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Environmental stress, oxytocin receptor gene (*OXTR*) polymorphism, and mental health following collective stress

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ABSTRACT

We examined whether the oxytocin receptor gene (*OXTR*) single nucleotide polymorphism (SNP) rs53576 genotype buffers the combined impact of negative social environments (e.g., interpersonal conflict/constraint) and economic stress on post-traumatic stress (PTS) symptoms and impaired daily functioning following collective stress (September 11th terrorist attacks). Saliva was collected by mail and used to genotype 704 respondents. Participants completed Web-based assessments of pre-9/11 mental health, acute stress 9–23 days after 9/11, the quality of social environments 1 year post-9/11, economic stress 18 months post-9/11, and PTS symptoms and impaired functioning 2 and 3 years post-9/11. Interactions between negative social environments and economic stress were examined separately based on *OXTR* rs53576 genotype (GG vs. any A allele). For individuals with an A allele, a negative social environment significantly increased PTS symptoms without regard to the level of economic stress experienced. However, for respondents with a GG genotype, negative social environments predicted elevated PTS symptoms only for those also experiencing high economic stress. Gender moderated associations between negative social environments, economic stress, and impaired functioning. The functioning of females was most affected by negative social environments regardless of genotype and economic stress, whereas the functioning of males was differentially susceptible to economic stress depending on *OXTR* genotype and negative social environments. These findings suggest that it is important to consider the combined impact of gender and ongoing stress in different domains as moderators of genetic vulnerability following collective stress.

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Introduction

It has long been recognized that the quality of one's social environment predicts myriad mental and physical health outcomes, especially in the context of coping with stressful life events (SLE). Indeed, high quality, supportive environments can buffer the effects of stressful experiences (Baumeister and Leary, 1995; Cohen, 1988; House et al., 1988; Uchino et al., 1996), whereas negative, unsupportive environments can exacerbate the effects of acute or chronic stressors (Gunnar et al., 1996; Lucas-Thompson, 2012; Serido et al., 2004). Recently, attention has turned to improving our understanding of the role individual differences play in our sensitivity to social environments.

Toward this end, the oxytocin system (OXT) has garnered theoretical and empirical attention as an evolutionarily-conserved moderator of mammalian social behaviors that comprise the caregiving behavioral system (Heinrichs and Domes, 2008; Heinrichs et al., 2009; MacKinnon and Luecken, 2008). The neuropeptide oxytocin, a central component of this system, helps shape social behaviors and plays a critical role in our

responses to the social environment around us; in stressful situations, oxytocin can also decrease behavioral and physiologic responses to stress (MacKinnon, 2008; see Meyer-Lindenberg et al., 2011 for a review). A rapidly growing body of evidence suggests that individual differences in OXT function may be key to understanding how social environments influence mental and physical health when coping with stress (e.g., Smith and Wang, 2012).

One way to study individual differences in OXT function is to examine behavioral phenotypes associated with variations in the oxytocin receptor gene (*OXTR*) single nucleotide polymorphisms (SNP). Although the relationship between *OXTR* SNP genotypes and OXT function in humans is not fully understood (e.g., Riem et al., 2011), *OXTR* SNPs have been associated with individual differences in social-cognitive, socio-emotional, and mental health outcomes (Chen et al., 2011; Meyer-Lindenberg et al., 2011; Rodrigues et al., 2009; Tost et al., 2010). One of the most studied *OXTR* polymorphisms is rs53576 (G/A), with recent studies demonstrating that people who carry an A allele exhibit deficits in socioemotional domains such as parenting (Bakermans-Kranenburg and van IJzendoorn, 2008; Feldman et al., 2007), empathy (Rodrigues et al., 2009), prosociality (Kogan et al., 2011), psychological resources (Saphire-Bernstein et al., 2011), and positive affect (Lucht et al., 2009). The rs53576 A allele has also been associated with severe

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social functioning deficits common in autism spectrum disorders (Wermter et al., 2010; Wu et al., 2005) and depression (e.g., Saphire-Bernstein et al., 2011). However, the pattern of findings is not consistent across studies investigating rs53576 differences in depression: in one, respondents with the GG genotype were significantly more likely to have unipolar depression (Costa et al., 2009), whereas another suggests that A allele carriers report having fewer psychological resources and more depressive symptomatology (Saphire-Bernstein et al., 2011). These discrepant findings highlight the need for more research examining the relationships among OXT function, social environments, and mental health.

In stressful situations, the oxytocin system may stimulate affiliative behavior (Taylor, 2006), and help attenuate hypothalamic–pituitary–adrenal axis responses (e.g., Chen et al., 2011). In so doing, the OXT functions to mobilize social supports and minimize the risk for developing depressive or anxious behaviors (Smith and Wang, 2012). As part of this system, the OXTR SNP rs53576 genotype appears to have stress-buffering effects with the GG genotype showing greatest sensitivity to the physiologic effects of oxytocin (e.g., Bakermans-Kranenburg and van IJzendoorn, 2008; Rodrigues et al., 2009; Tost et al., 2010). This sensitivity is thought to boost sociability and interpersonal awareness and make GG individuals more responsive to social approval cues (Tost et al., 2010). Indeed, individuals with at least one G allele seek more emotional support during stressful periods (if it is culturally acceptable; Kim et al., 2010), and benefit more from social support when anticipating and responding to acute stressors (Chen et al., 2011). Together, these findings suggest the rs53576 GG genotype may render individuals more sensitive or responsive to their social environments.

However, to date, this research has focused predominantly on the combined stress-buffering effects of oxytocin and *positive* social relationships. Negative experiences in one's social environment, particularly in response to affiliative attempts, may actually exacerbate the harmful effects of stress (Taylor, 2006). For example, women with high plasma levels of oxytocin are more focused on characteristics of the social environment and more distressed by negative social experiences than women with lower levels of oxytocin (Taylor et al., 2006). If the OXTR rs53576 GG genotype enhances oxytocin sensitivity or function, we would expect *negative* features of the social environment to potentiate the impact of stress on mental health for GG individuals more than they would for individuals carrying an A allele. To test this hypothesis, we drew from recent work demonstrating the negative impact of economic stress (i.e., foreclosures) on public mental health (McLaughlin et al., 2012) and examined interactions between negative, unsupportive social environments and the economic stress experienced after 9/11 (e.g., Rhee, 2005). Those who lack sufficient financial resources suffer in terms of their psychological well-being (e.g., Arling, 1987; Dooley et al., 1996; George, 1992; Krause, 1995; McLaughlin et al., 2012). Economic stress may also exacerbate social and family problems, by triggering conflict and coercion (e.g., Conger et al., 1993, 1994). In that sense, economic stress becomes a macro-level stressor that may have implications for how well individuals respond to more immediate stressors like interpersonal conflict.

Post-traumatic stress disorder (PTSD) is thought to result from dynamic $G \times E$ interactions (Broekman et al., 2007), with positive and negative social environments powerfully affecting its development and course (Charuvastra and Cloitre, 2008). Several researchers have argued that oxytocin may have therapeutic value for treating PTSD (Olff et al., 2010; Pitman et al., 1993), and there is evidence that administration of oxytocin reduces acute PTSD symptoms, at least to some extent (Yatzkar and Klein, 2010), supporting the idea that the OXT is related to post-traumatic stress symptoms. However, to our knowledge, there is no evidence linking the OXTR rs53576 polymorphism or combined OXTR rs53576 gene–social environment influences to PTSD symptomatology.

Although most research on posttraumatic stress response has focused on those who have directly experienced individual SLE, collective

stress can also affect the mental and physical health of those indirectly exposed (Cohn et al., 2004; Conejero and Etxebarria, 2007; Holman et al., 2008, 2011; Shedd et al., 2004; Wayment, 2004). Importantly, when many people in a community are simultaneously coping with a collective SLE, the social environment may experience strain and become less responsive to individuals seeking social support (Lee and Fairbank, 2000; Pennebaker and Harber, 1993). This strain makes a collectively-experienced stressor a particularly useful paradigm in which to study how the OXTR rs53576 genotype is associated with the combined impact of social and economic stress on PTS symptoms. Given this approach, however, it is important to acknowledge that many respondents are likely to report sub-clinical levels of PTS symptoms following indirect SLE exposure (e.g., Silver et al., 2002), and that for some people these symptoms may have little impact on their lives. Therefore, to fully understand the impact of these symptoms on respondents' lives, it is important to also examine the degree to which respondents' emotional health impacts their day-to-day functioning.

Toward this end, we examined gene–environment ($G \times E$) interactions between the OXTR rs53576 genotype, negative social environments, and economic stress in relation to 9/11-related post-traumatic stress (PTS) symptoms and impaired daily functioning using a nationwide 3-year prospective longitudinal study. We hypothesized that respondents with a GG genotype would be more sensitive and vulnerable to the cumulative effects of negative social environments and economic stress than individuals with an A allele. To test this hypothesis, we examined the interactions between negative social environments and economic stress separately for individuals with a GG genotype versus those with any A allele to determine if the GG genotype renders individuals more vulnerable to mental health symptoms in the face of negative social environments and economic stress. Furthermore, given the documented gender differences in rates of PTS symptoms/disorders (Creamer et al., 2001; Kessler et al., 1995; Stein et al., 1997), as well as evidence that the OXTR system evolved to affect males and females differently (Taylor, 2006), we examined whether associations between negative social environments, economic stress, and the outcomes of interest were moderated by participant gender.

Method

Overview of study

This study analyzed a subset of individuals who participated in a three-year prospective longitudinal study of a nationally representative sample of Americans. Participants in the larger study ($n = 2,729$) were surveyed 2–3 weeks, 2, 6, 12, 18, 24, and 36 months following the 9/11 attacks (Silver et al., 2006). In addition, pre-9/11 mental and physical health data had been collected prior to the attacks. Participants were recruited by Knowledge Networks, Inc. (KN), a firm that uses multistage random-digit-dialing probability sampling to recruit and maintain a nationally representative panel for web-based survey research. Surveys were administered electronically through a password-protected account. KN provides internet access (i.e., service and appliance) to recruits who do not have internet access to ensure panel representativeness. The study design has been detailed elsewhere (Silver et al., 2006).

Current study procedures

See Table 1 for a timeline of data collection for the current study. Participants for the current study were recruited from the larger study described above. The 1296 individuals from the larger study who had indicated that they could be contacted again were invited to participate in the genetic phase of the study; participants who were still members of the KN panel were paid \$50, and participants who were no longer members of the KN panel were paid \$75 for providing saliva. Of those who could be contacted again, 711 returned their saliva samples using OraGene kits mailed to their homes (55%

Table 1
Timeline of data collection.

	Pre-Sept 2001	Sept 2001	Sept 2002	Mar 2003	Sept 2003	Sept 2004	June 2008
MD-diagnosed mental health disorders	X						
Acute stress symptoms		X					
Negative social environment			X				
Economic stress				X			
Other recent stress			X	X	X	X	
Post-traumatic stress symptoms					X	X	
Impaired social/work functioning					X	X	
Saliva for genotyping							X

return rate). Seven hundred and four of the participants' oxytocin genotypes were successfully identified (99% call rate). The University of California, Irvine Institutional Review Board approved all research procedures.

Participants

Participants with identified oxytocin genotypes did not significantly differ from respondents without genetic data in terms of gender, household income, pre-9/11 mental health, 9/11 acute stress, 1-year negative social environment, 2-year PTS symptoms, or 3-year PTS symptoms. However, they were slightly older, 49.8 vs. 46.3 years, $t(2717) = 4.91$, $p < .001$, and reported slightly higher levels of 18-month economic stress, 1.82 vs. 1.70; $t(1595) = -2.24$, $p = .013$.

On average, the 704 participants were 49.8 years of age ($SD = 15.5$; range 18 to 101 years) and were evenly distributed with respect to gender (52.3% female). The majority of individuals were White, Non-Hispanic (74.9%), followed by Black, Non-Hispanic (8.92%), Hispanic (8.92%), and other, Non-Hispanic (7.19%). The median household income was between \$35,000 and \$39,999. The majority of the sample was married (65.5%), and relatively well educated, with 90.5% having at least a high school diploma and 29.3% having a college degree or higher.

Measures

Pre-9/11 mental health

Pre-9/11 mental health was assessed between June 2000 and September 9, 2001. Participants indicated the presence or absence of doctor-diagnosed depression and anxiety using questions modified from the Centers for Disease Control's National Center for Health Statistics annual National Health Interview Survey (NHIS) (US Department of Health and Human Services, 2000). A count of ailments (none, anxiety or depression, both) was created to control for pre-9/11 mental health.

9/11 acute stress

A modified version of the Stanford Acute Stress Reaction Questionnaire (SASRQ) assessed acute stress symptoms. Items were revised to a 6.5 grade Kincaid reading level; respondents reported whether they "experienced" or "did not experience" 9/11-specific symptoms. Individuals whose constellation of symptoms met DSM-IV criteria B, C, D, and E for Acute Stress Disorder (ASD; American Psychiatric Association, 2000) were classified as high acute stress ($N = 51$, 9.85%). As some DSM-IV 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 9–23 days post-9/11.

Negative social environment

Negative social environment was measured 1-year post-9/11 by having respondents rate how often (1 = Never, 5 = All the time)

they had a disagreement with, became openly angry with, or felt three potential targets (romantic partner, family, and close friends) did not want to hear respondents' feelings about 9/11 or fears of future terrorist attacks during the previous week. The mean of these nine items for all targets was used as an index of perceived negative social environment ($\alpha = .84$); because these scores were significantly positive skewed, log-transformed values were used in the analyses.

Economic stress

Perceived economic stress was measured 18-months post-9/11 using three items created for the current study. Participants were asked to describe the frequency with which they were unable to afford food or clothing for their family and unable to pay monthly bills using a 5-point Likert scale ranging from 1 (none at all) to 5 (all the time) ($\alpha = .77$). Because economic stress scores were significantly positively skewed, log-transformed values were used in the analyses.

Post-traumatic stress symptoms

At two and three years post-9/11, PTS symptoms were assessed using the PTSD Checklist-Civilian Version (PCL; Weathers et al., 1993), a widely used, appropriately sensitive, and well-validated 17-item self-report measure of intrusion, avoidance, and arousal symptoms with excellent reliability (e.g., Blanchard et al., 1996; Ruggiero et al., 2003) (all α s $> .92$). Respondents used a scale ranging from 1 (not at all) to 5 (extremely) to indicate how distressed they were by each symptom in the past month. Individuals' responses were summed to create a total severity score. Because PTS symptom scores were significantly positively skewed, log-transformed values were used in the analyses.

Impaired work/social functioning

Two and three years post-9/11, respondents were asked to indicate the frequency (1 = Never, 5 = All the time) with which their emotional health had interfered with their ability to perform regular daily activities in their work and social spheres, using two items drawn from the Rand SF-36 (Ware et al., 1994); the reliability, validity, and sensitivity of this measure have been previously documented (e.g., McHorney et al., 1993; Ware and Sherbourne, 1992). Higher scores indicate greater impairment in functioning. Mean scores were used as indices for each survey. Scale reliability was excellent at both time points (α s = .89).

Oxytocin genotype

The Center for Applied Genomics (TCAG; www.tcag.ca) in Toronto, Canada performed DNA extraction and genotyping. DNA was extracted from Oragene saliva self-collection kits (DNA Genotek) using the Autopure LS system and PUREGENE chemistry (Gentra systems) following the manufacturer's protocol. Genotyping was performed using Applied Biosystems' Taqman SNP genotyping technology. The 10 μ l reaction mix consisted of 5 μ l Taqman Genotyping Master Mix (Applied Biosystems), 0.15 μ l of 40 \times combined primer and probe mix, 5.0 μ l water and 50 ng of DNA template. Cycling conditions for the reaction were 95 $^{\circ}$ C for 10 min, followed by 40 cycles of 95 $^{\circ}$ C for 15 s and 62 $^{\circ}$ C for 1 min, and one final cycle of 10 $^{\circ}$ C. Samples were analyzed using the ABI 7900HT Sequence Detection System and analyzed using SDS v2.3 software.

Covariates

All analyses adjusted for self-reported age, household income, gender, pre-9/11 mental health (a count of pre-9/11 common mental health ailments, modified from the Centers for Disease Control's National Center for Health Statistics annual National Health Interview Survey) (US Department of Health and Human Services, 2000), 9/11-related acute stress (Cardena et al., 2000), and the experience of recent

stressors. Recent stress was assessed in the annual surveys by asking respondents to report whether they had experienced any of 37 negative events (e.g., serious illness or injury, natural disaster) in the past year (Silver et al., 2002). This measure was modified from the Diagnostic Interview Schedule section on trauma (Robins, Helzer, Croughan, Ratcliff, 1981) and expanded using open-ended coding of lifetime stressors reported in primary care (Holman et al., 2000), and has provided rates of specific events in this sample comparable to surveys conducted on other community samples (Breslau et al., 1998; Kessler et al., 1995). The total number of the events reported annually was created as a measure of recent stress.

Plan of analyses

Statistical analyses were conducted using STATA 12.0 (College Station, TX). *OXTR* rs53576 was recoded to GG vs. any A (AA/AG) to ensure sufficient power for the analyses. Bivariate correlations among study variables were examined (see Table 2). We examined the associations between negative social environments at 1 year post-9/11, economic stress at 18 months post-9/11, and subsequent outcomes 2–3 years post-9/11 using generalized estimating equation (GEE) models. GEE models are regression-based statistical methods that specify the contribution of time along with the other predictors for longitudinal outcomes. GEE models produce more efficient, unbiased estimates of longitudinal data compared to ANOVA-based methods (Zeger and Liang, 1986). Main effects of control and independent variables were tested first, with interactions among key variables tested subsequently. Stress variables were centered prior to computing the multiplicative interaction terms. Because hypotheses centered on differential effects of social and economic stressors for GG and any A individuals, interactions between negative social environments and economic stress were tested separately for individuals with GG and those carrying an A allele. To examine whether negative social environments and economic stress work together in similar ways for both males and females, three-way interactions between gender, negative social environments, and economic stress were tested within genotype (GG vs. any A). Per Aiken & West's guidelines (Aiken and West, 1991), interactions were plotted, with predicted values of the outcome based on high (one SD above the mean) and low (one SD below the mean) values. Simple slopes (using high and low values) were also calculated and statistically compared to zero for interpretation (Aiken and West, 1991; Preacher et al., 2006).

Results

Genotype

The *OXTR* rs53576 SNP was in Hardy–Weinberg equilibrium, $\chi^2(1) = 0.1, p > .05$, with 361 “GG”, 284 “AG”, and 59 “AA” respondents; there were no genotype-by-gender differences, $\chi^2(2) = 1.32, p = .52$, or genotype-by-ethnicity differences, $\chi^2(6) = 7.22, p = .30$. Genotype was not directly associated with either outcome. The call rate was 704/711 or 99.0%.

Bivariate correlations

Age differences in negative social environments, economic stress, and impaired functioning at 3-years were evident, with older participants reporting significantly fewer problems in these domains. When compared to females, males reported lower levels of economic stress, PTS symptoms, and impaired functioning. Income was related to the primary variables of interest, with negative social environments, economic stress, mental disorders, and impaired functioning being less evident in participants with more income. As expected, negative social environments, economic stress, PTS symptoms, and impaired functioning were all significantly and positively intercorrelated. Genotype was not directly associated with any other variables in the analyses.

GEE modeling

PTS symptoms

There were no gender differences in the patterns of associations between negative social environments, economic stress, and PTS symptoms for participants with the GG genotype or carriers of an A allele (see Table 3). Therefore, results for men and women were not examined separately for this outcome.

GG genotype. After controlling for theoretically-relevant covariates, there were significant main effects of both negative social environments and economic stress on PTS symptoms: more negative social environments and more frequent economic stress were associated with higher PTS symptoms (see Table 3). The expected interaction between negative social environments and economic stress in relation to PTS symptoms was also significant. As displayed in Fig. 1 (left panel), for respondents experiencing low economic stress,

Table 2
Bivariate correlations among major study constructs.

	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
Age	-.05	-.03	-.02	-.12**	.03	-.02	-.15***	-.18***	.02	.03	-.05	-.09*
Gender ^a	-	-.12**	.18***	.12**	.14***	.04	.06	.11*	.20***	.11**	.16***	.12**
Income	-	-	-.12***	-.04	-.15***	-.01	-.08*	-.36***	-.10*	.09*	-.23***	-.20***
Pre-9/11 mental health	-	-	-	.18***	.32***	-.07	.10*	.26***	.27***	.32***	.30***	.37***
9/11-related acute stress	-	-	-	-	.19***	-.05	.16***	.12**	.30***	.26***	.16***	.15***
Recent stressors	-	-	-	-	-	-.01	.16***	.25***	.37***	.41***	.29***	.37***
<i>OXTR</i> genotype ^b	-	-	-	-	-	-	-.03	.01	-.08	-.01	-.06	-.02
1-Year negative social environment ^c	-	-	-	-	-	-	-	.29***	.35***	.37***	.29***	.27***
18-Month economic stress ^c	-	-	-	-	-	-	-	-	.28***	.32***	.30***	.35***
2-Year PTS symptoms ^c	-	-	-	-	-	-	-	-	-	.73***	.54***	.22***
3-Year PTS symptoms ^c	-	-	-	-	-	-	-	-	-	-	.33***	.51***
2-Year impaired functioning ^c	-	-	-	-	-	-	-	-	-	-	-	.54***
3-Year impaired functioning ^c	-	-	-	-	-	-	-	-	-	-	-	-

* $p < .05$.

** $p < .01$.

*** $p < .001$.

^a 0 = male, 1 = female.

^b 0 = GG genotype, 1 = any A allele.

^c Log-transformed values.

Table 3

Generalized estimating equations (GEEs) examining the association between negative social environments, economic stress, and PTS^a symptoms 2- to 3-years post-9/11 for GG and any A individuals.

Variable	GG genotype			Any A allele		
	<i>b</i>	<i>SE</i>	<i>P</i>	<i>b</i>	<i>SE</i>	<i>p</i>
Time	.001	.006	.875	.005	.006	.399
Age	.001	.001	.011	.001	.001	.100
Household income	.002	.002	.070	.001	.002	.716
Gender ^b	.013	.012	.266	.024	.011	.036
Pre-9/11 mental health	.031	.013	.017	.015	.016	.334
9/11-related acute stress	.090	.027	.001	.067	.024	.004
Recent stressors	.013	.005	.011	.016	.006	.008
Negative social environments ^{a,c}	.223	.049	<.001	.176	.044	<.001
Economic stress ^{a,c}	.178	.043	<.001	.078	.050	.121
Negative social environments × economic stress	.689	.283	.015	.100	.279	.718
Gender × negative social environments × economic stress ^d	-.62	.57	.273	-.08	.54	.882
	Wald $\chi^2(10) = 201.5$			Wald $\chi^2(10) = 63.02$		

^a Log-transformed values.

^b 0 = male, 1 = female.

^c Centered prior to computing multiplicative interaction term.

^d Tested in an additional analysis (controlling for lower-order terms); other effects in table are not adjusted for this three-way interaction.

negative social environments were not significantly associated with reports of PTS symptoms. However, as expected, the added stress of a highly negative social environment was associated with significantly higher PTS symptoms for respondents experiencing high economic stress. When respondents reported low levels of negativity in their social environments, economic stress was not associated with PTS symptoms. In contrast, when social environments were highly negative, GG individuals experiencing high levels of economic stress reported significantly more PTS symptoms than those experiencing low levels of economic stress.

Any A allele. After controlling for theoretically-relevant covariates, there was a significant main effect of negative social environments on PTS symptoms, such that more negative social environments predicted more PTS symptoms (see Fig. 1 right panel, Table 3). There were no main effects of economic stress on PTS symptoms, nor was there a significant interaction between negative social environments and economic stress.

Impaired functioning

There were significant three-way interactions between gender, negative social environments, and economic stress for both genotype groups in relation to impaired functioning (see Table 4); therefore, the results for all participants are presented by genotype, followed by gender-specific findings within genotype.

All GG genotype participants. Overall, the same pattern evident for PTS symptoms was observed for impaired functioning (see Table 4); the pattern of simple slopes was very similar to that displayed in Fig. 1 (left panel). There were main effects of both negative social environments and economic stress such that more impaired functioning was evident for individuals with high levels of each stressor. However, these main effects were qualified by a significant interaction between the two stressor types. Overall, highly negative social environments were associated with more impaired functioning for respondents who were also experiencing high levels of economic stress, $b = 0.32$, $SE = 0.07$, $p < 0.0001$. For respondents experiencing low levels of economic stress, negative social environments were not associated with impaired functioning, $b = 0.04$, $SE = 0.08$, $p = 0.63$. When respondents reported a more positive (less negative) social environment, impaired functioning was not associated with economic stress, $b = 0.06$, $SE = 0.08$, $p = 0.44$. However, when social environments were highly negative, those experiencing high levels of economic stress reported significantly more impaired functioning than those reporting low levels of economic stress, $b = 0.33$, $SE = 0.09$, $p < 0.0001$.

Any A allele: all participants. Overall, before considering gender, the same pattern that was displayed in relation to PTS symptoms was observed for impaired functioning (see Table 4); the pattern of simple slopes was very similar to that displayed in Fig. 1 (right panel). More negative social environments predicted more impaired functioning,

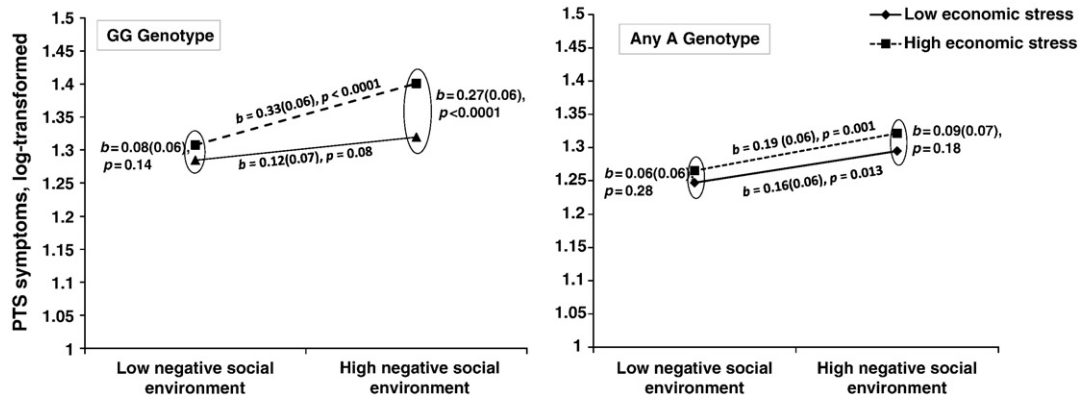


Fig. 1. Predicted values of negative social environments and economic stress in relation to PTS symptoms for individuals with a GG genotype and individuals with any A allele on the *OXTR* rs53576 SNP. Note: Among those with a GG genotype ($n = 361$), 143 and 218 had low and high levels of economic stress, respectively (based on a median split). Among those with any A allele ($n = 343$), 190 and 153 had low and high levels of economic stress, respectively.

Table 4

Generalized estimating equations (GEEs) examining the association between negative social environments, economic stress, and impaired functioning^a 2- to 3-years post-9/11 for GG and any A individuals.

Variable	GG genotype			Any A allele		
	<i>b</i>	<i>SE</i>	<i>P</i>	<i>b</i>	<i>SE</i>	<i>P</i>
Time	.002	.011	.846	.002	.011	.844
Age	-.001	.001	.261	.001	.001	.575
Household income	-.004	.003	.112	-.006	.002	.007
Gender ^b	.001	.017	.942	.011	.017	.505
Pre-9/11 mental health	.043	.015	.005	.089	.027	.001
9/11-related acute stress	.036	.032	.256	.042	.033	.204
Recent stressors	.020	.006	.001	.021	.009	.032
Negative social environments ^{a,c}	.178	.058	.002	.224	.058	<.001
Economic stress ^{a,c}	.195	.071	.006	.090	.063	.150
Negative social environments × economic stress	.935	.325	.004	.409	.424	.335
Gender × negative social environments × economic stress ^d	-1.16	.57	.042	-2.13	.74	.004
	Wald		<.001	Wald		<.001
	$\chi^2(10) =$			$\chi^2(10) =$		
	164.58			78.43		

^a Log-transformed values.

^b 0 = male, 1 = female.

^c Centered prior to computing multiplicative interaction term.

^d Tested in an additional analyses (controlling for lower-order terms); other effects in table are not adjusted for this three-way interaction.

but economic stress was not associated with impaired functioning, and negative social environments and economic stress did not interact to predict impaired functioning.

Associations for male participants. Examination of the two-way negative social environment by economic stress interaction separately by gender revealed that this interaction was significant for GG males, $b = 1.63$, $SE = 0.31$, $p < 0.0001$, and for males with any A allele, $b = 1.73$, $SE = 0.44$, $p < 0.0001$. The simple slopes indicated that negative social environments were associated with more impaired functioning for GG men who were also experiencing high levels of economic stress (see Fig. 2 left panel); however, negative social environments and impaired functioning were unrelated for men experiencing low levels of economic stress. When the social environment was highly negative, increases in economic stress were associated with more impaired functioning, but when the social environment was more positive (less negative), economic stress was unrelated to impaired functioning.

A similar pattern was evident for men with any A allele (see Fig. 2 right panel). The simple slopes for these participants indicated that negative social environments were associated with more impaired functioning when economic stress was high, $b = 0.50$, $SE = 0.10$,

$p < 0.0001$, but when economic stress was low, social environment and impaired functioning were unrelated $b = -0.01$, $SE = 0.10$, $p = 0.93$. When the social environment was highly negative, increases in economic stress were associated with more impaired functioning. However, when the social environment was more positive, male participants with an A allele who experienced high levels of economic stress actually reported significantly *lower* levels of impaired functioning than respondents reporting less economic stress.

Associations for female participants. The two-way interaction between negative social environments and economic stress was not significant for women who were homozygous for the G allele, $b = 0.32$, $SE = 0.52$, $p = 0.54$, or for women with an A allele, $b = -0.40$, $SE = 0.56$, $p = 0.48$. Regardless of genotype, there were main effects of negative social environments (GG: $b = 0.17$, $SE = 0.09$, $p = 0.05$, an A allele: $b = 0.22$, $SE = 0.09$, $p = 0.01$) but not economic stress (GG: $b = 0.15$, $SE = 0.10$, $p = 0.13$; an A allele: $b = 0.07$, $SE = 0.08$, $p = 0.44$; see Fig. 3 for the pattern of associations between negative social environments, economic stress, and impaired functioning for female participants).

Discussion

In the current longitudinal, national study, we provided the first empirical test we are aware of that addressed *OXTR* gene-environment interactions in relation to PTS symptoms and daily functioning after collectively-experienced stress. Results indicate that individuals homozygous for the rs53576 G allele were more vulnerable than individuals with an A allele to the combined effects of negative social environments and economic stress in terms of their 9/11-related PTS symptoms. However, the combined effects of genotype, negative social environments, and economic stress on daily functioning differed based on gender; females were more affected by negative social environments than economic stress regardless of genotype. In contrast, males showed impaired functioning when both the social environment was highly negative and there were high levels of economic stress, regardless of genotype. Interestingly, economically stressed men whose social environments were characterized by low levels of conflict/constraint had significantly *better* functioning if they carried an A allele, suggesting that this socially “vulnerable” genotype may facilitate better functioning in some stressful circumstances. These effects were evident controlling for pre-9/11 mental health, acute stress immediately following 9/11, recent stress, and relevant demographic characteristics.

Given evidence that individuals with the GG genotype are more adept in socioemotional domains (Kogan et al., 2011; Lucht et al., 2009; Saphire-Bernstein et al., 2011) and also appear to benefit

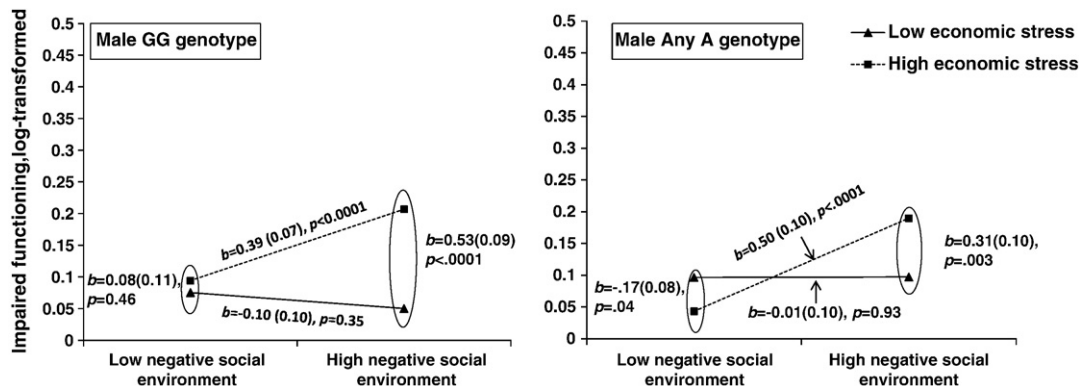


Fig. 2. Predicted values of negative social environments and economic stress in relation to impaired work/social functioning for males with a GG genotype and males with any A allele on the *OXTR* rs53576 SNP. Note: Among those with a GG genotype ($n = 179$), 101 and 78 had low and high levels of economic stress, respectively (based on a median split). Among those with any A allele ($n = 157$), 98 and 59 had low and high levels of economic stress, respectively.

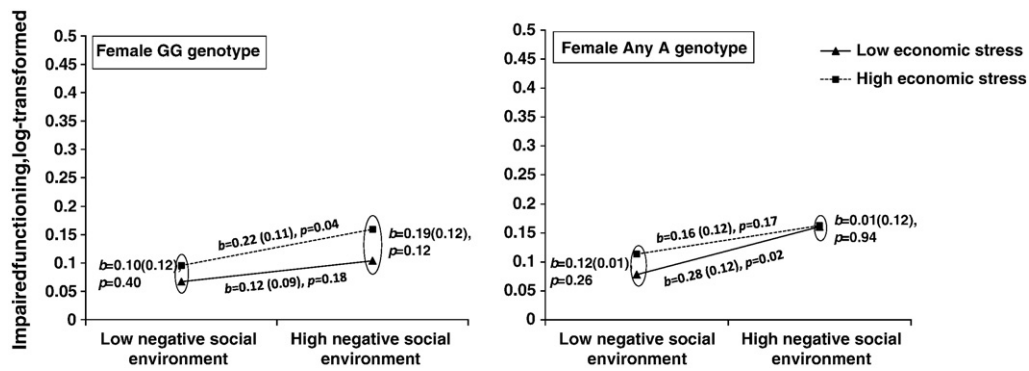


Fig. 3. Predicted values of negative social environments and economic stress in relation to impaired work/social functioning for females with a GG genotype and females with any A allele on the *OXTR* rs53576 SNP. Note: Among those with a GG genotype ($n = 182$), 82 and 100 had low and high levels of economic stress, respectively (based on a median split). Among those with any A allele ($n = 186$), 92 and 94 had low and high levels of economic stress, respectively.

more from positive social experiences (Chen et al., 2011; Kim et al., 2010) than A allele carriers, researchers have argued that the GG genotype confers sensitivity to social stimuli. Although past studies have focused almost exclusively on sensitivity to positive environmental characteristics, a recent study reported differential susceptibility in mothers' parenting behavior with the rs53576 SNP: researchers reported a cross-over interaction such that mothers with rs53576 GG genotype were significantly more or less sensitive to their children when inter-parental conflict was low or high, respectively. The parenting behavior of mothers carrying an A allele was unaffected by inter-parental conflict (Sturge-Apple et al., 2012). Our findings extend this and other past research by demonstrating in a large, ethnically diverse sample of men and women that social sensitivity linked to the GG genotype may increase an individual's vulnerability to PTS symptoms when coping with the additional burden of both negative social environments and economic stress. This vulnerability was evident in the daily functioning of the overall sample as well, although men were more sensitive than women to the accumulation of both economic and relationship stress.

This study provides the first evidence that (a) links the *OXTR* rs53576 SNP to PTS symptoms, and (b) demonstrates differential genetic susceptibility to PTS symptoms in the environmental context of ongoing social and economic stress. Under conditions of low economic stress, the GG genotype appeared protective against the detrimental mental health impact of highly negative social environments; under conditions of high economic stress, the GG allele no longer buffered the impact of negative social environments. In contrast to arguments that GG individuals are more sensitive to social experiences, when economic stress is not present, having a GG genotype appears to buffer the potential adverse mental health consequences associated with conflictual, emotionally constraining social relationships. Perhaps the greater social adeptness and psychological resources that are consistently found in individuals without the risky A allele (e.g., Rodrigues et al., 2009; Saphire-Bernstein et al., 2011) protect GG individuals from mental health problems when social but not economic problems are present. It may also be that the sensitivity of GG individuals to social environments becomes detrimental in circumstances characterized by compounded stress.

For individuals with an A allele, negative social environments predicted poorer mental health regardless of economic conditions. Past research suggests a pattern whereby economic stress may exacerbate social problems (Conger et al., 1993); that PTS symptoms in A allele carriers did not show the cumulative effects of both social and economic stressors suggests that these individuals may be less likely to experience exacerbation of social problems in the face of economic stress. It is also possible that GG individuals, who are more socially inclined and perhaps emotionally invested, stay engaged in social relationships that become more negative in the face of economic stress,

whereas those with the A allele disengage from difficult relationships when economic stress potentiates social conflict and coercion. Or perhaps, given the evidence that A allele carriers have socioemotional deficits (Bakermans-Kranenburg and van IJzendoorn, 2008; Feldman et al., 2007; Kogan et al., 2011; Lucht et al., 2009; Rodrigues et al., 2009; Saphire-Bernstein et al., 2011), could they simply be less emotionally responsive to the impact of a more distal stressor (economic stress)? Future research should address these questions by including measures of social isolation, disengagement, and/or withdrawal, and by examining genetic differences in responsiveness to proximal vs. distal forms of stress (Belsky and Pluess, 2009).

In contrast to the findings in relation to PTS symptoms, which were consistent for both males and females, *OXTR*, social environments, and economic stress had cumulative effects that were different for the daily functioning of males and females. Females had poorer functioning in the face of highly negative social environments, regardless of economic stress and genotype. However, males suffered in terms of functioning only when both economic and social problems were present. In addition, males with an A allele were the only group where having a positive social environment actually encouraged positive functioning in the face of economic stress, suggesting that males homozygous for the G allele benefited less (than men carrying an A allele) from high-quality social relationships in the presence of economic stress.

Despite arguments that the *OXTR* system has evolved to operate differently for males and females (Taylor, 2006), the evidence for gender differences in effects of *OXTR* has been mixed (Israel et al., 2009; Rodrigues et al., 2009; Tost et al., 2010; Wu et al., 2012). Gender similarities appear more likely in the effects of *OXTR* on stress reactivity, but gender differences are inconsistent in terms of genetic effects on social, emotional, and empathic functioning (Rodrigues et al., 2009; Tost et al., 2010). The observed gender differences in the effects of negative social environments are consistent with evidence that the link between social support and mental health is stronger for women than for men (Flaherty and Richman, 1989). This may be because women tend to have the types of social networks – larger and more diffuse – that predict better mental health and functioning (Antonucci, 1990; Fiori et al., 2006; Litwin and Landau, 2000). However, our results suggest that when the relationships in those networks are characterized by conflict and emotional constraint, women may suffer in terms of emotional functioning regardless of the presence or absence of other stressors. This is consistent with the idea that women and men use social networks differently when coping with stress (Taylor, 2006).

Our findings further suggest that men are especially vulnerable to the negative emotional effects of compounded stress, regardless of genotype. It is not clear, however, whether this is a function of the number of stressors, or the specific types of stress experienced (e.g.,

economic vs. interpersonal), with some stressors calling forth stronger responses depending in part on genotype and/or gender. The fact that the “any A” sample in our study did not appear to respond to economic stress with higher PTS symptoms suggests this possibility. Furthermore, why females did not appear affected by economic stress is unclear. Perhaps traditional gender roles sensitize men to the burden of economic stress. Nonetheless, our findings are consistent with prior research in this area that has shown women to be either less or equally affected by economic stress as men (see Mills et al., 1992; Voydanoff, 1990). Future research addressing *OXTR* genotypes and oxytocin function in relation to gender, HPA axis stress responses, and different types of stress would be useful in examining these different possibilities.

Although our data do not allow further explication of these somewhat counter-intuitive findings about gender differences, we note that recent research with humans has demonstrated gender-specific patterns of social behaviors linked to oxytocin administration (e.g., social competition in males vs. a familial focus in females) (Fischer-Shofty et al., 2012) as well as gender-related differences in emotional regulation (see Nolen-Hoeksema, 2012 for a review), both of which might influence daily functioning. As the GG genotype is considered more sensitive to systemic oxytocin, we suspect that genotype-based oxytocin sensitivity interacts with gender-specific social/emotional behaviors to affect daily functioning differently for men and women. Future research should address these issues using more controlled experimental methods.

Taken together, these findings are consistent with the differential susceptibility hypothesis which argues that some individuals have dispositional or genetic characteristics that render them more vulnerable to negative and responsive to positive environmental influences (Belsky and Pluess, 2009). We found that the rs53576 A allele appeared to function as a plasticity allele that renders men both vulnerable to and protected from economic stress depending on the social-environmental context. The current study suggests that this vulnerability may extend to sensitivity to cumulative stressors as well. Consistently, studies have suggested that it is the compounded or interactive association between stressors that shape the nature of cumulative effects over time (Serido et al., 2004; Turner et al., 2000). It appears that GG individuals (and males) may be most vulnerable to the accumulation of economic and relationship stressors. Where the differential susceptibility hypothesis extends diathesis-stress models is in terms of emphasizing potential increased susceptibilities to more positive, supportive environments. In keeping with that argument, our results raise the possibility that GG and male individuals benefit more from high-quality social relationships in ways that then buffer them from developing mental health problems or impaired functioning in the face of economic stress.

The mental health and impaired functioning observed in this study may also be more evident in the face of a collectively experienced stressor like 9/11 that taxes the social environment because many people are simultaneously seeking support (Lee and Fairbank, 2000; Pennebaker and Harber, 1993). In this strained social environment, individuals seeking social support may not receive it, and instead may encounter a social environment that constrains open expression of stress-related thoughts and feelings (Pennebaker and Harber, 1993). Under these circumstances, it makes sense that the more socially-sensitive *OXTR* rs53576 GG individuals might experience higher levels of stress-related symptoms, particularly when they are also experiencing economic stress. Past research has supported a similar pattern of negative social environments exacerbating mental health problems for individuals with high plasma levels of the hormone oxytocin (Taylor et al., 2006), but our study extends those findings by providing similar evidence in *OXTR* rs53576 GG individuals.

Finally, replication of gene-environment studies is important to verify the accuracy of a set of findings. Replicating these findings, however, could be challenging because effects are measured in a

national sample of respondents who were indirectly exposed to a major national collective stressor. Nonetheless, rates of doctor-diagnosed mental health problems did not increase after 9/11 in this subsample, so perhaps replication in a non-stressed community could be used for replication. Two important considerations could discourage this approach. First, the primary outcome in this study was stress-related PTS symptoms. We do not know if the findings identified here would carry over to other outcomes unrelated to stress per se. Given that this *OXTR* SNP is a known contributor to stress response (Rodrigues et al., 2009) we have doubts about the comparability of such an approach. Second, subtle subclinical changes in PTS symptoms and functioning may have occurred in our respondents even if the impact of 9/11 was not sufficiently strong to warrant a clinical diagnosis in most. As we have no way of assessing pre- to post-change in subclinical symptoms in this study, we could not reasonably assume similarity between our sample and a non-stressed replication sample.

Contributions and limitations

This study makes important contributions to our understanding of *OXTR* rs53576 genotype differences in social sensitivity and *OXTR*-environment influences on mental health and functioning. Our use of a sample drawn from a national panel of respondents to a three-year prospective longitudinal study of coping following a collective national stress allowed us to test our hypotheses in a more naturalistic setting. Moreover, the prospective nature of the study allowed us to examine the gene-environment interaction impact on long-term adjustment over time.

Nonetheless, our relatively small sample includes respondents who reported generally low levels of PTS symptoms on average; therefore, these findings should be replicated in larger samples with a wider range of stress-related symptomatology. Although the larger sample that this genetic study was drawn from was relatively representative of the country as a whole, the genetic study subsample was slightly older and had slightly higher levels of economic stress than those who did not participate in the genetic phase of the study. These differences limit the generalizability of our results. However, the distribution of genotypes observed in the current study is comparable to the population-based distribution for this SNP, suggesting less bias in the genetic findings. In addition, recent research provides evidence for gene-culture interactions in relation to well-being, leading authors to argue that cultures influence how biological predispositions are manifested behaviorally (Sasaki et al., 2011). Future research should examine *OXTR*-environment effects in cultures that value social affiliation to different degrees. Finally, we have presented findings from a single, population-based study using a measure of economic stress that has not been well-validated. It is not clear whether these findings would replicate with a stronger measure of economic stress. Despite the strengths of this study, our sample is relatively small for studying $G \times E$ interactions, thus the findings should be considered preliminary evidence.

Conclusion

The current study provides evidence for genetic differences in the effects of negative social and economic environments on mental health and functioning in a sample of individuals exposed to a collective stressor. The results extend prior research by providing evidence that the rs53576 GG genotype may render individuals more vulnerable to detrimental mental health outcomes in the face of combined social and economic stress, but may also provide differential susceptibility to positive social relationships in ways that protects mental health. At the same time, the rs53576 A allele may serve as a plasticity allele that, given the right circumstances, proves beneficial to economically stressed men. These results emphasize the importance of

considering the genetic characteristics in addition to broader ecological context in which social relationships operate to best understand emotional well-being and functioning.

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