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Evidence for evocative gene–environment correlation between child oxytocin receptor (OXTR) genotype and caregiver behavior

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ABSTRACT

A single nucleotide polymorphism in the oxytocin receptor (OXTR) gene has been associated with maternal caregiving; however, it is unclear whether links between OXTR variation and parenting can be explained via genetically-influenced child emotionality and behavior (i.e., gene–environment correlation). We tested this model in 409 three-year-old children and their primary caregivers. Relative to children with at least one G allele, children with two A alleles displayed significantly more negative emotionality and other negative behavior and had caregivers who displayed lower parenting confidence. Child behavior mediated the relationship between child genotype and parenting, suggesting that the effects of OXTR genotype on child behavior may be a critical, evocative mechanism not previously accounted for in research exploring the associations between OXTR genotype and parenting.

1. Introduction

The processes through which genes and the environment influence the emergence of risk for child disorder are the focus of much research in developmental psychopathology. One such process is through gene–environment correlation (rGE), which, in the present context, refers to mechanisms through which genetic and environmental risks become associated with one another (Elder, 1998). Despite the fact that rGEs have long been posited to play an important role in child maladaptation (Scarr & McCartney, 1983), only fairly recently have advances in molecular genetic methods permitted the investigation of associations between specific genes and environmental influences (e.g., Hayden et al., 2013; Pener-Tessler et al., 2013). One gene that has received little attention, despite its known implications for child development, is the oxytocin receptor gene (OXTR; Neumann, 2008).

Oxytocin is a neurohypophysial hormone produced within the parvocellular neurons of the paraventricular nuclei of the hypothalamus (Gimpl & Fahrenholz, 2001). Oxytocin functions as both a neurotransmitter and a hormone; when acting as a hormone, oxytocin serves to modulate neuroendocrine responses that regulate complex social and bonding behaviors (Gimpl & Fahrenholz, 2001), such as generosity (Zak, Stanton, & Ahmadi, 2007), trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), eye gaze (Guastella, Mitchell, & Dadds, 2008), and the ability to infer the affective mental states of others (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007); plasma oxytocin in humans and non-human mammals predicts parent–child bonding (Feldman et al., 2012; Lim & Young, 2006). In light of the critical effects of parent–child bonding and parenting on children's general development and adaptation to social environments (Meaney & Szyf, 2005), a better understanding of the role of oxytocin in these processes may clarify the biological substrates of early child adaptation and maladaptation.

A polymorphic site in the OXTR gene (rs53576), located on chromosome 3 of the human genome (Gimpl & Fahrenholz, 2001), has a single nucleotide polymorphism (SNP) with a guanine (G) to adenine (A) change within intron 3. Although the functionality of rs53576 is still unknown, having one or two copies of the A allele has been associated with an array of negative outcomes and individual difference factors. Individuals with one or two copies of this variant have higher rates of autism (Wu et al., 2005), lower empathy and greater stress reactivity (Rodrigues, Saslow, Garcia, John, & Keltner, 2009), lower social support seeking (Chen et al., 2011), lower positive and greater negative affect (Lucht et al., 2009), and greater depressive symptomatology (Saphire-Bernstein, Way, Kim, Sherman, & Taylor, 2011). With regard to parenting, caregivers with at least one copy of the A allele display less sensitive parenting (Bakermans-Kranenburg & Van Ijzendoorn, 2008) and decreased physiological reactivity to child distress (Riem, Pieper, Out, Bakermans-Kranenburg, & Van

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Ijzendoorn, 2011). Although the mechanisms by which rs53576 variation influences caregiver behavior are poorly understood, Tost et al. (2013) found that A allele carriers had reduced hypothalamic volume and higher structural and functional connectivity between the hypothalamus and the amygdala, which was subsequently linked to reward processing. This tentatively suggests that genetic variation at this locus could shape the extent to which interaction with offspring is experienced as rewarding. If so, parents with an A allele of this gene might be less motivated to engage in caregiving due to reduced reward motivation.

However, it is also possible that children's genetic variation at this locus shapes parent–child bonding. As genetic variation at the OXTR locus has been linked to poorer psychological outcomes and adjustment, as well as poorer caregiving, the intriguing possibility is raised that child behavior related to their OXTR genotype mediates rGEs between OXTR variants and parenting. More specifically, genetic variation at this locus may shape child behavior that, in turn, elicits specific caregiver behaviors through evocative processes. Previous research has focused on the effect of variation in parent OXTR genotype on parenting behavior (Bakermans-Kranenburg & Van Ijzendoorn, 2008); however, it is important to examine the role of child behavior in such processes, and whether rGEs are present (Jaffee & Price, 2007; Rutter, 2007).

Thus, we developed two *a priori* hypotheses regarding the effect of OXTR genotype on parent–child bonding behavior. First, we hypothesized that child rs53576 variations would be related to parenting and child negative emotionality and negative behavior. Second, we hypothesized the effect of OXTR genotype on child behavior would mediate the relationship between child OXTR genotype and parent behavior.

2. Material and methods

Participants were an unselected community sample of 409 children (208 girls; 50.9%) between 36- and 47-months of age (M = 40.72, SD = 3.51) and their primary caregivers recruited for a study of child temperament. Families were recruited through a university's research participant pool and advertisements placed in local daycares, recreational facilities, and websites. Children with significant medical or psychological problems were excluded from participation. The mean age of primary caregivers was 33.53 years (SD = 5.07) and they were usually children's mothers (N = 380; 93%). Family income varied widely (5.5% < $20,000; 11% = $20,000–$40,000; 22.7% = $40,001–$70,000; 31.2% = $70,001–$100,000; 29.5% > $100,001). Children were mostly Caucasian (90%) and were of average cognitive ability (M = 111.94, SD = 14.32; PPVT; Dunn & Dunn, 2007).

2.1. Procedures and measures

2.1.1. Task and coding procedure

Children and their primary caregivers participated in a semi-structured interaction task conducted in their home that was videorecorded for future coding.

2.1.1.1. Parenting assessment and coding. A task developed by the National Institute of Child Health and Human Development (NICHD Early Child Care Research Network, 1997; Ispa et al., 2004) was used, in which the primary caregiver and child were instructed to play together with three bags of toys. The pair was told to play with the toys in order and to put away one set of toys before moving onto the next set. This free play paradigm lasted approximately 10 min. Video-recordings of the task were coded by trained graduate and undergraduate raters using a coding manual that was based on the Teaching Tasks coding manual (Weinfield, Egeland, & Ogawa, 1997) and the Qualitative Ratings for Parent–Child Interactions scale (Cox & Crnic, 2003). Raters were trained to an intraclass correlation of .80 with a master coder (the first author). Once interrater reliability was established, intermittent reliability checks were performed on 15% of all recordings. Reliability was high (ICC = .86). Parent–child interaction tasks were coded on a total of 9 Likert scales encompassing 5 child-oriented parent behaviors (sensitivity, detachment, supportive presence, intrusiveness, hostility, and confidence in their ability to interact successfully with the child) and 4 child behaviors (negativity, compliance, affection, and avoidance).

2.1.2. DNA preparation and genotyping

DNA samples were collected from 409 participants using buccal swabs (Epicentre, Madison, WI, USA). The Qiagen DNA MicroKit® (Mississauga, ON, Canada) was used to extract DNA from epithelial cells. The SNP marker rs53576 (OXTR) was genotyped using TaqMan allelic discrimination assays. Briefly, TaqMan polymerase chain reactions (PCR) were performed in ABI StepOne™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) and analyzed using SDS v2.3 software (Applied Biosystems). Assay identification numbers for all of the TaqMan probes are available on request. Polymerase chain reactions were performed in 10-μL reaction volumes in 48-well plates and contained 10 ng of DNA. Thermal cycler conditions were 95 °C for 10 min and then 40 cycles of 95 °C for 15 s and 60 °C for 1 min. The SDS 2.2 software (Applied Biosystems) was used for allelic discrimination. For quality control, 10.0% of the samples were randomly chosen and genotyped as duplicates across and within a 48-well plate. As an additional quality control measure, a random subset of the sample (∼10%) was also reanalyzed by a technician blind to initial genotyping results. All duplicate and reanalyzed genotyping were concordant with initial results.

Genotype frequencies were as follows: A/A = 55 (13.5); A/G = 170 (41.7%); and G/G = 183 (44.9%). This genotype distribution is in Hardy–Weinberg equilibrium (X^2 (1) = 2.34, p = .13). Based on previous research (Chen & Johnson, 2011), the G variant was treated as dominant. As allelic frequency can vary across ethnic groups (Kidd et al., 1998), all analyses were repeated excluding non-Caucasian participants, yielding virtually identical results.

3. Data analyses

All analyses for this study were conducted in IBM SPSS Statistics version 21.0 (IBM Corp., 2012). Mediation was tested using PROCESS (Hayes, 2013), which employs a bootstrapping procedure. PROCESS uses an ordinary least squares regression-based path analytical framework for estimating direct and indirect effects in simple and multiple mediation models.

4. Results

Table 1 presents correlations between all major study variables and descriptives. All variables were normally distributed. Child OXTR genotype was significantly correlated with child negativity, avoidance, and child compliance (the latter at trend level), such that children with at least one G allele showed less negativity and avoidance, and greater compliance. Further, child OXTR genotype was correlated with parent confidence at a trend level, indicating that parent confidence was higher when children had at least one G allele. Girls were significantly less negative and more compliant, and higher family income was associated with higher parent sensitivity, less detachment, less intrusiveness, less hostility, and less child negativity and avoidance. As child negativity,