American Journal of Epidemiology
Vol. 169, No. 6
DOI: 10.1093/aje/kwn397
Advance Access publication February 19, 2009

Original Contribution

Modification of the Association Between Serotonin Transporter Genotype and Risk of Posttraumatic Stress Disorder in Adults by County-Level Social Environment

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Initially submitted July 9, 2008; accepted for publication November 25, 2008.

Although both genetic factors and features of the social environment are important predictors of posttraumatic stress disorder (PTSD), there are few data examining gene-social environment interactions in studies of PTSD. The authors examined whether features of the social environment (county-level crime rate and unemployment) modified the association between the serotonin protein gene (*SLC6A4*) promoter variant (*5-HTTLPR*) and risk of current PTSD in a sample of 590 participants from the 2004 Florida Hurricane Study. Interviews conducted in 2005 were used to obtain individual-level risk factor measures and *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, PTSD diagnoses. DNA was extracted from salivary samples. County-level crime and unemployment rates were assessed from Federal Bureau of Investigation and US Census data, respectively. There was a significant interaction between *5-HTTLPR* genotype and both crime rate (odds ratio = 2.68, 95% confidence interval: 1.09, 6.57) and unemployment rate (odds ratio = 3.67, 95% confidence interval: 1.42, 9.50) in logistic regression models predicting PTSD risk, after adjustment for individual-level determinants of PTSD. Stratified analyses indicated that the "*s*" allele of the *5-HTTLPR* polymorphism was associated with decreased risk of PTSD in low-risk environments (low crime/unemployment rates) but increased risk of PTSD in high-risk environments. These results suggest that social environment modifies the effect of *5-HTTLPR* genotype on PTSD risk.

crime; genetics; serotonin; serotonin plasma membrane transport proteins; SLC6A4 protein, human; social environment; stress disorders, post-traumatic; unemployment

Abbreviations: CI, confidence interval; *5-HTTLPR*, serotonin transporter polymorphism; OR, odds ratio; PTSD, posttraumatic stress disorder.

Posttraumatic stress disorder (PTSD) occurs following exposure to a potentially traumatic event (1). The majority of Americans are exposed to a potentially traumatic event during their lifetimes, although only a minority develop PTSD (2). Still, the disorder is common: At least 1 in 14 Americans meets criteria for the diagnosis of lifetime PTSD (2). Despite substantial research, our understanding of the factors that determine vulnerability to PTSD remains incomplete. Two recent meta-analyses found that extant risk factors explained only about 20% of the interpersonal variance in PTSD (3, 4). Clearly, new variables including genetic factors and features of the social environment need to be incorporated into models aimed at understanding PTSD risk.

Genetic influences account for approximately one-third of the variance in PTSD risk among persons exposed to trauma (5, 6). Two studies have shown an association between a common variable number of tandem repeats polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*), designated *5-HTTLPR*, and PTSD. In a Korean sample, the short ("*s*") *5-HTTLPR* allele, which is less transcriptionally efficient than the long

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(''*l*'') allele (7), was more prevalent among PTSD patients than among controls (8). In a sample of persons exposed to the 2004 Florida hurricanes (also used in the current study), the low expression variant of the *5-HTTLPR* polymorphism modified risk of posthurricane PTSD, but only under conditions of high hurricane exposure and low social support, a gene-environment interaction (9).

Features of the social environment influence both risk of exposure to potentially traumatic events and risk of PTSD among the exposed (10–12). For example, persons living in areas characterized by greater social disadvantage may be exposed to greater violence (10, 13–16) and may also be more susceptible to PTSD because of the fragmented and disorganized social support systems in such areas (3, 4, 12).

Genetic factors and the social environment may *jointly* shape risk of PTSD. Although investigators in 2 studies have reported gene-environment interaction in PTSD (9, 17), no studies, to our knowledge, have assessed how features of the social environment, beyond individual-level trauma exposure and social support, influence genetic determination of PTSD. Thus, we examined whether the social environment (county-level crime rate and unemployment rate) modified the association between the *5-HTTLPR* polymorphism and risk of current PTSD in a sample of hurricane-exposed adults.

MATERIALS AND METHODS

Sample

Data for this study were collected in a random digit dialing study of residents of 33 Florida counties in 2004, when Florida was hit by hurricanes Jeanne, Ivan, Frances, and Charley in rapid succession. We used the Waksberg (18) random digit dialing method to select households with telephones to be screened for potential participation. Telephone numbers were called 5 times at different times of day and were replaced if there was no answer after 5 calls.

Inclusion criteria were: 1) speaking English or Spanish; 2) having lived in Florida during at least 1 of the 2004 hurricanes; 3) currently living in a household in 1 of 33 hurricane-exposed counties; and 4) having sufficient physical and mental ability to participate in a telephone interview. Because the original study investigated predictors of postdisaster resilience among older adults, persons aged 60 years or more were oversampled. The response rate was 81%.

Verbal consent was obtained from all participants. Those who completed the diagnostic interview and returned saliva samples received $20. The institutional review boards at the relevant institutions approved all procedures. Interviews were conducted between April 5 and June 12, 2005. More details about the sampling procedure and methods of the 2004 Florida Hurricane Study are provided elsewhere (9, 19–21).

Assessment procedure

A national survey research firm with considerable experience in conducting diagnostic interviews by telephone performed the highly structured assessment interviews using the computer-assisted telephone interview format (22). Respondents were randomly selected using the most-recent-birthday method when multiple eligible adults were present within a household. Interviews averaged 26.5 minutes in length. A detailed description of the assessment procedure has been published elsewhere (20).

Current PTSD. Current PTSD (past 6 months) was assessed using the National Women's Study PTSD module, a widely used measure in population-based epidemiologic research (23). The National Women's Study PTSD module was validated in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (1), PTSD field trial against the Structured Clinical Interview for *DSM* Disorders; the interrater kappa coefficient was 0.85 for the diagnosis of PTSD, and comparisons with the Structured Clinical Interview for *DSM* Disorders yielded a kappa coefficient of 0.71 (24). A high correspondence between telephone and in-person administration of the National Women's Study PTSD module has also been documented (25). We operationalized the diagnosis of PTSD on the basis of *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, symptom requirements (i.e., 3 avoidance symptoms, 1 intrusion symptom, and 2 arousal symptoms), including functional impairment.

Social support. Social support 6 months before the hurricanes was assessed with a modified 5-item version of the Medical Outcomes Study module (26). Low social support was operationalized as a score less than or equal to 15 based on the cutoff score derived from prior work (22). This scale had good reliability ($\alpha = 0.86$).

Hurricane exposure. Hurricane exposure was assessed with 5 indicators identified as being related to posthurricane mental health functioning in previous research (27): 1) exposure to hurricane-force winds or major flooding; 2) lack of adequate access to food, water, electricity, telephone, or clothing for at least 1 week; 3) losses or significant damage in 2 or more of the following categories: furniture; sentimental possessions; automobiles; pets; and crops, trees, or garden plants; 4) displacement from home for at least 1 week; and 5) unreimbursed losses of $1,000 or more. Participants with 2 or more of these indicators were coded as having high hurricane exposure.

Exposure to other potentially traumatic events. Exposure to other potentially traumatic events was measured by asking participants whether they had been exposed to any of 5 potentially traumatic events and whether they had feared death or serious injury during exposure. The events queried about included: 1) experiencing a natural disaster; 2) having a serious accident at work; 3) being attacked with a weapon; 4) being attacked without a weapon; and 5) being in a war zone. The number of other potentially traumatic events was summed. Participants were categorized as experiencing 0, 1, or $\geq$2 events.

Crime rate. Data on crime were taken from the Federal Bureau of Investigation's Uniform Crime Reporting Program (Serious Crimes Known to Police, 1999 data (28)). The crime rate was defined as the number of crimes committed per 100,000 residents. High-crime counties were defined as those with a crime rate above the mean rate of the sampled counties.

Unemployment rate. Data on unemployment were taken from 2000 US Census Summary File 3 (29). High-unemployment counties were defined as those with an unemployment percentage above the mean percentage of the sampled counties.

Collection of DNA samples

Saliva samples were provided by 651 participants; valid ancestry data were available for 623 (95.7%), and valid *5-HTTLPR* data were available for 590 cases (90.6%). The likelihood of submitting a saliva sample was unrelated to sex, hurricane exposure, social support, or PTSD. Details on the response rate for saliva sampling and correlates of participation are summarized elsewhere (19).

Genotyping

DNA was extracted from saliva using PUREGENE kits (Gentra Systems, Minneapolis, Minnesota). We examined the functional variable number of tandem repeats polymorphism in the 5′-flanking promoter region of the gene (*SLC6A4*) encoding the serotonin transporter protein. This polymorphism (*5-HTTLPR*) has 2 common alleles that have been characterized according to their length as "long" ("*l*") (16 repeats) and "short" ("*s*") (14 repeats). Genotyping was performed via polymerase chain reaction followed by size fractionation as described elsewhere (30) with prior *Msp*I restriction endonuclease digestion for triallelic classification, which allowed classification of "*l*" alleles into "l_A" and "l_G" variants (l_G has lower reuptake efficiency, similar to the "*s*" allele). The accuracy of *s*/*l* genotyping was confirmed via reanalysis of 100% of the specimens. The uncommon "l_G" alleles were classified as "short" for analysis (both denoted below as "*s*′") (31). In addition, 36 markers were genotyped to obtain information on ancestry (32–35). We added 1 additional highly informative single nucleotide polymorphism marker, *SLC24A5* (36), to the panel described previously.

Ancestry proportion scores

Ancestry proportion scores were generated to control for population stratification; population differences in allele frequency are known to occur for the *SLC6A4* locus (37). Participants' ancestries were estimated with the set of 37 unlinked ancestry-informative markers through Bayesian cluster analysis, using the STRUCTURE software developed by Pritchard and colleagues (38, 39). For the STRUCTURE analysis, we specified the "admixture" and "allele frequencies correlated" models and used 100,000 burn-in iterations and 100,000 Markov chain Monte Carlo iterations.

Statistical analyses

We used generalized estimating equations logistic regression models in all analyses to calculate parameter estimates with robust standard errors and to account for potential clustering by county (40, 41). First, we examined the association between PTSD and each demographic characteristic (sex, age <60 years, race/ethnicity) and risk factor (employment status, low social support, high hurricane exposure, other potentially traumatic events, *5-HTTLPR* genotype, high crime rate, and high unemployment) individually, without adjusting for other covariates. The selected covariates were factors associated with PTSD in previous analyses of these data (20). Next, we fitted 4 logistic regression models. The first model regressed PTSD on high crime rate, with adjustment for all covariates. The second model included all of the above and added an interaction term for high crime rate × *5-HTTLPR* genotype. The third and fourth models paralleled those for crime rate, except that high unemployment replaced crime rate as the county-level variable.

RESULTS

Descriptive findings

Table 1 presents the characteristics of the sample participants and their association with current PTSD. Among adults with genotype data for *5-HTTLPR* ($n = 590$), the prevalence of current PTSD was 3.2% ($n = 19$). Low social support, high hurricane exposure, and exposure to other potentially traumatic events predicted significantly increased risk of current PTSD.

5-HTTLPR genotype frequencies were consistent with previous work (37). The frequency of the "*l*′/*l*′" genotype was higher among African-American adults (*l*′/*l*′: 34.8%; *s*′/*l*′: 47.8%; *s*′/*s*′: 17.4%) than among European-American adults (*l*′/*l*′: 25.1%; *s*′/*l*′: 54.9%; *s*′/*s*′: 20.0%), as shown elsewhere (37). However, this difference was not statistically significant ($n = 553$; χ^2 (2 df) = 1.09; $P = 0.58$). There was no difference in ancestral proportion score between persons with PTSD (mean = 0.12 (standard deviation, 0.27)) and persons without PTSD (mean = 0.06 (standard deviation, 0.20); *t* test: $t(18.63) = -0.98$; $P = 0.34$). Thus, even without correction based on ancestry coefficients, population stratification was unlikely to be a potential cause of false-positive findings.

Gene-social environment interaction

Table 2 presents results from the multivariable logistic regression models for crime rate and PTSD. In the main-effects model, low social support, high hurricane exposure, and exposure to other traumatic events were associated with significantly increased risk of PTSD. There was no significant main effect for *5-HTTLPR* genotype or county-level crime rate. In the interaction model, the interaction term for *5-HTTLPR* genotype × crime rate was significant ($P = 0.03$). Figure 1 presents the prevalence of PTSD for persons from high-crime-rate counties versus persons from low-crime-rate counties by *5-HTTLPR* genotype. Stratified analyses showed that the *s*′ allele of *5-HTTLPR* predicted decreased risk of PTSD among persons living in low-crime counties (odds ratio (OR) = 0.61, 95% confidence interval (CI): 0.34, 1.10) but increased risk in high-crime counties (OR = 1.54, 95% CI: 0.72, 3.30).

Table 3 presents results from the multivariable logistic regression models for unemployment rate and PTSD.

Table 1. Characteristics of Study Participants and Unadjusted Association Between Selected Risk Factors and a Current Diagnosis of Posttraumatic Stress Disorder ($n = 590$), 2004 Florida Hurricane Study, 2005

Variable[a]	Total ($n = 590$)		Current PTSD ($n = 19$)		No PTSD ($n = 571$)		Odds Ratio	95% Confidence Interval	*P* Value
	No.	%	No.	%	No.	%			
Female sex	375	63.6	13	68.4	362	63.4	0.79	0.25, 2.45	0.68
Age <60 years	134	22.7	7	36.8	127	22.2	1.96	0.81, 4.77	0.14
Race/ethnicity									
White	531	90.7	15	79.0	516	90.9			
Other[b]	56	9.5	4	21.1	52	9.2	0.39	0.13, 1.18	0.10
Employment status									
Employed	198	34.1	7	36.8	191	34.1			
Other[c]	382	65.9	12	63.2	370	66.0	1.12	0.41, 3.06	0.83
Low level of social support	223	37.9	13	68.4	210	36.9	3.55	1.30, 9.73	0.01
High hurricane exposure	268	45.4	14	73.7	254	44.5	3.42	1.51, 7.74	0.003
No. of other potentially traumatic events							1.72	1.04, 2.84	0.03
0	200	33.9	3	15.8	197	34.5			
1	182	30.9	6	31.6	176	30.8			
≥2	208	35.3	10	52.6	198	34.7			
5-HTTLPR genotype							0.89	0.52, 1.53	0.68
l′/*l′*	154	26.1	6	31.6	148	25.9			
l′/*s′*	316	53.6	9	47.4	307	53.7			
s′/*s′*	120	20.3	4	21.1	116	20.3			
High county-level crime rate	265	44.9	7	36.8	258	45.2	0.71	0.29, 1.70	0.44
High county-level unemployment rate	308	52.2	10	52.6	289	52.2	1.04	0.42, 2.53	0.94

Abbreviations: CI, confidence interval; *5-HTTLPR*, serotonin transporter polymorphism; *l′*, long allele; PTSD, posttraumatic stress disorder; *s′*; short allele (includes "*s*" and "l_G" alleles).

[a] For definitions of variables, see text.

[b] Included African-American, Hispanic, and Asian.

[c] Included being unemployed and looking for work; being retired and not working; being disabled or too ill to work; and being a student or homemaker.

In the main-effects model, low social support and high hurricane exposure were associated with significantly increased risk of PTSD. There was no significant main effect for *5-HTTLPR* genotype or county-level unemployment rate. In the interaction model, the interaction term for *5-HTTLPR* genotype × unemployment rate was significant ($P = 0.007$). Figure 2 presents the prevalence of PTSD for persons from counties with high unemployment versus those with low unemployment by *5-HTTLPR* genotype. Stratified analyses showed that the *s′* allele of *5-HTTLPR* predicted decreased risk of PTSD among persons living in low-unemployment counties (OR = 0.35, 95% CI: 0.14, 0.87) but increased risk in high-unemployment counties (OR = 1.46, 95% CI: 0.82, 2.61). Note that because of the loss of power in stratified analyses, only the effect of *5-HTTLPR* genotype in low-unemployment counties was statistically significant.

DISCUSSION

To our knowledge, this study was the first to document a significant interaction between a specific gene and features of the group-level social environment in the risk of a major disorder. We found that county-level crime rate and employment rate modified the association between *5-HTTLPR* genotype and risk of PTSD. Although our interpretation of results from the stratified analysis is constrained by low statistical power due to the relatively few PTSD cases in this sample, results suggest that the *s′* allele of the *5-HTTLPR* polymorphism was associated with decreased risk of PTSD in the low-risk environments (low crime/unemployment rates) but increased risk of PTSD in the high-risk environments. If replicated, this finding is an important extension of the literature, since previous investigations of gene-environment interaction in PTSD have considered only individual-level variables.

The interaction effect for *5-HTTLPR* genotype and crime/unemployment rate was significant after controlling for individual-level determinants of PTSD, including sex, hurricane exposure, other potentially traumatic events, and social support. This suggests not merely that the findings are a function of people's living in areas with greater exposure to potentially traumatic events or low social support, but rather that something else about the high-risk social

Table 2. Effect of County-Level Crime Rate and Serotonin Transporter Polymorphism (*5-HTTLPR*) Genotype on the Risk of a Current Diagnosis of Posttraumatic Stress Disorder (Final Logistic Regression Analysis) ($n = 590$), 2004 Florida Hurricane Study, 2005

Variable[a]	Main-Effects Model[b]			Interaction Model[c]		
	Adjusted OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value
Sex	0.77	0.24, 2.45	0.65	0.77	0.24, 2.42	0.65
Age <60 years	1.29	0.50, 3.35	0.56	1.24	0.48, 3.22	0.66
Ancestral proportion score[d]	1.41	0.32, 6.24	0.65	1.21	0.28, 5.32	0.80
Unemployed	0.72	0.25, 2.10	0.55	0.71	0.26, 2.02	0.53
Low level of social support	3.47	1.19, 10.10	0.02	3.38	1.17, 9.78	0.02
High hurricane exposure	3.26	1.41, 7.54	0.01	3.19	1.42, 7.16	0.005
Other potentially traumatic events	1.65	1.04, 2.63	0.04	1.66	1.04, 2.65	0.03
5-HTTLPR (*s′* allele)	0.83	0.52, 1.33	0.44	1.46	0.69, 3.07	0.32
High crime rate	0.71	0.30, 1.72	0.45	0.27	0.06, 1.23	0.09
5-HTTLPR × high crime rate				2.68	1.09, 6.57	0.03

Abbreviations: CI, confidence interval; *5-HTTLPR*, serotonin transporter polymorphism; OR, odds ratio; PTSD, posttraumatic stress disorder; *s′*, short allele.

[a] For definitions of variables, see text.

[b] Regression of PTSD on high crime rate, with adjustment for all covariates.

[c] Included all of the above terms plus an interaction term for high crime rate × *5-HTTLPR* genotype.

[d] Race/ethnicity estimated using unlinked genetic markers by Bayesian cluster analysis.

environment influences susceptibility to PTSD among carriers of the *s′* allele. Our finding that the *s′* allele was associated with decreased risk of PTSD in the low-risk social environments is similar to that of a study which found the *s*/*s* genotype to be protective against depressive symptoms among adults raised in a supportive family environment but to increase risk among those raised in a harsh environment (42). Animal studies have also found the *s*/*s* genotype to be protective under positive conditions of maternal rearing; effects were reversed under adverse conditions of peer rearing (43). These findings suggest that the *s*/*s* genotype is less a risk factor for PTSD or depression per se than a reflection of heightened sensitivity to environmental influences.

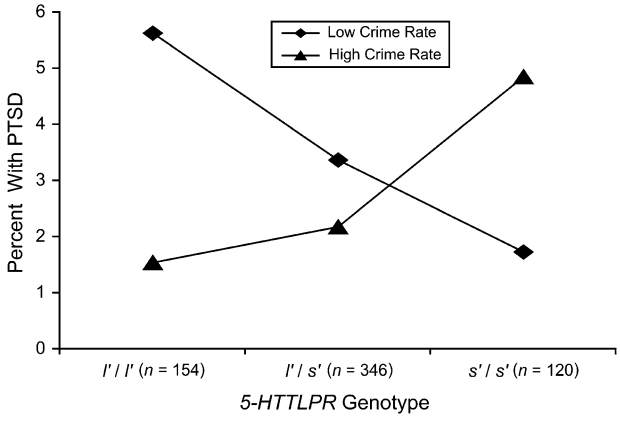

Figure 1. Prevalence of posttraumatic stress disorder (PTSD) by serotonin transporter polymorphism (*5-HTTLPR*) genotype and county-level crime rate (dichotomized as high vs. low), 2004 Florida Hurricane Study, 2005. *l*, long allele; *s*, short allele.

Human brain imaging studies suggest that carriers of the "*s*" allele are more attuned to negative emotional stimuli (44, 45). From an evolutionary perspective, such attunement may have been adaptive for survival, thus maintaining the frequency of the "*s*" allele in the population.

Limitations

There are at least 4 potential limitations of the data presented in this article. First, our sample was not representative. Although our response rate for the interview portion of the study was better than is typical (46), the rate of return of saliva samples was lower than optimal. However, nonparticipation in the genetic study was not significantly related to the major study variables of hurricane exposure, social support, or PTSD, suggesting that participation bias is unlikely to have influenced our findings (19). Second, it is possible that exposure to potentially traumatic events in the counties with adverse social environments was worse than that experienced in the low-crime/-unemployment counties. Although we controlled for hurricane exposure and other potentially traumatic events in our analyses, it is possible that some unmeasured aspect of these events is driving the association between social environment and PTSD. Third, these findings may not be generalizable to PTSD that follows other types of traumatic events. Finally, the number of affected persons was small, in the context of a reasonably large sample. Thus, we had very limited statistical power for stratified analyses.

Conclusions

This area of research is novel, and we can only offer early conjecture about the mechanisms through which the social

Table 3. Effect of County-Level Unemployment Percentage and Serotonin Transporter Polymorphism (*5-HTTLPR*) Genotype on the Risk of a Current Diagnosis of Posttraumatic Stress Disorder (Final Logistic Regression Analysis) ($n = 590$), 2004 Florida Hurricane Study, 2005

Variable[a]	Main-Effects Model[b]			Interaction Model[c]		
	Adjusted OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value
Sex	0.81	0.26, 2.52	0.72	0.79	0.26, 2.26	0.63
Age <60 years	1.40	0.56, 3.48	0.49	1.46	0.56, 3.82	0.44
Ancestral proportion score[d]	1.37	0.31, 6.15	0.68	1.31	0.30, 5.81	0.72
Unemployed	0.69	0.24, 1.97	0.48	0.66	0.23, 1.92	0.45
Low level of social support	3.41	1.18, 9.83	0.02	3.14	1.12, 8.79	0.03
High hurricane exposure	3.41	1.38, 8.46	0.008	3.53	1.45, 8.55	0.005
Other potentially traumatic events	1.62	0.98, 2.68	0.06	1.54	0.96, 2.47	0.07
5-HTTLPR (*s′* allele)	0.81	0.50, 1.32	0.40	1.34	0.77, 2.32	0.30
High unemployment rate	0.87	0.35, 2.17	0.76	0.30	0.09, 0.99	0.05
5-HTTLPR × high unemployment rate				3.67	1.42, 9.50	0.007

Abbreviations: CI, confidence interval; *5-HTTLPR* serotonin transporter polymorphism; OR, odds ratio; PTSD, posttraumatic stress disorder; *s′*, short allele.

[a] For definitions of variables, see text.

[b] Regression of PTSD on high unemployment rate, with adjustment for all covariates.

[c] Included all of the above terms plus an interaction term for high unemployment rate × *5-HTTLPR* genotype.

[d] Race/ethnicity estimated using unlinked genetic markers by Bayesian cluster analysis.

environment might influence the risk of PTSD. Much work is needed to either replicate or refute the findings documented here and to understand the mechanisms that may explain these observations. These data argue for extending gene-environment interaction studies to include features of the social environment in future research on population-representative samples. Although twin studies have shown that the heritability of a wide range of individual characteristics and behaviors is modified by environmental factors such as socioeconomic status in childhood (47, 48), early family adversity (49), and school environment (50), no studies to our knowledge have examined whether aspects of the social environment modify the association between specific genes and disorder. The relative risk of disease conferred by the social environment is likely to be lower than that conferred by individual-level risk factors. However, the ubiquity of exposure to social environmental variables suggests that their role in determining the population distribution of PTSD and other major mental disorders will be substantial.

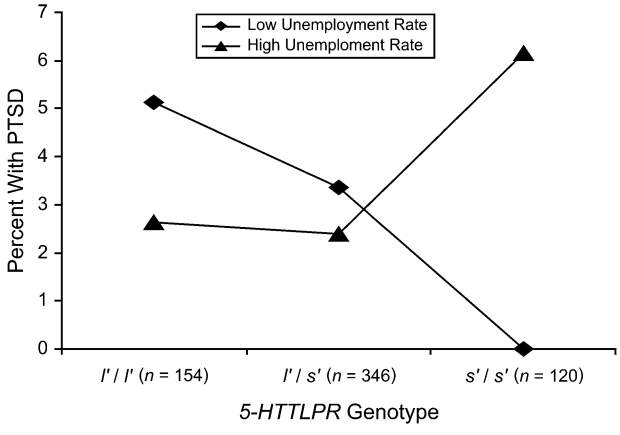

Figure 2. Prevalence of posttraumatic stress disorder (PTSD) by serotonin transporter polymorphism (*5-HTTLPR*) genotype and county-level unemployment rate (dichotomized as high vs. low), 2004 Florida Hurricane Study, 2005. *l*, long allele; *s*, short allele.

ACKNOWLEDGMENTS

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This research was supported by National Institutes of Health grants MH05220, MH07055, and DA15105. Dr. Koenen

was also supported by grants MH070627 and MH07828, Dr. Amstadter by grant MH083469, and Dr. Galea by grants MH078152, MH082729, and DA022720.

Conflict of interest: none declared.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
2. Kessler RC, Sonnega A, Bromet E, et al. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry.* 1995;52(12):1048–1060.
3. Ozer EJ, Best SR, Lipsey TL, et al. Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. *Psychol Bull.* 2003;129(1):52–73.
4. Brewin CR, Andrews B, Valentine JD. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *J Consult Clin Psychol*. 2000;68(5):317–336.
5. True WJ, Rice J, Eisen SA, et al. A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. *Arch Gen Psychiatry.* 1993;50(4):257–264.
6. Stein MB, Jang KJ, Taylor S, et al. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder: a twin study. *Am J Psychiatry.* 2002;159(10): 1675–1681.
7. Lesch KP, Bengel D, Heils A, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*. 1996;274(5292):1527–1531.
8. Lee HJ, Lee MS, Kang RH, et al. Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. *Depress Anxiety.* 2005;21(3): 135–139.
9. Kilpatrick DG, Koenen KC, Ruggiero KJ, et al. The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. *Am J Psychiatry.* 2007;164(11):1693–1699.
10. Breslau N, Wilcox HC, Storr CL, et al. Trauma exposure and posttraumatic stress disorder: a study of youths in urban America. *J Urban Health*. 2004;81(4):530–544.
11. DuMont KA, Widom CS, Czaja SJ. Predictors of resilience in abused and neglected children grown-up: the role of individual and neighborhood characteristics. *Child Abuse Negl*. 2007; 31(3):255–274.
12. Koenen KC, Stellman JM, Stellman SD, et al. Risk factors for course of posttraumatic stress disorder among Vietnam veterans: a 14-year follow-up of American Legionnaires. *J Consult Clin Psychol*. 2003;71(6):980–986.
13. Coulton CJ, Crampton DS, Irwin M, et al. How neighborhoods influence child maltreatment: a review of the literature and alternative pathways. *Child Abuse Negl*. 2007;31(11-12): 1117–1142.
14. Reyes JC, Robles RR, Colon HM, et al. Neighborhood disorganization, substance use, and violence among adolescents in Puerto Rico. *J Interpers Violence*. 2008;23(11): 1499–1512.
15. Obasaju MA, Palin FL, Jacobs C, et al. Won't you be my neighbor? Using an ecological approach to examine the impact of community on revictimization. *J Interpers Violence*. 2009; 24(1):38–53.
16. Melzer-Lange MD, Van Thatcher CD, Liu J, et al. Urban community characteristics and adolescent assault victims. *WMJ*. 2007;106(7):394–396.
17. Binder EB, Bradley RG, Liu W, et al. Association of *FKBP5* polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA*. 2008;299(11): 1291–1305.
18. Groves R, Biemer P, Lyberg L, et al. *Telephone Survey Methodology.* London, United Kingdom: Wiley Europe; 2001.
19. Galea S, Acierno R, Ruggiero K, et al. Social context and the psychobiology of posttraumatic stress. *Ann N Y Acad Sci.* 2006;1071:231–241.
20. Acierno R, Ruggiero KJ, Kilpatrick DG, et al. Risk and protective factors for psychopathology among older versus younger adults after the 2004 Florida hurricanes. *Am J Geriatr Psychiatry.* 2006;14(12):1051–1059.
21. Acierno R, Ruggiero KJ, Galea S, et al. Psychological sequelae resulting from the 2004 Florida hurricanes: implications for postdisaster intervention. *Am J Public Health*. 2007; 97(suppl 1):S103–S108.
22. Galea S, Ahern J, Resnick H, et al. Psychological sequelae of the September 11 terrorist attacks in New York City. *N Engl J Med*. 2002;346(13):982–987.
23. Ruggiero KJ, Rheingold AA, Resnick HS, et al. Comparison of two widely used PTSD-screening instruments: implications for public mental health planning. *J Trauma Stress*. 2006; 19(5):699–707.
24. Kilpatrick DG, Resnick HS, Freedy JR, et al. The posttraumatic stress disorder field trial: evaluation of the PTSD construct criteria A through E. In: Widiger TA, Frances AJ, Pincus HA, et al, eds. *DSM-IV Sourcebook*. Vol 4. Washington, DC: American Psychiatric Association; 1998:803.
25. Acierno R, Resnick H, Kilpatrick D, et al. Assessing elder victimization—demonstration of a methodology. *Soc Psychiatry Psychiatr Epidemiol*. 2003;38(11):644–653.
26. Sherbourne CD, Stewart AL. The MOS social support survey. *Soc Sci Med*. 1991;32(6):705–714.
27. Freedy JR, Saladin ME, Kilpatrick DG, et al. Understanding acute psychological distress following natural disaster. *J Trauma Stress*. 1994;7(2):257–273.
28. Federal Bureau of Investigation, US Department of Justice. *Table B6. Counties—Crime, Housing, and Building Permits*. Washington, DC: US Department of Justice; 2002. (http://www.census.gov/prod/2002pubs/00ccdb/cc00_tabB6.pdf). (Accessed January 9, 2007).
29. Bureau of the Census, US Department of Commerce. *2000 Census of Population and Housing, Summary File 3: Technical Documentation*. Washington, DC: US Department of Commerce; 2002. (http://www.census.gov/prod/cen2000/doc/sf3.pdf). (Accessed January 7, 2007).
30. Gelernter J, Kranzler H, Cubells JF. Serotonin transporter protein (*SLC6A4*) allele and haplotype frequencies and linkage disequilibria in African- and European-American and Japanese populations and in alcohol-dependent subjects. *Hum Genet.* 1997;101(2):243–246.
31. Stein MB, Seedat S, Gelernter J. Serotonin transporter gene promoter polymorphism predicts SSRI response in generalized social anxiety disorder. *Psychopharmacology (Berl).* 2006; 187(1):68–72.
32. Yang BZ, Zhao H, Kranzler HR, et al. Practical population group assignment with selected informative markers: characteristics and properties of Bayesian clustering via STRUCTURE. *Genet Epidemiol*. 2005;28(4):302–312.
33. Yang BZ, Zhao H, Kranzler HR, et al. Characterization of a likelihood based method and effects of markers informativeness in evaluation of admixture and population group assignment [electronic article]. *BMC Genet.* 2005;6:50.

34. Kaufman J, Yang BZ, Douglas-Palumberi H, et al. Social support and serotonin transporter gene moderate depression in maltreated children. *Proc Natl Acad Sci U S A*. 2004;101(49): 17316–17321.
35. Stein MB, Schork NJ, Gelernter J. A polymorphism of the β1-adrenergic receptor is associated with low extraversion. *Biol Psychiatry.* 2004;56(4):217–224.
36. Lamason RL, Mohideen MA, Mest JR, et al. SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans. *Science*. 2005;310(5755):1782–1786.
37. Gelernter J, Cubells JF, Kidd JR, et al. Population studies of polymorphisms of the serotonin transporter protein gene. *Am J Med Genet.* 1999;88(1):61–66.
38. Falush D, Stephens M, Pritchard JK. Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. *Genetics*. 2003;164(4): 1567–1587.
39. Pritchard JK, Rosenberg NA. Use of unlinked genetic markers to detect population stratification in association studies. *Am J Hum Genet.* 1999;65(1):220–228.
40. Hanley JA, Negassa A, Edwardes MD, et al. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol*. 2003;157(4): 364–375.
41. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics*. 1988;44(4):1049–1060.
42. Taylor SE, Way BM, Welch WT, et al. Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biol Psychiatry.* 2006;60(7):671–676.
43. Suomi SJ. Attachment in rhesus monkeys. In: Cassidy J, Shaver PR, eds. *Handbook of Attachment: Theory, Research, and Clinical Applications*. New York, NY: Guilford Press; 1999:181–197.
44. Pezawas L, Meyer-Lindenberg A, Drabant EM, et al. *5-HTTLPR* polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci*. 2005;8(6):828–834.
45. Hariri AR, Mattay VS, Tessitore A, et al. Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 2002;297(5580):400–403.
46. Galea S, Tracy M. Participation rates in epidemiologic studies. *Ann Epidemiol*. 2007;17(9):643–653.
47. Turkheimer E, Haley A, Waldron M, et al. Socioeconomic status modifies heritability of IQ in young children. *Psychol Sci.* 2003;14(6):623–628.
48. Tuvblad C, Grann M, Lichtenstein P. Heritability for adolescent antisocial behavior differs with socioeconomic status: gene-environment interaction. *J Child Psychol Psychiatry.* 2006;47(7):734–743.
49. Ouellet-Morin I, Boivin M, Dionne G, et al. Variations in heritability of cortisol reactivity to stress as a function of early familial adversity among 19-month-old twins. *Arch Gen Psychiatry.* 2008;65(2):211–218.
50. Boardman JD, Saint Onge JM, Haberstick BC, et al. Do schools moderate the genetic determinants of smoking? *Behav Genet.* 2008;38(3):234–246.