the assault.

Measures

DNA testing. Epicentre's Catch-all™ foam tip buccal cell swabs were used to collect saliva samples, and were used for DNA analysis. Genetic analyses were conducted on the 5-HTTLPR region of the SLC6A4 promoter area, the SNPs for DRD2 (rs6277 and rs6279) and the SNPs for FKBP5 (rs53800373 and rs1360780). DNA was extracted using QuickExtract DNA Extraction Solution 1.0 provided in the BuccalAmp DNA Extraction Kit (Epicentre Biotechnologies). Genotyping of the 5'-flanking promoter region of the SLC6A4 gene was evaluated according to Gelernter et al. (1997) as either "long" or "short" with respect to having either 16 or 14 repeats using standard polymerase chain reaction (PCR) methods and gel electrophoresis. Genotyping of the DRD2 and FKBP5 SNPs used the Agilent Step-OnePlus Real Time PCR methods with the TaqMan Master Mixes and standard validated primers as detailed at Life Technologies defined for each specific SNP (details on VIC/FAM primers available through https://bioinfo.invitrogen.com/genome-database).

Demographic data. Standard demographic information and general information obtained by the SANE nurse was provided to researchers. Information obtained included age and race, and reported zip code of the survivor's current residence.

Posttraumatic Stress Disorder Symptom Scale-Self Report (PSS-SR; Foa, Riggs, Dancu, & Rothbaum, 1993). PTSD symptomatic distress for the past two weeks was assessed with the PSS-SR-17. Participants responded to items regarding PTSD symptoms using a four-point Likert scale ranging from 0 (*not at all*) to 3 (*5 or more times per week / very much / almost always*). The PSS-SR has acceptable psychometric properties such as internal consistency (0.65 to 0.71) and test-retest (0.66 to 0.77; Foa et al., 1993). Internal consistency in this study at two months was 0.93.

Crime index. Using the FBI's Uniform Crime Report definition (UCR; most recent), the crime risk index is the likelihood that a crime will be committed in a zip code area compared against every other zip code in the United States (i.e., the risk of crime in a community compared to national average). Both crimes against persons and property

were included. The national average score is 100, such that a zip code index score of approximately 100 would be considered "average" crime risk, whereas an index score of 200 would indicate twice the national average crime risk.

Unemployment rate. Unemployment data were obtained from ZipAtlas (ZipAtlas.Com, 2011) an online resource that provided the percentage of people (i.e., 0-100%) unemployed within a given zip code area.

Analysis

Preliminary differences among demographic and distress variables were examined via analysis of variance (ANOVA) to determine if differences in genetic make-up and posttraumatic stress symptomology among different races should be considered. Hierarchical regression analyses were used to examine the primary hypothesis. Specifically, the PSS-SR two month total scores were entered as the criterion, while the five genetic variables, along with crime index and unemployment rate, were entered as predictors (see Table 1 for descriptives). The interaction term (i.e., gene region X employment/crime) was entered in the final block. Age was a control variable. Significance for all analyses was determined at the 0.05 level.

Table 1: *Descriptive Information for Criterion and Continuous Predictors in Regression Analysis*

	Possible Range	Range	*M*	*SD*
Two-month PSS-SR	0 - 51	1 - 48	31.6	13.5
Unemployment	0-100%	1.1 - 6.8	3.6	1.5
Crime	-----	25 - 232	139.9	58.5

Results

Results from ANOVA analyses revealed no differences among race and distress variables, suggesting that probable PTSD and these candidate genes do not significantly vary as a result of race. Additionally, no statistically significant results were obtained from the hierarchical regression analysis (see Table 2). Post-hoc exploratory ANOVA analyses were performed to further examine the data (see Table 3). Similarly, these analyses did not produce statistically significant results, but observations in the data are worthy of mention as they relate to results obtained by Koenen and colleagues (2009) regarding SLC6A4, 5-HTTLPR. Figure 1 demonstrates that the *s'* allele [i.e., genotype of *s'/s'* (short short) or *s'/l'* (short long)] may be indicative of increased risk of probable PTSD in the context of low unemployment. Figure 2 demonstrates that the *s'* allele may be indicative of decreased risk of probable PTSD in the context of low crime. Among both high unemployment and high crime, the *s'/l'* genotype suggests increased risk of probable PTSD.

Table 2: *Hierarchical Regression Analysis Predicting PTSD Symptomatic Distress With Gene and Environment Variables*

Gene Region	Step	Predictor Variable	β	R^2	ΔR^2
Unemployment	1	Age SLC6A4 Unemployment	-.08 -.17 .06	.05	.05
SLC64	2	SLC6A4 X Unemployment	-.04	.05 .05	.00 .05
Crime	1	Age SLC6A4 Crime Index	-.07 -.18 -.04		
	2	SLC6A4 X Crime	.23	.06	.01
Unemployment	1	Age DRD2rs6277 Unemployment	-.06 .04 .08	.03	.03
DRD2rs6277	2	DRD2rs6277 X Unemployment	-.98	.06	.03
Crime	1	Age DRD2rs6277 Crime Index	-.05 .05 -.06	.02	.02
	2	DRD2rs6277 X Crime	-.18	.02	.00
Unemployment	1	Age DRD2rs6279 Unemployment	-.07 -.16 .07	.05	.08
DRD2rs6279	2	DRD2rs6279 X Unemployment	.97	.08	.03
Crime	1	Age DRD2rs6279 Crime Index	-.06 -.16 -.05	.05	.05
	2	DRD2rs6279 X Crime	.00	.05	.00
Unemployment	1	Age FKBP5rs3800373 Unemployment	-.06 .01 .08	.02	.02
FKBP5rs3800373	2	FKBP5rs3800373 X Unemployment	-.17	.03	.00
Crime	1	Age FKBP5rs3800373 Crime	-.05 -.00 -.05	.02	.02
	2	FKBP5rs3800373 X Crime	.43	.04 .02	.02 .02
Unemployment	1	Age FKBP5rs1360780 Unemployment	-.06 -.01 .08		
FKBP5rs1360780	2	FKBP5rs1360780 X Unemployment	.88	.04	.02
Crime	1	Age FKBP5rs1360780 Crime	-.05 -.01 -.05	.02	.02
	2	FKBP5rs1360780 X Crime	-.23	.02	.00

*Note: * were not denoted since all of the relationships explored were non-significant*

Table 3: *Means and Standard Deviations for ANOVA Analyses Examining the Effects of Genotype and Environment Interaction Terms on PTSD Symptomatic Distress*

Genotype	Low Unemployment		High Unemployment		Low Crime		High Crime	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
SLC6A4								
short short	33.94	5.25	23.88	7.95	36.47	6.72	27.16	5.40
long long	27.40	4.54	30.19	5.17	41.68	9.33	26.74	3.53
long short	34.91	3.29	36.55	4.83	32.98	4.53	36.88	3.37
DRD2rs6277								
short short	36.48	5.49	39.33	13.47	39.87	6.72	32.87	7.85
long long	33.23	3.91	36.68	5.10	33.43	6.05	34.88	3.62
long short	27.99	4.49	29.04	4.09	28.32	5.14	28.49	3.08
DRD2rs6279								
short short	32.67	3.30	41.93	4.68	32.59	4.45	37.59	3.52
long long	31.83	7.13	41.22	7.12	24.78	12.62	38.72	5.61
long short	30.63	2.99	22.16	4.10	34.51	4.96	25.30	2.89
FKBP5rs3800373								
short short	32.98	3.55	34.40	4.76	36.07	4.52	32.08	3.59
long long	31.63	6.74	25.21	6.03	25.91	9.39	28.71	5.01
long short	32.10	4.26	35.32	6.48	26.54	7.66	34.49	3.89
FKBP5rs1360780								
short short	32.56	3.29	35.52	4.59	37.43	4.41	31.47	3.27
long long	29.69	6.87	25.30	6.93	22.96	9.53	29.19	5.53
long short	30.85	4.01	32.36	5.81	2 7.41	6.71	32.15	3.63

Discussion

These results suggest that the gene regions examined in this study (SLC6A4 5-HTTLPR, DRD2 rs6277 and rs6279, FKBP5 rs53800373 and rs1360780) did not interact with the recovery environment (i.e., employment and crime) to predict PTSD symptoms. Although the DRD2 and FKBP5 genes did not yield significant results, this study was the first to examine these genes within a group-level context. Follow-up SLC6A4 5-HTTLPR analyses, while not statistically significant, suggest trends contrary to Koenen and colleagues (2009) findings. Specifically, Koenen et al. found that the *s'* allele of 5-HTTLPR predicted decreased risk of PTSD in low unemployment counties but increased risk in high unemployment counties among hurricane survivors. However, the current study found that the *s'* allele of 5-HTTLPR may suggest heightened risk of probable PTSD among low unemployment zip codes and mixed results among high unemployment zip codes among sexual assault survivors. Further, the previous study found that the *s'* allele of 5-HTTLPR predicted decreased risk of PTSD in low crime counties but increased risk in high crime counties. The current study, too, found that the *s'* allele of 5-HTTLPR may suggest decreased risk of probable PTSD in low crime zip codes, but, the *s'* allele of 5-HTTLPR demonstrated a mixed role among high crime zip codes. These observations suggest a limitation regarding the conclusion that the *s'* allele for the 5-HTTLPR is "protective" in low-risk environments while "vulnerable" in high-risk environments.

For this sample of sexual assault survivors, it appears that the genetic vulnerabilities

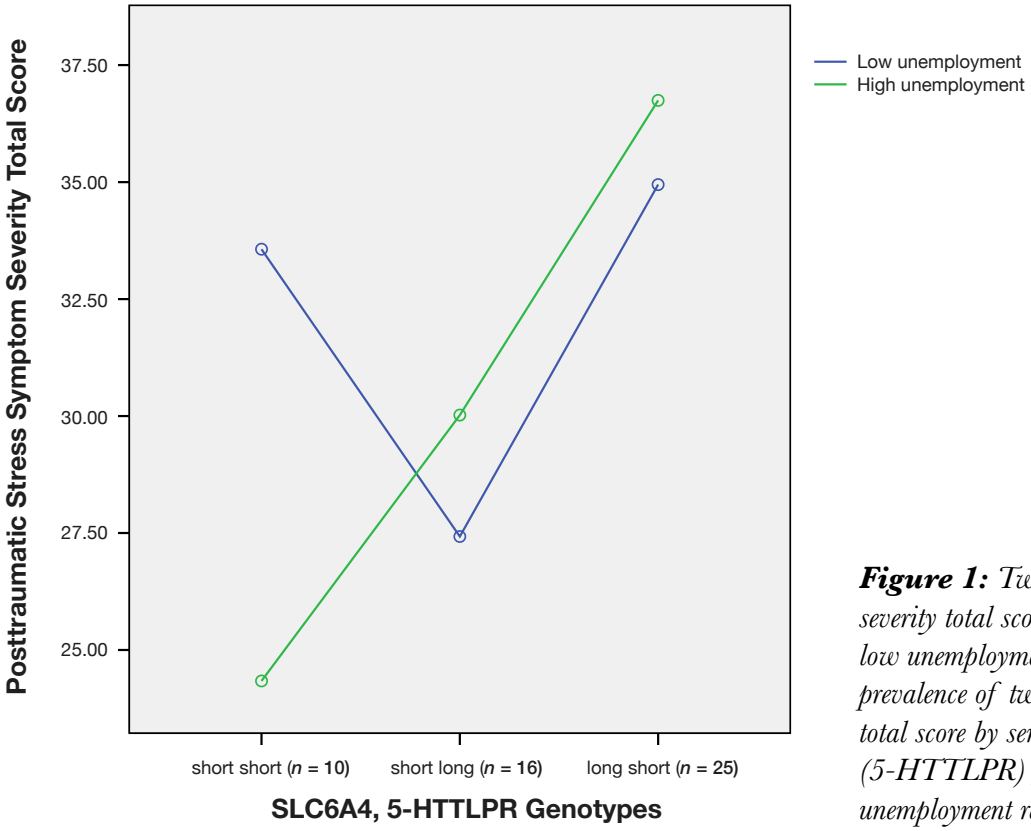

Figure 1: *Two-month posttraumatic stress symptom severity total score and genotype among high and low unemployment zip codes. This figure illustrates prevalence of two-month posttraumatic stress symptom total score by serotonin transporter polymorphism (5-HTTLPR) genotype and zip code-level unemployment rate (dichotomized as high vs. low).*

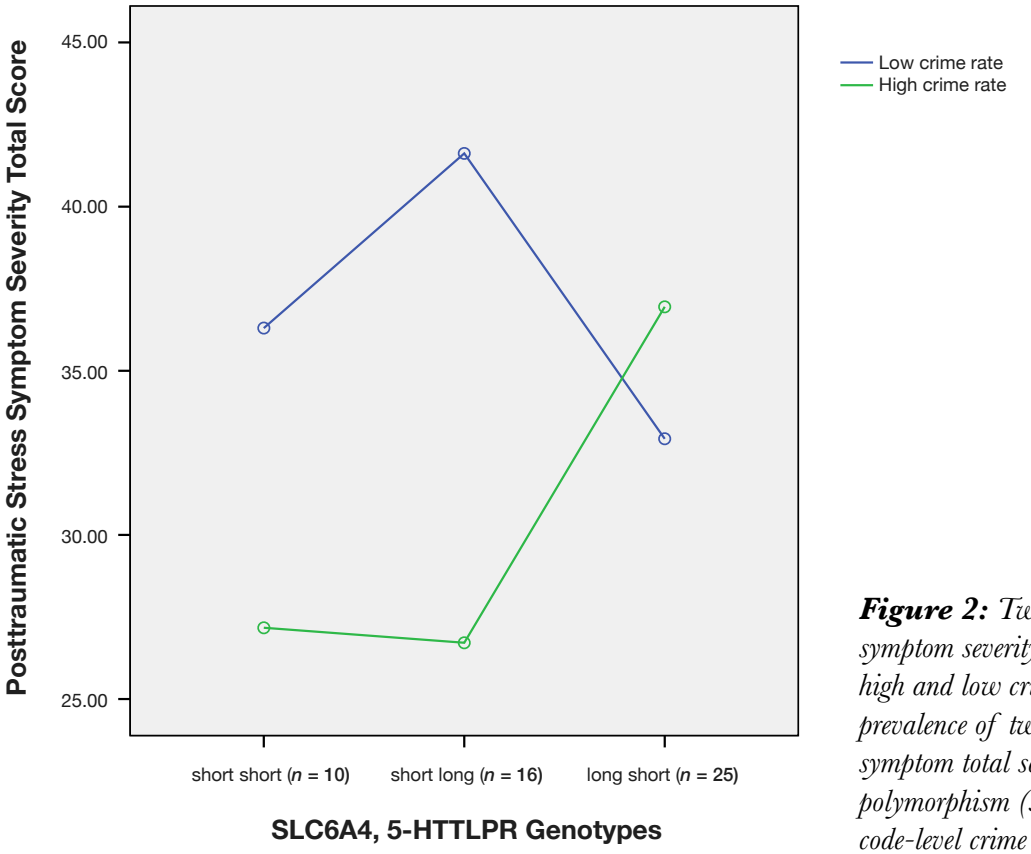

Figure 2: *Two-month posttraumatic stress symptom severity total score and genotype among high and low crime zip codes. This figure illustrates prevalence of two-month posttraumatic stress symptom total score by serotonin transporter polymorphism (5-HTTLPR) genotype and zip code-level crime index (dichotomized as high vs. low).*

analyzed have a limited susceptibility to environmental effects at the zip code level. The previous and current results encourage further exploration of the interactive effects of genetics and social environment on PTSD vulnerability among diverse groups of trauma survivors. Interpretation of these results should be made in consideration of the limitations. First, the sample size of the current study was small and may be responsible for diminished power and lack of statistically significant relationships [similar to the PTSD sample in Koenen's (2009) study]. Second, this sample is only representative of women who chose to receive an examination following a sexual assault. Therefore, these results may not generalize to traumatic events other than rape, or among other rape survivors who choose not to self-report for a medical examination. Further, previous trauma exposure was not controlled for in the current study; therefore it is possible that multiple traumas could alter the results. Additionally, this data was taken from a larger longitudinal study examining the effectiveness of a video intervention aimed at reducing psychological distress following a sexual assault. The lack of findings may also be a result of the intervention. It is further noted that unemployment, in this sample, may not have been a meaningful group-level variable to examine as the range was restricted (i.e., the unemployment rates of the zip code areas analyzed did not vary considerably; See Table 1). Finally, while the novel use of zip code as the basis of social environmental analyses offered more precise information, it also has drawbacks. For example, the zip code provided by participants may not reflect recent relocation during the study or the community in which the participant spends the majority of their time. Moreover, zip codes may contain non-congruent areas that may not necessarily capture the accurate degree of crime or unemployment an individual experiences.

Conclusions

Despite areas of weakness, the current study contributes to the literature in novel ways. This study replicates the notion of examining group-level vulnerabilities to PTSD; a departure from the typical gene-environment interaction study. This study consisted of self-report PTSD symptoms within two months of an interpersonal trauma, resulting in a more immediate and controlled elapsed time between the trauma and assessment than is common, and extends the investigation from disaster survivors to sexual assault survivors. This study also extended genetic investigations by not only examining the SLC6A4 gene, but DRD2 and FKBP5 genes also. Finally, this study took a more detailed methodological approach to examining group-level differences by examining zip code data rather than county data.

Future research may include dynamics among other types of traumatic events and other trauma-exposed populations. Besides unemployment and crime, a variety of group-level settings could be considered. All relevant individual-level variables should be controlled for to ascertain a degree of certainty that relationships are likely due to the social environment only. An examination of how recovery environment may affect psychological outcome could also be considered. Determining the extent to which the social environment affects PTSD vulnerability may inform the development and persistence of PTSD symptoms, and future intervention strategies.

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