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Social Constraints, Genetic Vulnerability, and Mental Health Following Collective Stress

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A repeat-length polymorphism of the serotonin promoter gene (5-HTTLPR) has been associated with depression and posttraumatic stress disorder (PTSD) in trauma-exposed individuals reporting unsupportive social environments. We examine the contributions of the triallelic 5-HTTLPR genotype and social constraints to posttraumatic stress (PTS) symptoms in a national sample following the September 11, 2001 (9/11) terrorist attacks. Saliva was collected by mail from 711 respondents (European American subsample $n = 463$) of a large national probability sample of 2,729 adults. Respondents completed web-based assessments of pre-9/11 mental and physical health, acute stress 9 to 23 days post-9/11, PTS symptoms, and social constraints on disclosure regarding fears of future terrorist attacks 2–3 years post-9/11. Social constraints were positively associated with PTS symptoms 2–3 years post-9/11. The triallelic 5-HTTLPR genotype was not directly associated with PTS symptoms, but it interacted with social constraints to predict PTS symptoms 2–3 years post-9/11: Social constraints were more strongly associated with PTS symptoms for individuals with any s/lg allele than for homozygous l/l individuals. Constraints on disclosing fears about future terrorism moderate the 5-HTTLPR genotype-PTS symptom association even when indirectly exposed to collective stress.

Scientists have long sought to understand why some people are resilient following adversities that render others vulnerable to mental health problems (e.g., posttraumatic stress symptomatology). To explain this variability in response to stressful life events

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(SLE), researchers have investigated how social environments shape the phenotypes associated with potential disease-related genotypes (Caspi et al., 2003; Kilpatrick et al., 2007). Although several candidate genes have been proposed as part of the dynamic gene–environment ($G \times E$) etiology of posttraumatic stress disorder (PTSD; e.g., 5-HTTLPR, BDNF; Broekman, Olff, & Boer, 2007), the 5-HTTLPR repeat-length polymorphism is particularly interesting due to its role in regulating the neurotransmitter serotonin, which appears to contribute to changes in the brain related to PTSD (e.g., hippocampal volume, increased sensitivity to fear stimuli; Hariri et al., 2002; Ravindran & Stein, 2007). Although conflicting evidence exists (Grabe et al., 2009; Thakur, Joobar, & Brunet, 2009), the 5-HTTLPR low-expression short (s/lg) alleles (vs. high-expression long-a [la] allele) are thought to increase an individual's vulnerability by promoting greater emotional reactivity to stress (Hariri et al., 2002).

There is also mounting evidence that the genetic contribution to the impact of stress on mental health is malleable—it can be shaped by the social environment (Galea et al., 2006). Consistent with research demonstrating that positive and negative social experiences powerfully affect the development and course of PTSD (Charuvastra & Cloitre, 2008), preliminary evidence suggests that the 5-HTTLPR repeat length polymorphism s/lg allele

may protect the mental health of individuals in some low-risk social environments (Koenen et al., 2009; Taylor et al., 2006), while rendering individuals in high-risk social environments more vulnerable to depression and/or PTSD (Caspi et al., 2003; Kilpatrick et al., 2007; Taylor et al., 2006), though these findings have recently been challenged (Risch et al., 2009). These studies have considered the role of child abuse, risky family environments, macro-level crime and unemployment, and social support. What have not been addressed are other quite common, yet subtle, ways social ties may influence our responses to stress.

Although talking about one's thoughts and feelings following SLE is not always necessary or helpful (Seery, Silver, Holman, Ence, & Chu, 2008), sharing them with others can be beneficial for many people (Frattaroli, 2006; Lepore, Ragan, & Jones, 2000). When individuals want to talk but feel their support networks do not want to hear about their experiences, however, the perceived constraint on emotional disclosure may have deleterious effects on health and well-being. Indeed, in both experimental and field-based studies, individuals reporting social constraints on disclosure report higher levels of intrusive thinking—a symptom associated with PTSD and psychological distress (Lepore, Silver, Wortman, & Wayment, 1996)—than individuals with low social constraints. Inhibiting verbal disclosure may also negatively affect physical health by sustaining stress-related autonomic arousal (Berry & Pennebaker, 1993; Frattaroli, 2006). As carriers of the 5-HTTLPR polymorphism *s/lg* alleles have heightened stress reactivity (see Caspi, Hariri, Holmes, Uher, & Moffitt, 2010), we would expect them to be most negatively affected by social constraints that inhibit discussion of their fears. If social constraints on disclosure potentiate already heightened stress reactivity in *s/lg* carriers, they could magnify risk for subsequent mental and physical health problems.

Finally, to our knowledge, the $G \times E$ research on coping with SLE has focused exclusively on individuals who have directly experienced highly stressful events. However, collectively experienced stressors may affect mental and physical health in indirectly exposed individuals as well (Cohn, Mehl, & Pennebaker, 2004; Conejero & Extrebarria, 2007; Holman et al., 2008). In fact, collective stressors may lead to community-based social responses that impede individual recovery. That is, many people simultaneously sharing stories of their experience with the stressor can strain the broader social environment to the point of shutting down responsiveness to individuals seeking support (Pennebaker & Harber, 1993).

We examine the combined impact of 5-HTTLPR genotype and social constraints on discussing fears of future terrorist attacks following the 9/11 terrorist attacks in a subsample drawn from our nationwide 3-year prospective longitudinal study. In keeping with recent research we use the triallelic 5-HTTLPR genotype based on the tandem-repeat length polymorphism (short vs. long alleles) and a related single nucleotide polymorphism that identifies long alleles as either "G" or "A." The long G (*lg*) allele is functionally

similar to the short length polymorphism so it is classified with the short allele (*s/lg*). Given these functional classifications, we expect respondents whose genotype includes any *s/lg* allele to be more vulnerable to the negative effects of social constraints following 9/11 than individuals who have the homozygotic long A (*la/la*) genotype. We expect these individuals to report higher levels of PTS symptomatology than the *la/la* individuals who also experience high social constraints. Under low social constraint conditions, we expect *s/lg* allele carriers to report lower PTS symptoms than individuals with the *la/la* genotype.

METHOD

This project builds upon a 3-year prospective longitudinal study (Silver, Holman, McIntosh, Poulin, & Gil-Rivas, 2002) conducted with a nationally representative sample of 2,729 individuals. This is the only large-scale longitudinal study of coping with a collective, national stressor that has a nationally representative sample; mental and physical health data collected prior to the attacks; immediate (2–3 weeks) post-9/11 acute stress symptoms; 3 years of longitudinal follow-ups of cognitive, social, and emotional functioning, including 9/11-related PTS symptoms; and assessments of both lifetime and ongoing exposure to stressful life events.

The original 9/11 study was conducted in collaboration with Knowledge Networks, Inc. (KN; New York, NY), a web-based survey research firm that uses multistage probability sampling with random-digit-dialing (RDD) telephone methods to recruit and maintain a nationally representative panel. Their methods provide a known, non-zero probability of selection for every person in the United States living in a household that has a telephone. Surveys are administered on the web. Knowledge Networks provides free Internet service and a WebTV appliance for recruits who have no web access to ensure representativeness of their panel. Panel members are notified of surveys via e-mail to a KN-provided, password-protected account. Participation in every survey is voluntary, and panel members can withdraw from participation at any time. The study design and sampling has been detailed elsewhere (Holman et al., 2008; Silver et al., 2002). The UC Irvine Institutional Review Board reviewed and approved all study procedures.

Participants and Procedure

Participants for this study were recruited from the larger study described above. As part of their agreement with panelists, KN is allowed to recontact ex-panelists unless they have made themselves "unavailable" for future contact. In the summer of 2008, the 1,296 available respondents from the original study were contacted to request their participation in this follow-up study. Consenting participants provided saliva samples using an OraGene® test kit that was mailed to their homes. Each kit was marked with the respondent's identification number from the 9/11 study so that

the genetic results and pre-existing survey data could be merged. Seven-hundred eleven respondents returned the kits (55% return rate).

Measures

Pre-9/11 mental and physical health was assessed between June 2000 and September 9, 2001. Adult panelists completed an on-line health survey, modified from the Centers for Disease Control's National Center for Health Statistics annual National Health Interview Survey (NHIS; U.S. Department of Health and Human Services, 2000). Respondents were asked, "Has a medical doctor ever diagnosed you as suffering from any of the following ailments?" with prompts for 35 physical and mental health ailments. Approximately 8–9% of the pre-9/11 health survey respondents had missing data for some physician-diagnosed ailments. As the Little and Rubin MCAR test for these data was nonsignificant ($p > .10$; Little & Rubin, 1987), missing data were imputed within age groups using the expectation maximization (EM) method.

Items from this survey provided the baseline mental and physical health assessments for the original study respondents. Two indices were created: a total count of the pre-9/11 physician-diagnosed physical health ailments and a count of common mental health ailments (none, anxiety or depression, both). These indices were used as baseline pre-9/11 physical ($M = 3.62$, $SD = 3.20$) and mental health ($M = 0.21$, $SD = 0.52$) control variables in the analyses.

Between September 20 and October 4, 2001, a national probability sample, drawn from the KN panel, completed a modified version of the Stanford Acute Stress Reaction Questionnaire (SASRQ; Cardena, Koopman, Classen, Waelde, & Spiegel, 2000). Items were revised to a 6.5-grade Kincaid reading level, and respondents reported whether they "experienced" or "did not experience" symptoms specific to the 9/11 attacks ($M = 1.20$, $SD = .19$). Individuals whose constellation of symptoms met Criteria B, C, D, and E for acute stress disorder (ASD; i.e., three or more dissociative symptoms, one or more reexperiencing-intrusive symptom, one or more avoidance symptom, and one or more arousal/anxiety symptom) according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000) were classified as having "high" levels of acute stress. Because some *DSM-IV-TR* criteria were not assessed (e.g., feeling fear, horror, helplessness; symptom duration), respondents were not assumed to have ASD. All respondents who provided genetic data completed the SASRQ.

September 11th-related PTS symptoms were assessed annually using the PTSD Checklist-Civilian Version (PCL; Weathers, Litz, Herman, Huska, & Keane, 1993), a well-validated 17-item self-report measure of intrusion, avoidance, and arousal symptoms with excellent reliability (all α s $> .92$). Respondents used a scale ranging from 1 (*not at all*) to 5 (*extremely*) to indicate how distressed

and bothered they were by symptoms related to the 9/11 attacks over the prior 7 days. The PTS symptom severity was calculated by averaging the 17 items. As we did not assess all *DSM-IV-TR* PTSD criteria (e.g., duration of symptoms) and most respondents were not directly exposed to 9/11, we address predictors of PTS symptoms, not PTSD diagnosis, as measured 2 years ($M = 1.30$, $SD = .44$) and 3 years ($M = 1.31$, $SD = .45$) following 9/11. Because PTS symptoms were positively skewed at each time point, log-transformed values were used in analyses.

Respondents' 9/11-related exposure was assessed in the year following the attacks using items modified from prior research on disaster exposure (degree of exposure to and loss from the attacks, including hours of 9/11-related television coverage watched in the week following the attacks; Koopman, Classen, & Spiegel, 1994). Individuals were categorized into one of three levels of exposure: direct exposure—in the World Trade Center (WTC) or Pentagon, seeing or hearing the attacks in person, or having a close relationship with someone in the targeted buildings or airplanes (i.e., meeting Criterion A1 for ASD and PTSD; 3.6%); live media exposure—watching the attacks on television live as they occurred (63.2%); and no live exposure—seeing video replay or learning of the attacks only after they occurred (33.2%).

Lifetime exposure to stressful events was assessed in the year following 9/11/01 by asking participants whether they ever experienced 37 different negative events (e.g., child abuse, combat) and their age(s) when they occurred. This measure, modified from the Diagnostic Interview Schedule trauma section (Robins, Helzer, Croughan, Williams, & Spitzer, 1981) was expanded to include stressful events drawn from primary care patients' reports of lifetime stress (Holman, Silver, & Waitzkin, 2000), and has provided rates of events consistent with other community samples (e.g., Breslau et al., 1998). Continuous count variables were computed representing the number of pre-9/11 childhood (under 17 years; $M = 1.91$, $SD = 2.96$) and adulthood stressors ($M = 5.39$, $SD = 4.55$). Ongoing post-9/11 stress was assessed annually for 3 years following 9/11 using this measure, and computed as a count of SLE occurring post-9/11.

The frequency with which respondents were talking about their fears of future terrorism was assessed with the question "In the past week, how often have you talked about your fears about possible future terrorist attacks?" regarding their interactions with three different targets (significant other, family, close friends). Items were scored on a 5-point scale ranging from 1 (*never*) to 5 (*all the time*). The mean score of these three items had excellent reliability (2-years post-9/11, $M = 1.61$, $SD = 0.80$; 3-years post-9/11, $M = 1.64$, $SD = 0.84$; α s $\geq .90$).

The frequency with which respondents experienced social constraints was assessed using a 5-point scale ranging from 1 (*never*) to 5 (*all the time*) to describe the extent to which they felt their significant other, family, and close friends did not want to hear them talk about their fears about future terrorism. Social constraint scores were averaged across all three targets at 2 years ($M = 1.32$,

$SD = 0.75$) and 3 years ($M = 1.35$, $SD = 0.76$) post-9/11. These indices had excellent reliability ($\alpha s \geq .93$).

Genotyping of the serotonin transporter gene *SLC6A4* repeat-length polymorphism and the associated polymorphism rs25531 was done at The Center for Applied Genomics (TCAG) in Toronto Canada using respondents' saliva samples. Genomic DNA was processed using protocols validated for use with OraGene® saliva kits (DNA Genotek, Ontario, Canada). The length polymorphism of serotonin transporter (*SLC6A4*) gene promoter was typed by fragment analysis. Polymerase chain reaction (PCR) amplification of genomic DNA and size-separation was performed on an ABI capillary electrophoresis sequencing instrument (AB 3730XL®; Applied Biosystems, Foster City, CA) in a 96-well microplate format, and fragment sizes identified with the instrument's software.

The *SLC6A4*-HTTLPR polymorphism was PCR-amplified using the following primers from Gelernter et al. (1997): forward 5'-ATGCCAGCACCTAACCCCTAATGT-3'; reverse 5'-GGACCGCAAGGTGGGCGGGA-3'. The forward primer was 5'-labeled with HEX fluorescent dye for visualization. The predicted amplified product lengths of the HTTLPR polymorphism are 419 bp (long allele) and 375 bp (short allele), and in practice, the mobility on an AB 3730XL® DNA analyzer was 412 bp and 370 bp, respectively. To genotype the polymorphism rs25531 within this fragment, an aliquot of amplified PCR products was digested overnight using the enzyme *MspI* and run a second time on the 3730XL® DNA analyzer. The *MspI* restriction enzyme cuts the PCR fragment if the G, but not the A, allele is present at rs25531. A second restriction site 3' to rs25531 is not polymorphic. In conjunction with the pre-digest length polymorphism data, the genotype of rs25531 was determined using *SLC6A4*-HTTLPR undigested/digested fragment length (bp) combinations to infer rs25531 variants as follows: 412/321 as long-a; 370/278 as short-a; 412/149 as long-g; 370/149 as short-g.

Analytic Strategy

Regression analyses were used to examine predictors of PTS symptoms 2 and 3 years after 9/11. Participant age, gender, pre-9/11 mental and physical health, 9/11-related exposure and acute stress, lifetime SLE, and amount of talking about future terrorism were included as controls (See Table 1 for bivariate correlations). Main effects of genotype (any s/lg allele vs. la/la alleles) and social constraints were examined first, followed by interactions between genotype and social constraints. Multiplicative interaction terms were calculated (with social constraint centered before computing the interaction term). Models tested whether concurrent social constraints were associated with PTS symptoms at 2- and 3-years post-9/11. Variance inflation factor and tolerance diagnostics suggested that collinearity was not problematic. To aid interpretation, significant interactions were plotted using one standard deviation

Table 1. Bivariate Correlations Among PTS Symptoms, Social Constraints, and Potential Control Variables

	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.
1. PTS symptoms (2 years)	.73***	.45***	.35***	.11*	.23***	.04	.31***	.15**	.11*	.24***	.27***	.34***	.19***	.01	.07
2. PTS symptoms (3 years)		.40***	.47***	.03	.17***	.03	.38***	.19***	.18***	.21***	.20***	.32***	.29***	-.01	.10
3. Social constraints (2 years)			.41***	.01	.11*	.09	.17***	.07	.05	.09	.01	.25***	.19***	.02	-.03
4. Social constraints (3 years)				.02	.10*	.14**	.14**	.17***	.19***	.23***	.04	.24***	.20***	.09	-.01
5. Any short allele (0 = LL)					.04	.05	.04	-.02	-.01	.06	-.04	.05	.01	.07	-.03
6. Gender (0 = male)						-.07	.18***	.11*	.09	.08	.08	.10*	-.01	.01	.01
7. Age							-.08	.25***	-.18***	.25***	-.16***	.10	.15**	.19***	-.09*
8. Pre-9/11 mental health								.30***	.12**	.21***	.17***	.04	.09	-.02	.09*
9. Pre-9/11 physical health									.01	.28***	.02	.11*	.18***	.12*	-.04
10. Childhood SLE										.36***	.10*	.08	.02	.02	.07
11. Adult SLE											.06	.15**	.19***	.11*	-.04
12. 9/11-related acute stress												.07	-.04	-.08	.07
13. Talking about 9/11 (2 years)													.53***	.02	.15**
14. Talking about 9/11 (3 years)														.04	.06
15. Live media exposure to 9/11															-.17***
16. Direct 9/11 exposure															

Note. $N = 463$. The reference group for live media and direct exposure is no live exposure. PTS = Posttraumatic stress; SLE = stressful life events.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 2. Demographic and Control Variable Mean or Percent by Genotype

Variable	Any short			Homozygotic long A		
	<i>n</i>	<i>M</i> or %	<i>SD</i>	<i>n</i>	<i>M</i> or %	<i>SD</i>
Pre-9/11 mental health	336	0.22	0.52	127	0.17	0.51
Pre-9/11 physical health	336	3.99	3.37	127	4.08	3.06
Childhood SLE	322	2.01	2.89	122	2.04	2.59
Adulthood SLE	322	5.89	5.06	123	5.33	3.65
Acute Stress	336	1.21	0.19	127	1.21	0.18
PTSD symptoms (2 year/3 year)	274/303	1.31/1.33	0.46/0.53	96/108	1.22/1.29	0.43/0.48
Talking about 9/11-related fear (2 year/3 year)	274/318	1.60/1.65	0.80/0.84	94/116	1.50/1.63	0.73/0.85
Social constraints (2 year/3 year)	253/300	1.34/1.35	0.81/0.77	90/110	1.34/1.32	0.84/0.78
Age	336	51.77	15.33	127	49.90	15.87
Female (%)	176	52.4		61	48.0	
Education (%)						
High school degree	121	36.1		48	37.8	
College degree	99	29.6		42	33.1	
Exposure (%)						
Live TV	207	64.5		70	57.4	
Direct exposure	5	1.6		3	2.5	

Note. Short genotypes are short/short, short/long g, and long g/long g. SLE = stressful life events; PTSD = posttraumatic stress disorder.

above (high) and below (low) mean social constraint values. Simple slopes were calculated and statistically compared to zero for interpretation (Aiken & West, 1991; Preacher, Curran, & Bauer, 2004).

RESULTS

Attrition Analysis

Individuals who provided saliva samples did not differ from respondents who did not provide saliva in terms of pre-9/11 mental health status, acute stress symptoms, gender, ethnicity, educational status, income, or mental health disorders across the 3-year study. Respondents who provided saliva were somewhat older, odds ratio (*OR*) = 1.01, 95% confidence interval (*CI*) [1.003, 1.02], *p* = .007, and more likely to be married than widowed, *OR* = 0.39, 95% *CI* [0.22, 0.69], *p* = .001. There were nonsignificant trends for participants who provided saliva to report more adulthood trauma, *OR* = 1.03, 95% *CI* [0.99, 1.06], *p* = .07; and pre-9/11 physical disorders than those who did not provide saliva, *OR* = 1.03, 95% *CI* [0.99, 1.08], *p* = .09.

5-HTTLPR Genotype

This study includes 463 European American respondents from the original study whose triallelic 5-HTTLPR genotypes were *s/s*, *s/lg*, or *lg/lg* = 119 (25.7%), *la/lg*, *la/s* = 217 (46.8%), *la/la* = 127 (27.4%). Both the repeat length and rs25531 polymorphisms were

in Hardy-Weinberg equilibrium (*ps* > .80). There were no gender differences, $\chi^2(1, N = 463) = 0.70$, *p* = .40, in genotype coding (any *s/lg* vs. *la/la*); and genotype was not associated with pre-9/11 mental or physical health, *F*(2, 460) = 0.53, *p* = .59, *F*(2, 460) = 0.09, *p* = .91, respectively; lifetime SLE, *F*(2, 442) = 0.56, *p* = .57; exposure to the 9/11 attacks, $\chi^2(4, N = 443) = 3.19$, *p* = .53; or social constraints, *F*(2, 340) = 0.48, *p* = .62, *F*(2, 407) = 0.17, *p* = .85, at 2- and 3-years post-9/11, respectively. Table 2 presents demographic and control variable information by genotype.

Post-9/11 Talking About Fears and Constraints

Over the 3 years following 9/11, 48–49% of respondents reported talking about their fears of future attacks at least a little. Approximately one quarter of the sample reported feeling constrained at least a little of the time because their social ties did not want to hear about their fears of future attacks.

PTS Symptoms, 2-Years Post-9/11

Two-years post-9/11, significantly higher PTS symptoms were associated with ongoing stress, being female, reporting high 9/11-related acute stress, and talking about future terrorism (Table 3). Controlling for potential confounding variables, neither genotype nor social constraints were associated with PTS symptoms 2-years post-9/11 (social constraints was associated with more PTS

Figure 1a (top, 2 year) & 1b (bottom, 3 year). Any short allele (s/s, s/lg, lg/lg vs. la/la allele) and social constraints in relation to posttraumatic stress (PTS) symptoms.

* $p < .05$. ** $p < .01$. *** $p < .001$.

symptoms before control variables were included). However, genotype interacted with social constraints to predict higher PTS symptoms. Examination of simple slopes revealed a significant positive association between social constraints and PTS symptoms for individuals with an s/lg allele but not for those individuals without an s/lg allele (see Figure 1a). Under low social constraints, genotype was unrelated to PTS symptoms; under high social constraints, respondents with an s/lg allele reported significantly higher PTS symptoms than those with the la/la genotype.

PTS Symptoms, 3-Years Post-9/11

Three years post-9/11 social constraints was associated, but genotype was not associated, with higher PTS symptoms when controlling for potential confounding variables (genotype was marginally associated with PTS symptoms before control variables were added). PTS symptoms were positively associated with ongoing stress, being female, pre-9/11 mental health problems, 9/11-related acute stress, and talking about fears of future terrorism. Social

Table 3. Serotonin and Social Constraints in Relation to PTS Symptoms 2 and 3 Years After 9/11

Variable	2 Years				3 Years			
	Without controls		With controls		Without controls		With controls	
	<i>b</i>	<i>SE</i>	<i>b</i>	<i>SE</i>	<i>b</i>	<i>SE</i>	<i>b</i>	<i>SE</i>
Any short allele	−0.022	0.022	−0.019	0.019	−0.044	0.024	−0.029	0.022
Social constraints	0.032**	0.013	0.017	0.011	0.043**	0.014	0.031**	0.012
Any short allele × social constraints	0.044**	0.015	0.039**	0.013	0.042**	0.016	0.032*	0.015
Gender (0 = male)			0.032***	0.005			0.020	0.010
Age			0.000	0.001			0.000	0.000
Pre-9/11 mental health			0.015	0.011			0.051***	0.012
Pre-9/11 physical health			0.001	0.002			−0.001	0.002
Childhood SLE			−0.002	0.002			0.003	0.002
Adulthood SLE			0.001	0.001			−0.002	0.001
Ongoing stress			0.032***	0.005			0.023***	0.005
Exposure								
Indirect			−0.001	0.010			−0.011	0.011
Direct			0.027	0.041			0.050	0.045
9/11-related acute stress			0.055**	0.019			0.052**	0.017
Talking about fear of future terrorism			0.024***	0.006			0.026***	0.006

Note. Sample size at 2 years was 340; sample size at 3 years was 383. PTS symptom scores were log-10 transformed. Reference group for exposure to the 9/11 attacks is “no live exposure.” SLE = stressful life events.

* $p < .05$. ** $p \leq .01$. *** $p \leq .001$.

constraints also interacted with genotype to predict PTS symptoms (Figure 1b): There was a significant positive association between social constraints and PTS symptoms for individuals with and without short alleles (Table 3; Figure 1b). Although both simple slopes were significantly different from zero, the significant interaction term indicated that the association between social constraints and PTS symptoms for individuals with an *s/lg* allele was significantly stronger than the relationship between social constraints and PTS symptoms for *la/la* individuals. Under low social constraints, genotype was unrelated to PTS symptoms; under high social constraints, respondents with an *s/lg* allele reported significantly higher PTS symptoms than those with the *la/la* genotype.

DISCUSSION

In this national, prospective longitudinal study we extend previous findings suggesting that 5-HTTLPR genotype, SLE exposure, and social environments interact to predict trauma-related PTSD symptoms (Caspi et al., 2003, Kilpatrick et al., 2007). We demonstrate that vulnerability to PTS symptoms conferred by the 5-HTTLPR *s/lg* allele following collective stress (9/11) can be exacerbated by social constraints on disclosure regarding fears of future terrorist attacks. Our findings remain robust even after controlling for pre-9/11 mental and physical health, lifetime and ongoing SLE, exposure to the attacks, and acute stress immediately

post-9/11. The salience of these findings is highlighted by the fact that, since the attacks, the fear of terrorist attacks was repeatedly and collectively reinforced through warnings issued by the federal government.

To our knowledge, this is the first study addressing combined $G \times E$ effects on PTS symptoms in a national sample of individuals exposed to the same event—the 9/11 attacks—with baseline health status documented before a specific stressor, early assessment of acute stress symptoms, and 3 years of follow-up mental health data. With this prospective, longitudinal design we controlled for many potential confounds (e.g., ongoing stress) and examined PTS symptoms over time following collective stress.

Prior research addressing the social context of the relationship between 5-HTT genotype and post-SLE mental health focused on individuals directly exposed to an event (e.g., Caspi et al., 2003; Kaufman et al., 2006). Our focus on individuals indirectly exposed to collective stress—some of whom reported never experiencing lifetime SLE before 9/11—extends this work and suggests that prior or direct personal exposure to SLE are not necessary conditions to elicit $G \times E$ interactions with the triallelic 5-HTTLPR polymorphism activity. Although many researchers are studying the biological pathways connecting childhood stress with chronic illnesses (e.g., Miller & Chen, 2010), little is known about biological processes that may link indirect stress exposure to mental and physical health problems. Given the potential public health

implications of identifying serious health consequences of indirect exposure to traumatic stress, our findings suggest this may be an important area for future research.

As our respondents were exposed to the attacks primarily through the media, these findings suggest that media reports of an uncontrollable, unknown threat (e.g., terrorism) may spread the event's impact geographically (Wright, Ursano, Bartone, & Ingraham, 1990) and trigger risk appraisals that render some individuals more vulnerable to PTS symptoms (Marshall et al., 2007). Given that the *s/lg* allele heightens the excitability of anxiety/fear pathways in the brain and the tendency to respond more strongly to perceived threats (Caspi et al., 2010), we would expect *s/lg* allele carriers to be more sensitive to these media reports than individuals with the *la/la* genotype. For all individuals, but especially *s/lg* allele carriers, those who want to talk about their fears, social constraint on this disclosure could further exacerbate or prolong PTS symptoms by making it even more difficult to shut down fear processing in the brain. These findings highlight the importance of considering $G \times E$ effects on mental health following both direct and indirect exposure to collective SLE.

Finally, this study focuses on social constraints, a less commonly studied dimension of social responses known to exacerbate PTS-like symptoms (Lepore et al., 1996), and negatively impact health (Frattaroli, 2006). This is an important contribution to research addressing $G \times E$ effects on PTSD given that both inhibition of emotional disclosure (constraints) and the 5-HTTLPR genotype have both been associated with stress-related physiologic arousal (Berry & Pennebaker, 1993; Caspi et al., 2010). As there is a large body of research suggesting that PTSD increases one's risk for developing a variety of physical health problems, especially cardiovascular disease (e.g., Kubzansky & Koenen, 2009), future research should address whether the $G \times E$ context involving social constraints and the 5-HTTLPR genotype helps to explain the mental–physical health connection following stress/trauma.

Limitations

Although the sample for the original study closely paralleled the U.S. population census, our subsample is not representative. Compared to the original sample, our respondents are older, more likely to be widowed, with slightly (not significantly) more health problems, and adulthood trauma. To prevent interethnic variation in genotype from confounding our findings, we restricted analyses to European American individuals. These differences limit generalizability of our findings. Although we prospectively controlled for pre-9/11 mental health and early acute stress reactions—both strong correlates of personality traits—potentially confounding personality characteristics were not included in our analyses (See Kuzelova, Ptacek, & Macek, 2010). As PTS symptom levels reported by our respondents are generally low, these $G \times E$ relationships should be replicated in larger, representative samples reporting higher levels of stress-related symptoms. We also did not

examine the macro-level social environmental factors that may influence the $G \times E$ effect on PTSD (Koenen et al., 2009). Future studies would ideally include multilevel models that identify salient $G \times E$ interactions using other micro- and macro-level social environments simultaneously (Galea et al., 2006). Finally, although hypothesis-driven candidate-gene $G \times E$ studies provide important context for understanding the gene-PTSD link, genome-wide association studies are also critical for characterizing the multi-genetic predictors of PTS responses (Cornelis, Nugent, Amstadter, & Koenen, 2010).

CONCLUSION

We provide preliminary evidence of social influence on the relationship between the serotonin transporter polymorphism and PTS symptoms in a sample of individuals exposed to collective stress. We have extended prior research by addressing the $G \times E$ process in indirectly exposed individuals some of whom had never experienced lifetime SLE. Through our focus on social constraints, we have expanded the range of social processes known to moderate the gene–mental health relationship, and identified a potential new approach to understanding the interface between stress-related mental and physical health problems.

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