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ARTICLE

Oxytocin and the emergence of individual differences in the social regulation of stress

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Abstract

The ability to use social support to regulate stress is critical to mental and physical health. Here, we posit that the oxytocin system contributes to the variability in individual responses to social support. We first review the evidence that oxytocin is related to both social functioning and stress regulation. We focus on results from molecular genetics suggesting that individual variations in both of these functions are associated with natural variations in the oxytocin receptor gene (*OXTR*). We then describe research that exploits this natural variation to directly and experimentally test relationships between the oxytocin system, social support, and stress regulation in both infants and adults. On the basis of our findings, we propose a novel theoretical model of how biological processes might interact with psychological beliefs about relationships—even in infants—to affect long-term patterns of social regulation of stress.

1 | INTRODUCTION

One of the best resources for coping with stress is social support (Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Simply speaking to a friend or having a hand to hold can lower both psychological and physiological responses to stressful experiences (Coan, Schaefer, & Davidson, 2006; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). Furthermore, the quality of an individual's social relationships predicts long-term health outcomes (House, Landis, & Umberson, 1988). In fact, the effects of adequate social support on mortality risk are comparable to or greater than the effects of exercising or quitting smoking (Holt-Lunstad, Smith, & Layton, 2010).

In this focused review, we examine why individual differences exist in people's ability to use social input to regulate stress. We focus on the role of the oxytocin system, which has been theorized to underlie the social buffering of stress (Ditzen & Heinrichs, 2014; Hostinar, Sullivan, & Gunnar, 2014). We argue, on the basis of recent findings from molecular genetics, that the oxytocin system contributes to individual differences in the ability to use social support to regulate stress. We employ a developmental lens to explore possible mechanisms through which oxytocin—for example, by influencing early developing emotional processes and cognitive expectations—could have broad consequences on sensitivity to social support throughout the lifespan.

2 | GENERAL FUNCTIONS OF THE OXYTOCIN SYSTEM

Oxytocin is a neuropeptide that is naturally produced in the brain and released during childbirth, breastfeeding, sexual activity, coordinated social behavior, and affectionate physical contact (Donaldson & Young, 2008; Feldman, 2012; Heinrichs, von Dawans, & Domes, 2009). By delivering neuropeptides such as oxytocin through a nasal spray, researchers can experimentally manipulate levels of those neuropeptides in the brain (Born et al., 2002; Chang, Barter, Ebitz, Watson, & Platt, 2012; Striepens et al., 2013).

Research using the intranasal administration method has demonstrated that oxytocin—beyond simply being an output of social interaction—itself regulates social behavior and cognition (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). A single dose of oxytocin has been shown to increase gazing at others' eyes (Guastella, Mitchell, & Dadds, 2008), to reduce negative reactions to faces that had been paired with electric shocks (Petrovic, Kalisch, Singer, & Dolan, 2008), and to increase trust, as measured by the willingness of people to "invest" money with strangers for an uncertain higher payoff (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; see Van IJzendoorn & Bakermans-Kranenburg, 2012, for a meta-analysis confirming the original effect; see also Nave, Camerer, & McCullough, 2015 for a more critical review). Broadly speaking, therefore, social interaction and oxytocin seem to be linked through a feedback loop in which specific social contexts (e.g., breastfeeding, coordinated social behavior, and physical contact) promote oxytocin release—and—once released, oxytocin regulates social cognition and behavior.

Oxytocin release provides a theoretically plausible biological pathway through which social input could moderate stress responses. Oxytocin's capacity to promote social affiliation and bonding may be due in part to its ability to dampen responses in the amygdala (a brain region that reacts to potential social threats) to emotional faces, such as those displaying fearful or angry expressions (Kanat, Heinrichs, & Domes, 2014). Oxytocin plays a broad role in regulating the physiological stress response of various species (Hostinar et al., 2014). The mammalian stress response—commonly called the "fight or flight" response—involves a cascade of hormonal messengers including release of cortisol by the adrenal gland. In humans, a single dose of oxytocin reduced cortisol release in response to a stressful social experience, especially in interaction with social support (Heinrichs et al., 2003). Oxytocin also plays a role in monkeys' ability to use social support to regulate stress (Winslow, Noble, Lyons, Sterk, & Insel, 2003). Compared to mother-reared rhesus monkeys, nursery-reared monkeys (who are raised under conditions of maternal deprivation) have lower oxytocin levels in the central nervous system and are less able to use social companions to buffer their stress responses.

3 | INDIVIDUAL DIFFERENCES

Although oxytocin's core functions in regulating social behavior and stress reactivity can be considered universal in our species, the efficiency with which oxytocin fulfills these functions seems to differ between individuals (Bartz, Zaki, Bolger, & Ochsner, 2011; Kumsta & Heinrichs, 2013). A molecular genetic approach provides a means of identifying relevant individual differences encoded by genes and linking these differences to variability in psychological and behavioral outcomes. For example, common variants of the oxytocin receptor gene (*OXTR*)—which is responsible for encoding the oxytocin receptor protein—seem relevant to understanding individual differences in social behavior and stress regulation.

A single nucleotide polymorphism (SNP) is a variation affecting one single nucleotide (A, T, G, and C) within a sequence of DNA. Some individuals, for instance, might have an "A" allele at the specified location in the sequence, whereas others have a "G" allele at the same location. Because each person inherits two copies of each gene (one from each parent), we can speak of individuals who are *homozygous G* (carriers of two copies of the G allele, or "GG"), *homozygous A* (carriers of two copies of the A allele, or "AA"), or *heterozygous AG*, for a given SNP. In the case of the oxytocin receptor, such genetic variations may influence the strength of the oxytocin signal in the brain by affecting the number and/or distribution of receptors, or the efficiency with which they operate.

In recent years, the process of genotyping—that is, determining the specific sequence of DNA possessed by a particular individual—has become relatively straightforward and cost-effective. Cheek cells can be collected quickly and

painlessly from either adults or infants through a saliva sample or cotton swab. The remainder of the process occurs in a specialized lab. After DNA is isolated from the collected cells, genotyping can be completed using polymerase chain reaction or other methods.

Here, we focus on the two most widely studied *OXTR* SNPs, rs53576 and rs2254298, which have been associated with variation in both social functioning and stress responsiveness (see Kumsta & Heinrichs, 2013 for a recent review). Clinical diagnoses of autism spectrum disorder have been associated with both SNPs (see Ebstein, Knafo, Mankuta, Chew, & San Lai, 2012 for a detailed review of over a dozen studies focusing on *OXTR* variants and autism). The A allele of rs53576 is linked to reduced trust (Krueger et al., 2012), heightened heart rate responses while anticipating being startled, and greater self-reported stress reactivity (Rodrigues, Saslow, Garcia, John, & Keltner, 2009). Both SNPs have been associated with variation in the structure and function of the amygdala and hypothalamus, brain regions involved in responses to threat (Inoue et al., 2010; Tost et al., 2010).

Thus, converging evidence suggests that individual differences in social functioning and stress regulation are influenced by natural variation in the oxytocin system, as indexed by SNPs of *OXTR*. Next, we review recent studies conducted by ourselves and other research groups that examine *OXTR*'s role in individual differences in the social regulation of stress, directly and experimentally. In considering the results from both infant and adult samples simultaneously, we outline a developmental trajectory through which genetic variation in *OXTR* could contribute to infants' beliefs and expectations regarding their relationships with close others, through which adults' differential responses to social support could arise.

3.1 | *OXTR* and social regulation of stress in adults

Two existing studies support the idea that variation in *OXTR* may explain individual differences in adults' social regulation of stress. In one study, participants were asked to recall their biggest stressor in the past 3 months and describe how they had coped with it, using a standardized coping inventory (Kim et al., 2010). Among individuals for whom explicit social support-seeking is culturally normative (Caucasian Americans), those with at least one copy of the G allele of rs53576 reported higher tendency to seek emotional social support when distressed than those homozygous for the A allele (Kim et al., 2010).

Second, a study conducted in our lab showed that the A allele of *OXTR* rs53576 was associated with reduced responsiveness to social support received in anticipation of stress (Chen, Kumsta, et al., 2011). Half of our participants were randomly assigned to receive social support from a close female friend while preparing for a stressful task (the Trier Social Stress Test for Groups, von Dawans, Kirschbaum, & Heinrichs, 2010), and half were assigned to prepare alone. We collected salivary cortisol samples and subjective stress ratings from participants throughout the procedure, as well as DNA samples. The stress-protective effects of social support were varied by genotype. Specifically, only individuals with one or two copies of the G allele (AG/GG) of rs53576 showed significantly less cortisol secretion in response to social support. In contrast, the cortisol levels of individuals homozygous for the A allele did not differ significantly as a function of social support. Furthermore, social support decreased feelings of anxiety only in carriers of one or two G alleles.

These results suggest that the oxytocin system plays a role in individual patterns of sensitivity to social support in the context of stress. It is likely that the general tendency to seek social support is influenced by one's past experience with social support (Winslow et al., 2003) and expectation that future social support will be effective. Speculatively, genetic variation influencing the functioning of the oxytocin system may contribute to individual differences in beliefs about the role of social support in regulating stress.

3.2 | *OXTR* and social regulation of stress in infants

Individual differences in patterns of seeking and accepting social support are apparent even in the first year of life. Contrasting patterns, including both *secure* and *insecure* attachment styles, have been established through extensive

research using the Strange Situation Procedure (Ainsworth, Blehar, Waters, & Wall, 1978)—a standardized laboratory procedure involving two brief and mildly stressful separation episodes between the infant and primary caregiver. Infants who readily seek out their caregiver when stressed and are easily soothed are considered securely attached. Infants who do not seek out the caregiver when stressed—or who do but are not readily comforted—are considered insecurely attached (*avoidant* or *resistant*, respectively). Patterns of attachment in infancy predict a number of socioemotional outcomes later in life, including self-esteem, quality of peer relationships, and risk for psychopathology (Weinfield, Sroufe, Egeland, & Carlson, 1999).

Traditional attachment theory (Bowlby, 1958) posits, and our own empirical evidence confirms (Johnson, Dweck, & Chen, 2007; Johnson et al., 2010), that infants vary in their beliefs and expectations about their caregivers' behaviors. These beliefs, in turn, influence infants' tendencies to seek and respond to social support in the face of stress.

The oxytocin system may contribute to infants' beliefs and expectations about their caregivers' behaviors in at least two ways. First, how the caregiver behaves toward the infant early in life influences the infant's beliefs and expectations (Ainsworth et al., 1978). Individual differences in mothers' behavior (supportive presence, intrusiveness, and clarity of instruction) towards their 1- to 3-year-old toddlers during series of problem-solving tasks have been associated with variability of *OXTR* (Bakermans-Kranenburg & van Ijzendoorn, 2008). Specifically, mothers carrying the A allele of rs53576 demonstrated lower levels of sensitive responsiveness to their toddlers than those homozygous for the G allele at rs53576. In another study, parents homozygous for the G allele at rs2254298 had lower levels of oxytocin in their blood, which was in turn associated with a decreased tendency to touch their children during a social interaction (Feldman et al., 2012).

It is worth noting, however, that maternal behavior only explains a small to moderate proportion of the individual differences in infant attachment status (De Wolff & Ijzendoorn, 2006). Two studies conducted in our lab, described below, suggest that the oxytocin system may also influence infants' use of their caregivers to regulate their stress by shaping attentional biases relevant to their cognitive representations of caregivers. This contribution of oxytocin to infant attachment status may help to account for the substantial proportion of individual differences in infant attachment behavior left unexplained by variability in caregiver behavior.

First, we directly examined the relationship between *OXTR* variation and 1-year-old infants' abilities to use comfort from their primary caregivers to calm after a stressful experience (Chen, Barth, et al., 2011). Using the Strange Situation Procedure, we classified 176 infants as securely or insecurely attached on the basis of their caregiver-directed behaviors upon reunion. We collected DNA samples from saliva and genotyped the infants at both the rs53576 and rs2254298 loci. We separated our infants by ancestry (77 Caucasian and 99 infants of non-Caucasian ancestry).[1] No association was found between rs53576 and infant attachment security. (This null finding will be revisited in Section 4.) The A allele of *OXTR* rs2254298, however, was associated with secure attachment in the non-Caucasian infants.[2] Our findings with non-Caucasian infants provide initial evidence for the role of oxytocin in the early development of social stress regulation.

Second, we tested 12-month-old infants on an emotion-based attentional-capture task, wherein pictures of a woman's face expressing happy, neutral, or fearful emotions appeared in the center of a computer screen followed, 1 s later, by the appearance of a geometric target on the right or left of the screen (Johnson & Chen, 2011). Individual differences in the attention to emotion were associated with both individual differences in attachment status and polymorphisms at the rs2254298 locus of *OXTR*. Specifically, insecurely attached infants and infants who were homozygous for the G allele were slower to shift their attention away from the fearful face (suggestive of a "fear bias") than securely attached infants and those carrying the A allele of rs2254298.

3.3 | Theoretical model for the emergence of individual differences in the social regulation of stress

Given our empirical evidence, our theoretical model for oxytocin's role in the social regulation of stress goes beyond other influential theories (e.g., the Taylor et al. (2000) "tend and befriend" model) that postulate a role

for the oxytocin system in individual differences in the tendency to *seek out* (e.g., Kim et al., 2010) or *provide* (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2008) social support. Our model suggests a role for oxytocin in individual differences in *responses* to social support following stress. On the basis of empirical evidence from both infants and adults (Chen, Barth, et al., 2011; Chen, Kumsta, et al., 2011; Johnson & Chen, 2011), we posit that individual differences in oxytocin signaling (e.g., release and/or uptake of the neuropeptide, indexed by variability of *OXTR*) are relevant during at least two stages of a key psychological feedback loop that operates in the context of acute stress (Figure 1). Our theoretical model delineates a role for oxytocin in the early development of stable cognitive representations of relationships, which in turn influence how individuals use social support to regulate their stress.

4 | DISCUSSION

The two studies described in this focused review provide preliminary evidence linking natural variation in the oxytocin system to individual differences in the social regulation of stress. We observed a relationship between common variants of the oxytocin receptor gene and reactions to social support in infants as well as adults, suggesting that the relationship is early emerging and persistent.

A number of open questions remain regarding the associations obtained using the molecular genetic approach. The enterprise of linking complex psychological and behavioral patterns to single SNPs has been criticized on the basis of the difficulty that is often encountered in replicating findings (Bakermans-Kranenburg & van IJzendoorn, 2014). Given the complexity of the psychological and behavioral patterns under study, the challenge of replication in this domain is perhaps unsurprising.

The broader picture currently emerging from our own research and research by other groups suggests that transmission of rs53576 and rs2254298 is relatively independent (in other words, these two SNPs exhibit low linkage disequilibrium, see Chen, Barth, et al. 2011 and Chen et al., 2015) and that they are not redundant markers for the same phenotypic outcomes. For example, our studies showed an association between physiological responses to social support and rs53576, whereas attachment status (secure vs. insecure) was linked to rs2254298 but not rs53576 (consistent with the results of a study by Gillath, Shaver, Baek, and Chun, 2008, who reported no association between rs53576 and adults' attachment status).

However, many open questions remain around the mechanisms through which rs2254298 and rs53576 variants might, for example, have independent, additive, or interactive effects on specific human social behaviors. Further questions exist regarding how to interpret the patterns of association between particular alleles (A vs. G) and the—

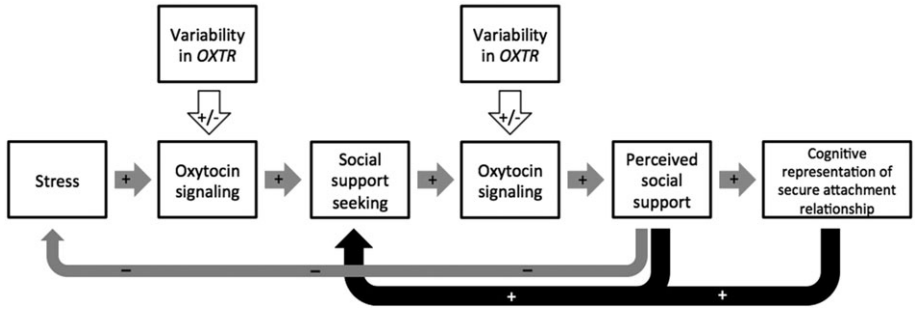

FIGURE 1 A theoretical model for the development of individual differences in the social regulation of stress. White arrows indicate genetic modulators of oxytocin signaling in the brain. Grey arrows indicate transient effects of acute stress. Black arrows indicate a long-term feedback loop through which stable individual differences arise in the tendencies to both seek and benefit from social support. We theorize that genetic variants of *OXTR* are relevant during at least two stages of the psychological feedback loop that connects stable cognitive representations of relationships to the use of social support in the context of acute stress

sometimes seemingly inconsistent—phenotypic outcomes reported across different studies and in different samples. For example, the A allele of rs2254298 has previously been associated with greater self-reported autism spectrum traits in healthy males and greater self-reported attachment anxiety in healthy females (Chen & Johnson, 2012), as well as increased risk for autism in an East Asian sample (Wu et al., 2005) but decreased risk for autism in a Caucasian sample (Jacob et al., 2007; see Endnote 3 and Ebstein et al., 2012 for further discussion of this "flip-flop" phenomenon).

Progress on these questions will likely require more comprehensive genetic analyses (for instance, examining the role of multiple SNPs at once, e.g., Chen et al., 2015). Using tools such as neuroimaging to clarify intermediate steps in the complex pathway between genes, cognition, and behavior (Meyer-Lindenberg & Weinberger, 2006), and explicitly accounting for variables such as life experience, may also help to clarify some of the conflicting findings that have been reported in adult samples. For example, rather than conferring "risk" for poorer socioemotional outcomes, certain alleles (such as the A allele of rs53576) may be better characterized as conferring differential susceptibility to environmental effects than other alleles (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Boyce & Ellis, 2005). By conferring a lower sensitivity to social input, certain variants of *OXTR* associated with poorer outcomes in healthy samples may be associated with *enhanced* health outcomes in cases of deprived or problematic early social environments (Bradley, Davis, Wingo, Mercer, & Ressler, 2013; McQuaid, McInnis, Stead, Matheson, & Anisman, 2013). It follows that null effects reported in single studies and meta-analyses in which samples with different early experiences are combined may in fact obscure meaningful underlying patterns of contrasting genotype–phenotype associations.

As almost all of the existing literature linking variability of *OXTR* to behavior has used adult samples, we also urge future researchers to undertake additional research with infant samples. By reducing variability arising from environmental influences and life experiences, research with infants may clarify some of the conflicting findings that have been reported in adult samples.

An intriguing issue raised by the current findings is how the reported genetic effects can be reconciled with prior theories (e.g., Ainsworth et al., 1978; Bowlby, 1958) regarding the role of psychological beliefs and life experiences on infants' attachment behaviors. We suggest that explanations of infants' sensitivity to social support based on beliefs and experiences are not mutually exclusive with explanations based on heritable differences in biology or physiology. Instead of arguing in favor of the preeminence of nature or nurture, we propose a few possibilities to suggest how they may have interactive effects on infants' sensitivity to social support.

First, oxytocin system activity could directly alter expectations relevant to social support sensitivity. Oxytocin release, perhaps by influencing the relative accessibility of positive versus negative social memories about one's attachment figures (Bartz et al., 2010), seems to be capable of temporarily altering expectations about relationships. For example, insecurely attached adults who were administered intranasal oxytocin tended to interpret ambiguous attachment-related scenarios (e.g., involving solitude or separation) more positively (Buchheim et al., 2009). Second, the oxytocin system could influence early developing emotional and cognitive processes that have downstream consequences on infants' beliefs about other people. For instance, our research suggests that infants with at least one A allele at rs2254298 show more attentional capture towards happy faces, whereas infants homozygous for the G allele show more attentional capture towards fearful faces (Johnson & Chen, 2011). Such attentional biases might predispose different infants to unique subjective interpretations of objectively similar caregiver behaviors. Third, it is possible that our infant effects are driven in part by parents' genotype. As previous research has linked variability of *OXTR* rs53576 to parenting style (Bakermans-Kranenburg & van Ijzendoorn, 2008), future studies on infants' behavior should take into consideration potential links between *OXTR* variability and caregivers' beliefs about their infants.

To distinguish between these and alternate possibilities of how oxytocin system function and psychological beliefs—independently or in interaction with each other—contribute to the social regulation of stress, future studies could fruitfully incorporate a greater diversity of measures than the ones reviewed here. It is our hope that our review of open questions in this field will spur additional research to clarify how genetic variance and environmental influences contribute to the phenomenon of sensitivity to social support.

ENDNOTES

[1] Although relative allele frequencies are similar in the three non-Caucasian populations that have been studied to date (see www.hapmap.org), Caucasians show a distinctly different allele distribution. Thus, conducting separate analyses on these two subsamples avoids potential statistical confounds due to population stratification. Descriptively, the four subgroups in the non-Caucasian sample (East Asian, South Asian, and Hispanic, as well as infants of mixed heritage) all showed the same pattern of *OXTR*-attachment results, with a larger proportion of the infants with the A allele classified as securely attached, relative to infants with the GG genotype.

[2] The specificity of a particular effect to a particular population (as appears in this study, with rs2254298 being associated with attachment security only in the non-Caucasian infants) has also been documented in other studies (see Ebstein et al., 2012 for a lengthier discussion of this issue). One possible explanation involves patterns of linkage disequilibrium between the functional loci and the associated markers used in these studies—for example, a functional SNP of *OXTR* could be linked to the rs2254298 A allele in the Chinese Han population but the G allele in the Caucasian population. Possible interactions with other genetic or cultural factors may also affect our ability to detect oxytocin receptor function in some populations more easily than in others.

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