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

Rachel G. Lucas-Thompson [a,*], E. Alison Holman [b]

[a] Department of Human Development and Family Studies, Colorado State University, Fort Collins, CO 80523-1570, USA
[b] Program in Nursing Science, University of California, Irvine, CA 92697-3959, USA

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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.

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

* Corresponding author. Fax: +1 970 491 7975.
E-mail addresses: Lucas-Thompson.Rachel.Graham@colostate.edu (R.G. Lucas-Thompson), aholman@uci.edu (E.A. Holman).

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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 × 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 PTS 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 × 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%