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Associations between oxytocin receptor gene (OXTR) polymorphisms, childhood trauma, and parenting behavior

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Abstract

Maternal oxytocin is connected to aspects of parenting including sensitivity, warmth, positive affect, and affectionate touch. Oxytocin receptor (OXTR) gene polymorphisms are associated with circulating oxytocin levels, altered brain activity, and parenting behaviors. This study aimed to replicate prior work on OXTR SNPs rs1042778 and rs53576 in relation to maternal sensitivity, explore associations with other aspects of parenting (i.e., negative parenting), evaluate observational and self-report measures of parenting in relation to OXTR SNPs, and examine whether childhood trauma exposure moderates the relation between OXTR SNPs and parenting. Mothers (N=100) were observed during two teaching interaction tasks with their 7-month-old infant, completed questionnaire and interview measures related to parenting and trauma history, and provided saliva specimens to derive OXTR genotypes. Mothers with OXTR rs1042778 TT genotypes demonstrated lower behavioral sensitivity, lower engagement, higher intrusiveness, and more frequent frightened/frightening behavior than mothers with TG or GG genotypes. Genotype interacted with childhood trauma history such that mothers who had experienced childhood trauma were more likely to demonstrate frightened/frightening behavior if they had the TT genotype on rs1042778 relative to the TG or GG genotype; however, small cell sizes for this interaction suggest replication is warranted. Contrary to expectations, mothers with the TT genotype on rs1042778 self-reported that they had less impaired bonding than mothers with TG or GG genotypes. Results are discussed with respect to prior work with oxytocin in lower-versus higher-risk samples, and the potential role of mothers' self-awareness in explaining discrepancies between results from observational versus self-report measures of parenting.

Keywords

Oxytocin; Oxytocin receptor gene (OXTR); parenting; maternal sensitivity; childhood trauma

Conflict of Interest

The authors declare that they have no conflicts of interest.

A growing body of work suggests that the neuropeptide oxytocin plays a central role in many aspects of parenting including bonding, warmth, sensitive responsiveness, and behavioral and biological synchrony (Szymanska, Schneider, Chateau-Smith, Nezelof, & Vulliez-Coady, 2017). Mothers' oxytocin levels increase over the course of pregnancy, and higher oxytocin levels are associated with greater maternal-fetal bonding (Levine, Zagoory-Sharon, Feldman, & Weller, 2007). Oxytocin levels during pregnancy and the early postpartum period are associated with maternal behaviors including positive affect, affectionate touch, and attachment-related thoughts (Feldman, Weller, Zagoory-Sharon, & Levine, 2007). Parents who are socially engaged, and have synchronous and positive interactions with their infants tend to have higher plasma and salivary oxytocin levels (Feldman, Gordon, & Zagoory-Sharon, 2011), but this effect may be specific to mothers providing affectionate physical contact to their child (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010). Studies of intranasal oxytocin administration have shown that oxytocin is associated with increased trust to one's in-group, improved recognition of facial expressions of emotions, and fathers' increased responsiveness to their children during play (Graustella & MacLeod, 2012; Naber, van IJzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010; Van IJzendoorn & Bakermans-Kranenburg, 2012).

Recent work shows that genetic variability in the oxytocin receptor (OXTR) gene (e.g., single nucleotide polymorphisms [SNPs] rs1042778, rs53576, 2254298), is associated with structural and functional differences in limbic system circuitry including the amygdala, hypothalamus, and cingulate gyrus (Kumsta & Heinrichs, 2013), and is also associated with differences in peripheral oxytocin (Feldman et al., 2012; Feldman, Gordon, Influs, Gutbir, & Ebstein, 2013). This provides a plausible rationale that the association of OXTR so-called "risk alleles" with behavioral phenotypes may be mediated by their effects on brain function and circulating oxytocin levels. OXTR gene polymorphisms are linked to numerous social and emotional processes relevant to parenting, including physiological reactivity to infant crying (Riem, Pieper, Out, Bakermans-Kranenburg, & van IJzendoorn, 2011), empathy and stress reactivity (Rodrigues, Saslow, Garcia, John, & Keltner, 2009), and maternal sensitivity (Bakermans-Kranenburg & van Ijzendoorn, 2008).

Several studies have reported the rs1042778 and rs53576 OXTR gene polymorphisms appear to be associated with differences in parenting behaviors. Specific aspects of both positive and negative parenting are independently linked to important outcomes including children's self-regulation, depressive symptoms, language and cognitive development, and social competence (Barnett, Gustafsson, Deng, Mills-Koonce, & Cox, 2012; Calkins & Johnson, 1998; Dallaire et al., 2006; Raby, Roisman, Fraley, & Simpson, 2015). Parents who are rs1042778 "risk allele" homozygotes (TT genotype) touch their infant less often during play than parents who are not (GT or GG genotype; Feldman et al., 2012). Similarly, mothers who are rs53576 'risk' allele homozygotes (AA genotype) show less warmth in behavioral coding of parent-child interaction than mothers with AG or GG genotypes (Klahr, Klump, & Burt, 2015), whereas mothers who do not carry the rs53576 risk allele (GG genotype) are more sensitive and responsive with their toddlers than mothers who are risk allele carriers (Bakermans-Kranenburg & van Ijzendoorn, 2008). Thus far, negative parenting has not been associated with OXTR SNPs rs1042778 or rs53576 (Michalska et al.,

2014). In a double-blind trial, intranasal oxytocin administration was associated with increased preference for infant faces, but only for those who had the GG genotype on rs53576 (Marsh et al., 2012). Thus, parents with the TT genotype on rs1042778 or the AA genotype on rs53576 appear to be at greater risk for demonstrating less sensitive parenting behaviors.

However, evidence is mounting that oxytocin may not operate as expected in high-risk populations of mothers such as those with insecure attachments (Bartz et al., 2010; Strathearn, Fonagy, Amico, & Montague, 2009), borderline personality disorder (Bartz et al., 2011), or postnatal depression (Mah, Van IJzendoorn, Smith, & Bakermans-Kranenburg, 2013). Prior work demonstrates associations between maternal childhood maltreatment or stress and oxytocin levels in urine (Mizuki & Fujiwara, 2015), cerebrospinal fluid (Heim et al., 2009), and plasma (Opacka-Juffry & Mohiyeddini, 2012). Furthermore, studies of genetic interaction with childhood maltreatment suggest that some OXTR genetic differences might better define differential susceptibility in different environmental contexts rather than overall “risk” per se. Although research has not yet examined OXTR and childhood maltreatment in relation to parenting outcomes, studies have evaluated these variables in relation to outcomes such as emotion dysregulation and internalizing problems. In a study of low-income, urban, African American adults, women who were non-carriers of the rs53576 A “risk” allele (GG genotype) who experienced childhood abuse were more likely to have emotion dysregulation and disorganized adult attachment styles than carriers (AG and AA genotypes) who appeared to be relatively protected from the effects of childhood abuse (Bradley et al., 2011). Similarly, in other research, adolescents who had the rs53576 GG genotype and a history of maltreatment reported more internalizing symptoms, and perceived that they had lower levels of social support despite no genotype-group differences in maltreatment type, duration, or severity; no effect of genotype was detected among non-maltreated adolescents (Hostinar, Cicchetti, & Rogosch, 2014). Thus, while rs53576 GG-homozygotes (risk-allele non-carriers) engage in more sensitive parenting in lower-risk samples (Bakermans-Kranenburg & van Ijzendoorn, 2008), they also appear to demonstrate greater susceptibility to the effects of childhood maltreatment (Bradley et al., 2011; Hostinar et al., 2014) regarding their own emotional and behavioral regulation and perceptional sensitivity.

The current study

In this report, we examine for observed parenting and then for self-reported parenting: (1) the association between OXTR SNPs (rs1042778 and rs53576) and parenting, and (2) the effect of OXTR SNPs, childhood maltreatment, and their interaction in predicting parenting. All analyses were repeated in a subsample of participants of European ancestry due to potential phenotype differences. Thus, the goal of this study was to replicate prior work on the association between OXTR SNPs and observed maternal sensitivity, and to extend the literature by including more differentiated measures of maternal sensitivity and other positive and negative parenting behaviors. Further, this study evaluated both observational and self-report measures of parenting, and examined whether childhood maltreatment moderates the association between OXTR SNPs and parenting.

In line with prior work, we hypothesized that mothers with the TT genotype (risk allele homozygotes) on rs1042778 or the AA or AG genotype (risk allele carriers) on rs53576 would show less positive parenting on both observational and self-report measures of parenting. Prior work has not found associations between OXTR and negative parenting, so this was examined in an exploratory manner. Further, we hypothesized that mothers who were risk allele non-carriers on rs53576 (i.e., GG) would be more susceptible to the effects of childhood maltreatment on parenting behavior. Given the absence of prior research on interactions between childhood maltreatment and rs1042778, these analyses were exploratory.

Methods

Analyses were based on data drawn from two studies that examined the parenting of infants in the context of risk. The Maternal Anxiety during the Childbearing Years ("MACY" MH080147) study is a longitudinal study of the effects of childhood trauma history and maternal psychopathology on parenting behavior. The Perinatal Infant Mother Attachment Cortisol Study ("PIMACS" MH065062) is a longitudinal study of the impact of stress and depression on parenting behavior. Both studies were reviewed and approved by the University of Michigan Institutional Review Board (MACY: HUM00004126; PIMACS: HUM00051612). Participants included in MACY were recruited during pregnancy up to 4 months postpartum from prenatal care clinics or through community advertisements. Participants included in PIMACS were recruited during the first trimester of pregnancy through obstetrical practices and community advertisements. MACY oversampled for women with child maltreatment histories (64%) whereas PIMACS oversampled for women with history of major depression (66%). Data collection for MACY spanned from 4 to 18 months postpartum, whereas data collection for PIMACS spanned from the first trimester of pregnancy to 14 months postpartum. Both studies involved assessments at various timepoints in the obstetric clinic, the home, the university-based playroom, or by phone. Because numerous constructs and measures were common across these two studies, data were merged into one larger database to answer questions about how maternal genetic risk, specifically on the OXTR genes 1042778 and 53576, relates to parenting behavior for mothers with and without a history of childhood trauma.

Participants

Participants for this study included those in the MACY or PIMACS cohorts who had data available for both maternal OXTR genotypes and observed parenting behavior during the mother-infant teaching tasks and/or self-report parenting data. Of the larger sample of 279 participants (192 MACY, 87 PIMACS), 100 participants (81 MACY, 19 PIMACS) had both genetic and parenting data available and were included in the current report. Genetic specimen collection was added to each study after data collection had already begun, so availability of complete (genetic and behavioral) data was not intended to relate to any participant characteristics. The proportion of participants with complete data was greater among the MACY subsample (42%) than the PIMACS subsample (22%), $X^2(N = 279) = 10.78$, $p < .01$. The subsample with complete data did not differ from those with incomplete data with regard to maternal age, race/ethnicity, or level of depressive symptoms. However, a

greater proportion of those with complete data reported experiencing a traumatic event in childhood; demonstrated lower Engagement, lower Positive Affect, and higher Frightened/Frightening behavior during the observed mother-infant interactions; and self-reported greater bonding impairment than mothers with incomplete data.

Descriptive statistics for the demographic and psychosocial characteristics of the mothers in this study are reported in Table 1. Mothers were between 20 to 45 years old at study intake. The majority self-reported as White, and two-thirds had experienced childhood maltreatment. Among those who experienced childhood maltreatment ($N = 64$), all endorsed having experienced childhood abuse, with a subset ($N = 46$) also endorsing exposure to childhood neglect. A substantial portion of the sample met criteria for Post-Traumatic Stress Disorder (PTSD) or Major Depressive Disorder (MDD) in their lifetime. Mothers were excluded from each study if they had serious psychopathology (MACY: any history of schizophrenia or bipolar disorder, or problems with alcohol or drugs in the last 3 months; PIMACS: any history of substance abuse, eating disorders, bipolar disorder or current depression), if they were not fluent in English, or if their child was born more than 6 weeks prematurely.

Procedures

History of Childhood Maltreatment.—A dichotomous code for childhood maltreatment was derived from standard questionnaire measures in each study. For participants from the MACY sample, history of childhood maltreatment was derived from both the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998) and the Trauma Meaning-Making Interview (Simon, Kobielski, & Feiring, 2008). The CTQ is a 28-item self-report questionnaire that was administered to mothers at four months postpartum, with items being rated on a 5-point Likert scale from 1 (never true) to 5 (very often true). The CTQ includes 5 scales: Emotional Abuse, Physical Abuse, Sexual Abuse, Physical Neglect, and Emotional Neglect. Using cut scores provided in the manual (e.g., ≥ 9 on the Emotional Abuse scale), the scales have sensitivity of .79 to .89 and specificity of .82 to .86. In the current study, mothers were classified as having experienced childhood trauma if they obtained a score above the threshold on one or more of the scales of the CTQ. MACY participants also completed the Trauma Meaning-Making Interview at 6 months postpartum, during which they were asked to describe their experiences of maltreatment during childhood and how they currently understand these experiences, and complete a table indicating the age and perpetrator for each of their childhood abuse experiences. This information was used to cross-validate their report of childhood maltreatment on the CTQ. For four mothers, these two reports differed, with scores below threshold on the CTQ, but endorsement of childhood maltreatment during the Trauma Meaning-Making Interview. These individuals were all classified as having experienced childhood maltreatment in the current analyses.

For participants from the PIMACS sample, history of childhood trauma was derived from the Structured Clinical Interview for DSM IV (SCID; First, Spitzer, Gibbon, & Williams, 2002). Within this interview, participants were asked to report any traumatic events they have experienced, along with the age they were when the event happened. This information

was used to determine whether they had experienced maltreatment (i.e., child abuse or child neglect) before the age of 18.

Observed parenting behavior.—Parenting behaviors in both samples were coded from videotapes of mother-infant interaction during two brief (3-minute) teaching tasks during a home visit at 7 months postpartum. The coding schemes, although not identical, were overlapping in constructs in MACY and PIMACS and several maternal behaviors were coded on similar dimensions. This similarity in coded parenting behaviors enabled the data to be merged across samples on these particular dimensions.

The teaching tasks were designed to be too difficult for a 7-mongh-old infant to perform alone, without assistance from the mother. During the first teaching task, mothers were instructed to teach their child how to place a set of blocks into a bucket, and during the second task, to stack a set of nesting cups and then knock them down. In the MACY sample, videotapes of these interactions were then coded using the MACY Infant-Parent Coding System (MIPCS, Earls, Muzik, & Beeghly, 2009), which consists of 5-point (1–5) anchored Likert scales assessing various aspects of maternal behavior and affect. Coders were blind to background variables, participants' history, and the study hypotheses. Inter-rater reliability for maternal behavior and affect codes was evaluated on a subset of 40 randomly selected videos (40/197 = 20%) using intraclass correlations (ICC). ICCs ranged from .793 to .993 (*M* ICC = .879), indicating very good reliability.

In the PIMACS sample, videotapes of the mother-infant teaching interactions were coded using the Parent Infant Interaction Scale (PIIS; Miller, Rosenblum, MacKenzie, & McDonough, 2004) based on a modified version of Main and Hesse's coding scheme (Main & Hesse, 1990). In this scoring system, various dimensions of parental behavior and affect were assessed on 4-point (0–3) anchored Likert scales. Average inter-rater reliability for maternal behavior and affect codes on a subset of 31 videos (31/120 = 25%) was good (*M* ICC= .754; range = .604 to .844). Frightened/Frightening behavior was rarely observed, so reliability estimates were not able to be calculated for this variable. This variable was therefore collapsed into a dichotomous code of present (1) versus absent (0) for analytic purposes in both the MACY and PIMACS samples.

In order to combine the MACY and PIMACS data, common dimensions of maternal-infant interactions during the teaching tasks were identified from the codebooks (e.g., Engagement in MACY with Involvement in PIMACS). Scales were included in the combined analysis only if the constructs were substantially overlapping in both coding schemes (e.g. a 5 on the MACY Engagement was ranked as the "mother engages in infant interactions and activities all of the time", and PIMACS ranked a 3 in Involvement as that the "mother is involved with and focused on infant throughout the segment") as determined by expert consensus by two of the authors (MB and MM). A z-score transformation was performed on each scale to allow MACY and PIMACS scales to be combined in one scale using a common metric. The combined parenting scales included: Behavioral Sensitivity, Engagement, Positive Affect, Intrusiveness, Hostility, Anxiety and Frightened/Frightening behavior.

Self-reported parenting.—At 4 months postpartum, participants from the MACY subsample completed the Postpartum Bonding Questionnaire (PBQ; Brockington et al., 2001; Brockington, Fraser, & Wilson, 2006), a 25-item self-report questionnaire that assesses maternal postpartum attachment and bonding problems toward her infant in the postpartum period. Items are rated on a 6-point Likert scale from 0 (always) to 5 (never), with eight items reverse scored. Higher scores are indicative of higher levels of bonding disturbance. The PBQ comprises three subscales (Impaired Bonding, Rejection and Anger, Anxiety about Care) and a Total Bonding Impairment composite score. A fourth subscale, Risk for Abuse, was not included in the current study due to mandated reporting requirements. The PBQ subscales have adequate sensitivity for any bonding disorder (Impaired Bonding .93, Rejection and Anger .57, Anxiety about Care .43) and severe bonding disorder (Impaired Bonding 1.0, Rejection and Anger .89, Anxiety about Care .56), and specificity compared to a clinical interview (Impaired Bonding .85, Rejection and Anger 1.0, Anxiety about Care .96; Brockington et al., 2001).

Mother OXTR genotypes

DNA was obtained from maternal saliva specimens (collected in Oragene vials from DNAGenotek Inc.). DNA was extracted using the “QuickGene-810” membrane protocol (FujiFilm, Inc. Japan), quantified by picoGreen and gel electrophoresis, and plated at 96 well plates normalized to 600 ng. Genotyping of OXTR rs1042778 and rs53576 was performed at the University of Michigan DNA Sequencing Core using an Illumina BeadStation using Illumina Infinium technology. In line with previous work, OXTR rs1042778 was dichotomized into lower-risk (TG, $N = 48$; GG, $N = 34$) and higher-risk (TT, $N = 18$) groups (Feldman et al., 2012), and OXTR rs53576 was dichotomized into lower-risk (GG, $N = 46$) and higher-risk (AG, $N = 50$; AA, $N = 4$) groups (Bakermans-Kranenburg & van Ijzendoorn, 2008).

Analysis plan

Genotype groups were first dichotomized (TG, GG vs. TT for OXTR rs1042778; GG vs. AG, AA for OXTR rs53576) for later analysis; lower-risk genotypes (TG, GG on rs1042778 and GG on rs53576) were coded as 0, and higher-risk genotypes (TT on rs1042778 and AG, AA on 53576) were coded as 1. Bivariate correlations were run between all variables of interest (childhood maltreatment, observed parenting, self-reported parenting, OXTR rs1042778 and rs53576). Multivariate Analysis of Variance (MANOVA) was used to examine the association between dichotomous genotype groups and parenting variables; all observed parenting variables were included in one MANOVA and all self-reported parenting variables were included in a separate MANOVA. A chi-square test was substituted for the dichotomous Frightened/Frightening behavior variable.

Multivariate Analysis of Covariance (MANCOVA) was used to examine the association between dichotomous genotype groups, childhood maltreatment, and their interaction on parenting variables; again, all observed parenting variables were included in one MANCOVA and all self-reported parenting variables were included in a separate MANCOVA. A chi-square test was again substituted for the dichotomous Frightened/Frightening behavior variable.

All analyses were repeated in the subsample of mothers who were of European ancestry, as determined by self-report. Stratification of samples by ancient ancestry in genetic association analyses are crucial to avoid false-positives due to potential differences in gene frequencies across ancestry groups confounded by differences in phenotype (e.g., population stratification). We did not have sufficient *N* of mothers of other ancestry, so here we focused only on mothers of European ancestry.

In order to correct for multiple comparisons (4 tests per dependent variable: MANOVA or chi-square test, and MANCOVA or chi-square test for both OXTR rs1042778 and 53576), a Bonferroni correction was used; results were considered statistically significant if they were at or below $p = .013$.

Results

Means and standard deviations for genotype groups on observed parenting scales and the Postpartum Bonding Questionnaire are provided in Table 2. Correlations between all variables of interest (childhood maltreatment, observed parenting variables, self-reported bonding impairment variables, and OXTR genotypes) suggest that childhood maltreatment is associated with lower levels of observed behavioral sensitivity, engagement, and positive affect, and higher levels of hostility during the mother-infant teaching tasks; no associations were revealed for self-reported bonding impairment (Table 3). There were high intercorrelations among observed parenting variables and among self-reported bonding impairment variables, all in the expected directions. Observed parenting and self-reported bonding impairment had few significant intercorrelations; the only associations that reached statistical significance were an inverse association between observed frightened/frightening behavior and two measures of self-reported bonding impairment (anxiety about care and total bonding impairment). The TT genotype on OXTR rs1042778 was associated with lower behavioral sensitivity, lower engagement, higher intrusiveness, and higher frightened/frightening behavior, as well as lower self-reported bonding impairment (all component subscales). The AG and AA genotype on OXTR rs53576 were associated with significantly lower hostility, but no other observed parenting or self-reported bonding impairment variables.

Associations between OXTR and measures of observed parenting

OXTR rs1042778.—The MANOVA results revealed a significant association between rs1042778 and observed parenting (Table 4). Specifically, the TT genotype was significantly associated with lower behavioral sensitivity, lower engagement, and higher intrusiveness. All effect sizes were comparable when the analysis was repeated among the subsample of participants of European descent (Table 4). A chi-square test revealed that those with the TT genotype were more likely to exhibit frightened/frightening behavior than those with the TG or GG genotype, $X^2(N = 98) = 8.92$, $p < .01$, $\phi = 0.30$ (European subsample $\phi = 0.15$).

In the MANCOVA with both OXTR rs1042778 and childhood maltreatment, there was an overall significant main effect of genotype and childhood maltreatment, but the interaction between the two variables was nonsignificant (Table 5). Specifically, the TT genotype was significantly associated with lower behavioral sensitivity, lower engagement, higher

intrusiveness, and higher anxiety relative to the TG or GG genotype (Figure 1). Childhood maltreatment was associated with lower engagement and lower anxiety. One univariate genotype by childhood maltreatment interaction attained statistical significance, such that observed anxiety was highest among those with the TT genotype who had no childhood maltreatment. Of note, however, only six participants had both the TT genotype and no history of childhood maltreatment, so the potential influence of one participant's scores is greater among this subgroup. Effect sizes were largely comparable when analyses were conducted on a subsample of participants of European descent, but the effect of OXTR on maternal engagement and anxiety were somewhat attenuated, as was the multivariate main effect of childhood maltreatment (see Table 5). A chi-square test revealed an interaction between childhood maltreatment and genotype for frightened/frightening behavior, $X^2(N = 96) = 8.67$, $p < .01$, $\phi = 0.30$ (European subsample $\phi = 0.15$; Figure 2). Although genotype was not associated with frightened/frightening behavior among individuals with no history of childhood maltreatment, $X^2(N = 32) = 0.24$, $p = .63$, $\phi = -0.09$ (European subsample $\phi = -0.09$), there was a significant association among individuals with a history of childhood maltreatment, $X^2(N = 64) = 13.64$, $p < .01$, $\phi = 0.46$ (European subsample $\phi = 0.32$). It should be noted that this effect was due to 3 of 11 participants with a history of childhood maltreatment and a TT genotype demonstrating frightened/frightening behavior.

OXTR rs53576.—MANOVA results revealed that there was no significant main effect of OXTR rs53576 on observed parenting (Table 4). There was, however, one significant univariate effect suggesting that mothers with the GG genotype demonstrated higher hostility than mothers with the AG or AA genotypes. All effect sizes were comparable when the analysis was repeated among the subsample of participants of European descent (Table 4). A chi squared test revealed no significant effect of rs53576 genotype on frightened/frightening behavior, $X^2(N = 98) = 0.04$, $p = 0.83$, $\phi = -0.02$ (European subsample $\phi = -0.02$).

In the MANCOVA with both OXTR rs53576 and childhood maltreatment, there was an overall significant main effect of childhood maltreatment, but the main effect of OXTR and the OXTR by childhood maltreatment interaction were nonsignificant (Table 5). Specifically, childhood maltreatment was associated with lower engagement. There was also one significant univariate effect of OXTR such that the GG genotype was associated with higher hostility than the AG or AA genotype. Effect sizes were largely comparable when the analysis was repeated in the subsample of participants of European descent, but the multivariate OXTR by childhood maltreatment interaction was attenuated (Table 5). A chi-square test revealed no association between childhood maltreatment, OXTR rs53576 and frightened/frightening behavior in either the full sample, $X^2(N = 96) = 0.05$, $p = 0.83$, $\phi = -0.02$, or the subsample of participants of European descent, $X^2(N = 65) = 0.04$, $p = 0.84$, $\phi = -0.03$.

Associations between OXTR and self-reported bonding impairment

OXTR rs1042778.—MANOVA results revealed a significant association between rs1042778 and self-reported bonding impairment (Table 4). Specifically, the TT genotype was significantly associated with lower impaired bonding, lower rejection and anger, and

lower anxiety about care, relative to the TG or GG genotypes (Figure 3). All effect sizes were comparable, but somewhat attenuated, when the analysis was repeated in the subsample of participants of European descent (Table 4).

In the MANCOVA with both OXTR rs1042778 and childhood maltreatment, all multivariate and univariate main effects and interactions were statistically nonsignificant, and effect sizes were comparable in the subsample of participants of European descent (Table 5).

OXTR rs53576.—MANOVA results revealed no significant association between rs53576 and self-reported bonding impairment, and this was true for both multivariate and univariate effects (Table 4). Effect sizes were comparable in the subsample of participants of European descent.

In the MANCOVA with both rs53576 and childhood maltreatment, all multivariate and univariate main effects and interactions were statistically nonsignificant; effect sizes were comparable in the subsample of participants of European descent (Table 5).

Discussion

The first goal of this study was to independently replicate prior OXTR reports that mothers who were rs1042778 risk-allele homozygotes (TT) and rs53578 risk allele (A) carriers show less sensitive parenting (Bakermans-Kranenburg & van Ijzendoorn, 2008; Feldman et al., 2012; Klahr et al., 2015). Our findings are consistent with prior work by Feldman et al. (2012) showing that mothers who were risk-allele homozygotes (TT) in rs1042778 exhibit significantly lower behavioral sensitivity. However, our results contrast with research by Klahr et al. (2015) demonstrating a significant association with rs53576. Our results show that A risk allele carriers and non-carriers do not differ in level of behavioral sensitivity during mother-infant interaction, so in this sample, rs53576 is not associated with observed parenting characteristics.

The present study also goes beyond prior work, by conducting analyses of several additional aspects of positive and negative parenting behavior (i.e., Engagement, Intrusiveness, Hostility and Frightened/Frightening behaviors). Our findings suggest that OXTR rs1042778 is related to both positive and negative parenting behaviors. Specifically, rs1042778 risk allele homozygotes (TT) tend to have lower levels of engagement and higher levels of intrusiveness and frightened/frightening behavior during mother-infant interaction. This finding is consistent with the effect on observed behavioral sensitivity seen in this sample, and also in line with prior research suggesting maternal TT-homozygotes are at greatest risk for poorer parenting outcomes. However, our findings for rs53576 run counter to our hypotheses based on prior reports (Bakermans-Kranenburg & van Ijzendoorn, 2008): A-carriers in the present study do not exhibit poorer parenting quality than non-carriers, and in fact on one measure of parenting (hostility), A-carriers engage in more optimal parenting than non-carriers. However, the effects for rs53576 are small, and may be due to chance. It is also possible that the small number of risk allele homozygotes in our sample (AA, $N = 4$) may have limited our ability to detect effects of rs53576 on parenting.

To evaluate whether our findings reflect differences in gene frequencies across ancestry groups, we repeated all analyses in the subsample of participants who were of European descent. Although some power is lost in this smaller sample, the majority of findings in both the full sample analysis and the European subsample have similar effect sizes, suggesting that effects are not driven by specific ancestry groups. However, main effects of rs1042778 on maternal positive affect and anxiety, and the chi squared test examining rs1042778 by childhood maltreatment interactions on frightened/frightening behavior were somewhat attenuated in the European subsample. These outcome variables that showed smaller effect sizes among the European subsample were those that had either low frequency (anxiety, frightened/frightening behavior) or fewer scores in the extremes (positive affect) in our sample, suggesting that our sample did not have sufficient *N* when excluding non-European ancestry groups.

Prior research suggests that childhood maltreatment may interact with OXTR genetic associations (Bradley et al., 2011; Hostinar et al., 2014). However, to our knowledge, potential interactions with OXTR and childhood maltreatment in the context of parenting outcomes have not been reported. Our findings suggest that parents who are homozygous for the rs1042778 “risk” allele (TT genotype) are at risk for higher rates of frightened/frightening behavior if they have also experienced childhood maltreatment. This is consistent with the observed main effects of the rs1042778 TT genotype for poorer parenting behaviors (greater levels of intrusiveness and lower levels of engagement and sensitivity). However, our findings were based on a small sample size (i.e., of 11 participants with TT genotypes who experienced childhood maltreatment, 3 demonstrated frightened/frightening behavior). Thus, it is not yet known whether this finding is generalizable, and it must be replicated in larger samples. Significant interactions with childhood maltreatment were not observed in other parenting behaviors. Although previous studies report that the effects of child maltreatment or stress interactions are moderated by rs53576 (Bradley et al., 2011; Cicchetti, Rogosch, Hecht, Crick, & Hetzel, 2014; Hostinar et al., 2014), this is to our knowledge the first report of a significant child maltreatment by rs1042778 interaction on parenting behavior.

Another novel feature of our study is that it evaluates both observational and self-report data on parenting in relation to OXTR genotypes. As predicted, our findings suggest that OXTR rs1042778 risk genotypes are associated with less sensitive observed parenting, but counter to expectations, also to *better* self-reported parenting. Specifically, the mothers with the TT genotype in our sample report less bonding impairment than mothers with TG or GG genotypes, and this is also true for each of the subscales examined. Discordance between observed and self-reported parenting is consistent with previous findings in the broader parenting literature, particularly among at-risk mothers (Bailey, DeOliveira, Wolfe, Evans, & Hartwick, 2012; Bennett, Sullivan, & Lewis, 2006; Driscoll & Easterbrooks, 2007; Fitzgerald, Shipman, Jackson, McMahon, & Hanley, 2005). Further, there is evidence that both childhood maltreatment (Bailey, Moran, & Pederson, 2007) and OXTR risk genotypes (Lucht et al., 2013; Schneider-Hassloff et al., 2016) are associated with lower self-awareness or impaired ability to infer mental states in others. Specifically, OXTR polymorphisms on rs53576 are related to alexithymia in adulthood, as well as neural activity in areas of the brain related to mentalizing (Schneider-Hassloff et al., 2016). In our sample, which is

overrepresented for mothers with histories of childhood maltreatment, it is possible that childhood maltreatment and/or OXTR risk genotypes contributed to impaired self-awareness, such that mothers who were at greater risk (i.e., due to genotype or maltreatment history) were also less aware of any difficulty they may have had in bonding with their child. Thus, these higher-risk mothers may demonstrate poorer parenting behavior in observational tasks, but at the same time self-report lower levels of problems. In other words, it may be that the significant difference between OXTR rs1042778 genotypes in self-reported bonding impairment are a reflection of group differences in self-awareness as it relates to bonding. An important direction for future work will be to examine both observed and self-reported parenting in relation to OXTR genotypes in larger and more diverse samples to determine whether the discrepancy across observed and self-report measures is replicated among all parents or only among those parents who have experienced childhood trauma.

The results of this study should be interpreted in light of several limitations. Our sample was small and included a low frequency of certain genotypes which may have limited power and our ability to detect some effects, particularly child trauma by OXTR polymorphism interactions. More specifically, our sample includes a limited number of higher-risk homozygotes on rs53576 (AA; $N = 4$), which may have impaired our ability to detect effects of the A allele on parenting. Further, only one effect of OXTR rs53576 attained statistical significance (hostility), and it was small in magnitude and in the opposite direction than we expected. Thus, this finding should be interpreted with caution, and replication in larger, more diverse samples is warranted.

There is evidence that different kinds of childhood maltreatment are differentially related to children's later outcomes (Bailey et al., 2012). However, our measures of childhood maltreatment were relatively broad, and the nature of our sample does not allow for clear differentiation between abuse and neglect (i.e., all who endorsed neglect had also endorsed abuse). Future work in samples with a wider range of childhood maltreatment exposure is necessary to determine whether abuse and neglect differentially relate to parenting for different OXTR groups.

Despite these limitations, this study also has several noteworthy strengths. First, multiple dimensions of parenting behavior were assessed, including both positive and negative parenting observed and coded from videotapes of mother-infant teaching tasks and a self-report bonding impairment questionnaire. Further, due to the nature of the cohorts from which the current data were drawn, mothers in the current sample reported a high frequency of trauma, stress, and depression, allowing us to examine more clearly how OXTR relates to parenting among mothers who are at higher risk for problems.

In sum, this study replicates previous findings regarding OXTR rs1042778 and parenting, and extends prior work by providing a more nuanced understanding of the specific positive and negative parenting behaviors that relate to OXTR polymorphisms. As well, our findings suggest that some OXTR effects (i.e., on frightened/frightening behavior) may be moderated by maternal childhood maltreatment history, and the discrepancy between our findings for observed versus self-reported parenting raise important questions for future research about

whether OXTR polymorphisms and/or childhood maltreatment history might have effects on mothers' self-awareness related to their parenting.

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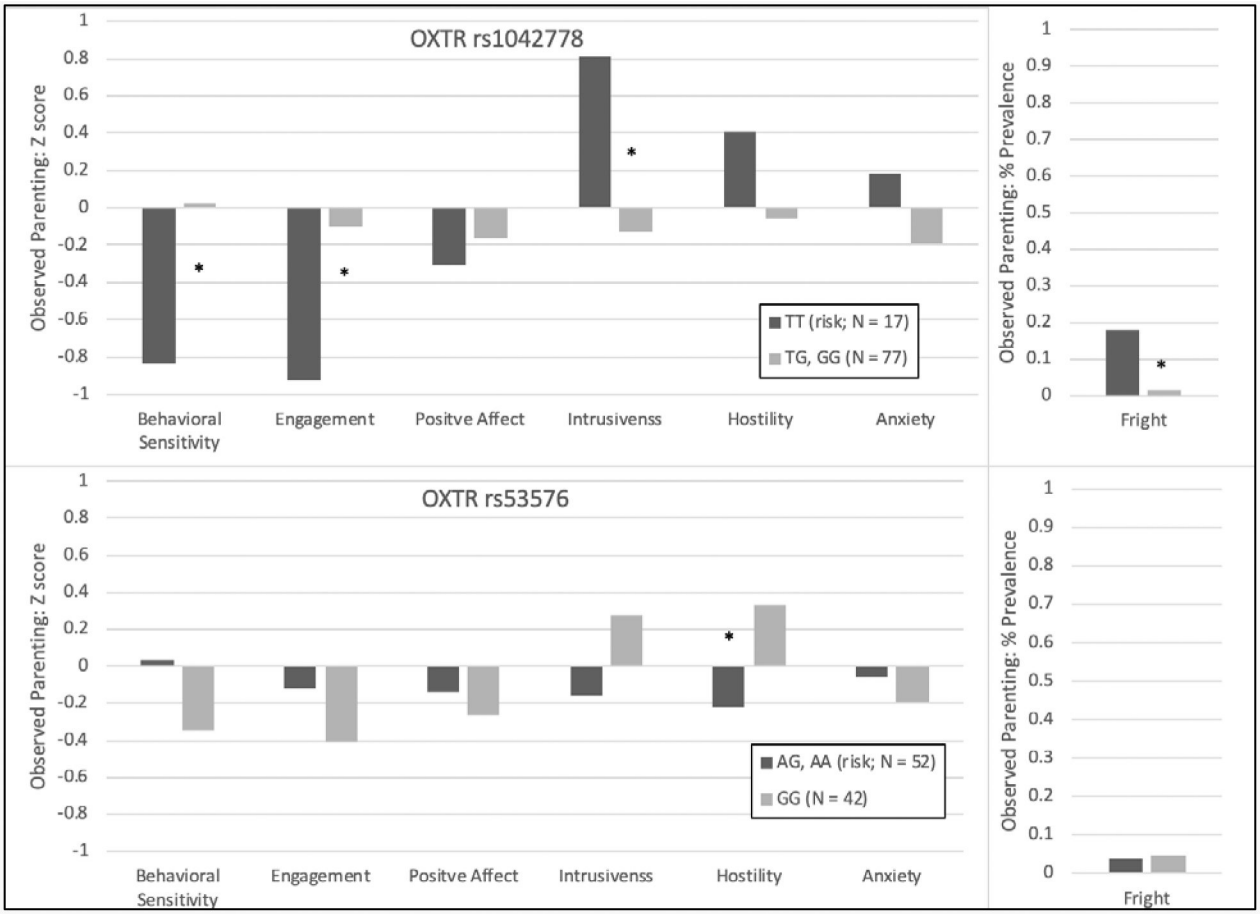

Figure 1.

Observed parenting behavior (*Z* scores, % prevalence) by maternal OXTR genotype (rs1042778 top, rs53576 bottom). * $p < .013$

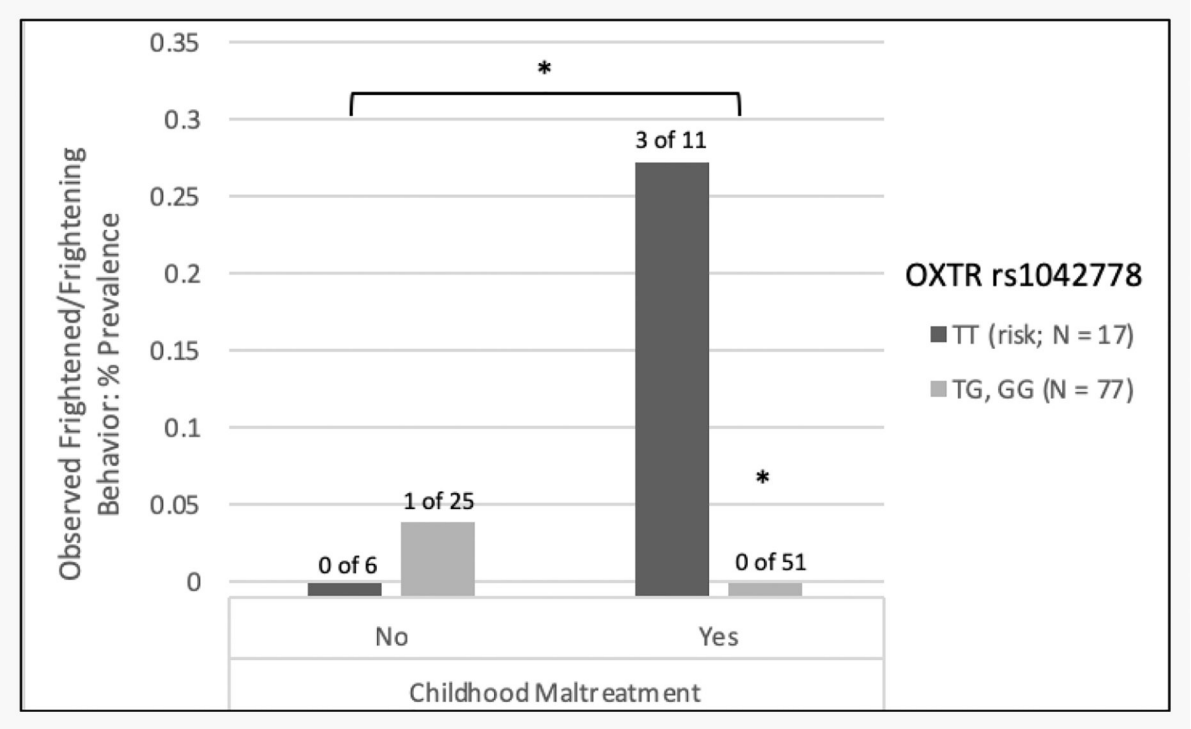

Figure 2.

Observed frightened/frightening behavior by maternal OXTR genotype on rs1042778 for mothers with and without a history of childhood maltreatment. * $p < .013$

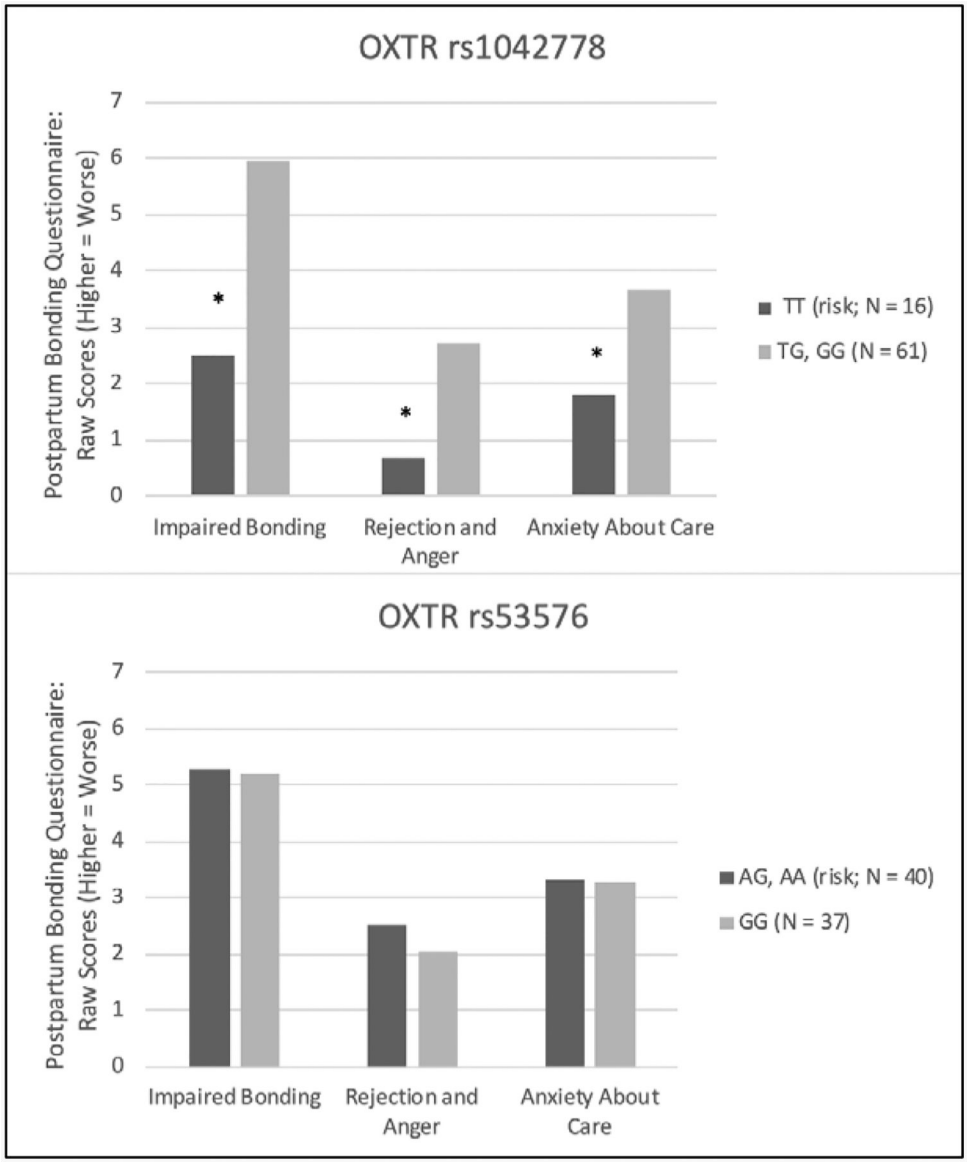

Figure 3.

Postpartum Bonding Questionnaire (raw scores) by maternal OXTR genotype (rs1042778 top, rs53576 bottom). * $p < .013$

Table 1.

Maternal demographic and psychosocial characteristics

	MACY	PIMACS	Total Sample
N	81	19	100
Age (years)	29.90 (5.95)[a]	31.53 (4.54)	30.21 (5.72)
Married or living with partner	60 (74.07%)[b]	19 (100%)	79 (79.00%)
Education			
Median	Bachelor's Degree	Bachelor's Degree	Bachelor's Degree
HS diploma or less	10 (12.50%)	0 (0.00%)	10 (10.10%)
Income			
Median	$50,000-$54,999	$75,000	$55,000-$59,999
Less than $25,000	22 (27.16%)	1 (5.56%)	23 (23.23%)
Race/Ethnicity			
White	53 (65.43%)	15 (78.95%)	68 (68.00%)
African American	16 (19.75%)	1 (5.26%)	17 (17.00%)
Latina	3 (3.70%)	1 (5.26%)	4 (4.00%)
Asian or other Pacific Islander	4 (4.94%)	1 (5.26%)	5 (5.00%)
Bi-Racial	2 (2.47%)	1 (5.26%)	3 (3.00%)
Other	3 (3.70%)	0 (0.00%)	3 (3.00%)
Childhood Maltreatment	62 (78.48%)	2 (11.11%)	64 (66.00%)
Lifetime PTSD diagnosis	43 (55.84%)	0 (0.00%)	43 (44.79%)
Lifetime MDD diagnosis	40 (50.00%)	4 (21.05%)	44 (44.00%)

[a] Mean (Standard Deviation)

[b] N (%)

MACY = Maternal Anxiety during the Childbearing Years study. PIMACS = Perinatal Infant Mother Attachment Cortisol Study. PTSD = Post-traumatic Stress Disorder. MDD = Major Depressive Disorder.

Table 2.

Descriptive statistics for observed and self-reported parenting variables by maternal OXTR genotype

	rs1042778		rs53576		Full Sample
	TT (risk)	TG, GG	AG, AA (risk)	GG	
Observed Parenting (Z scores)	*N* = 18	*N* = 80	*N* = 54	*N* = 44	*N* = 98
Behavioral Sensitivity	−0.78 (0.74)[a]	0.04 (0.94)	0.05 (0.88)	−0.30 (1.02)	−0.11 (0.96)
Engagement	−0.80 (0.96)	−0.12 (0.94)	−0.16 (1.05)	−0.35 (0.87)	−0.24 (0.97)
Positive Affect	−0.22 (0.78)	−0.19 (0.89)	−0.18 (0.94)	−0.22 (0.78)	−0.20 (0.86)
Intrusiveness	0.75 (0.74)	−0.15 (0.98)	−0.16 (0.94)	0.24 (1.04)	0.02 (1.00)
Hostility	0.35 (0.97)	−0.06 (0.88)	−0.21 (0.71)	0.29 (1.04)	0.01 (0.90)
Anxiety	0.15 (1.00)	−0.15 (0.72)	−0.04 (0.84)	−0.15 (0.71)	−0.09 (0.79)
Frightened/Frightening	3 (16.67%)[b]	1 (1.25%)	2 (4.54%)	2 (3.70%)	4 (4.08%)
PBQ (Raw scores)	*N* = 16	*N* = 61	*N* = 40	*N* = 37	*N* = 77
Impaired Bonding	2.50 (3.01)	5.97 (4.31)	5.28 (4.08)	5.22 (4.57)	5.25 (4.30)
Rejection and Anger	0.69 (1.25)	2.72 (2.66)	2.53 (2.61)	2.05 (2.54)	2.30 (2.57)
Anxiety About Care	1.81 (1.76)	3.69 (2.33)	3.30 (2.11)	3.30 (2.60)	3.30 (2.35)

PBQ = Postpartum Bonding Questionnaire

[a] Mean (SD)

[b] *N* (%)

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Table 3.

Correlations (below diagonal) and *N* (above diagonal) for predictor variables

			1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
Observed parenting behavior	1.	Childhood Maltreatment (0 = no, 1 = yes)		94	94	94	94	94	94	94	75	75	75	75	95	95
	2.	Behavioral Sensitivity	−.20*		98	98	98	98	98	98	77	77	77	77	98	98
	3.	Engagement	−.37**	73**		98	98	98	98	98	77	77	77	77	98	98
	4.	Positive Affect	−.23*	.38**	.51**		98	98	98	98	77	77	77	77	98	98
	5.	Intrusiveness	.16	−.83**	−.51**	−.17+		98	98	98	77	77	77	77	98	98
	6.	Hostility	.20+	−.58**	−.42**	−.33**	.45**		98	98	77	77	77	77	98	98
	7.	Anxiety	−.12	−.13	−.07	−.24*	.13	.21*		98	77	77	77	77	98	98
	8.	Fright (0 = no, 1 = yes)	.04	−.14	−.12	.04	.10	.22*	−.09		77	77	77	77	98	98
PBQ	9.	Impaired Bonding Subscale	.11	.17	.12	−.05	−.14	−.09	.02	−.17		77	77	77	77	77
	10.	Rejection and Anger Subscale	.18	.19	.16	−.09	−.13	−.08	.08	−.18	.81**		77	77	77	77
	11.	Anxiety about Care Subscale	−.01	.21+	.17	.14	−.16	−.02	.07	−.29*	.56**	.52**		77	77	77
	12.	Total Bonding Impairment	.12	.21+	.16	−.01	−.16	−.08	.05	−.23*	.95**	.89**	.75**		77	77
OXTR	13.	rs1042778 (0 = TG, GG, 1 = TT (risk))	.01	−.34**	−.27**	−.01	.35**	.18+	.15	.30**	−.33**	−.32**	−.33**	−.37**		100
	14.	rs53576 (0 = GG, 1 = AG, AA (risk))	.09	.18+	.10	.02	−.20+	−.28**	.07	−.02	.01	.09	.00	.03	.04	

PBQ = Postpartum Bonding Questionnaire

+ p<.10,

* p<.05,

** p<.01

Table 4.

MANOVA results for the effects of OXTR (rs1042778, rs53576) on observed parenting (top) and self-reported bonding impairment (bottom)

	OXTR: rs1042778				OXTR: rs53576			
	Wilks' Λ	**F**	**η_p^2**	**Euro[a] η_p^2**	**Wilks' Λ**	**F**	**η_p^2**	**Euro η_p^2**
OXTR	0.83	3.04*	0.17	0.20	0.89	1.81	0.11	0.09
Behavioral Sensitivity		12.13*	0.11	0.11		3.20	0.03	0.01
Engagement		7.75*	0.08	0.05		0.92	0.01	0.00
Positive Affect		0.02	0.00	0.01		0.04	0.00	0.00
Intrusiveness		13.28*	0.12	0.17		3.89	0.04	0.01
Hostility		3.17	0.03	0.01		7.84*	0.08	0.05
Anxiety		2.13	0.02	0.00		0.49	0.01	0.01
OXTR	0.86	4.07*	0.14	0.12	0.98	0.55	0.02	0.05
Impaired Bonding		9.14*	0.11	0.07		0.00	0.00	0.03
Rejection and Anger		8.74*	0.10	0.07		0.64	0.01	0.04
Anxiety About Care		8.96*	0.11	0.09		0.00	0.00	0.00

*$p < .013$

[a]Analysis repeated among subsample of participants of European descent.

Table 5.

MANCOVA results for the effect of OXTR (rs1042778, rs53576), childhood maltreatment, and their interaction on observed parenting (top) and self-reported bonding impairment (bottom).

	OXTR: rs1042778				OXTR: rs53576			
	Wilks' Λ	**F**	**η_p^2**	**Euro[a] η_p^2**	**Wilks' Λ**	**F**	**η_p^2**	**Euro η_p^2**
OXTR	0.81	3.42*	0.19	0.20	0.86	2.31	0.14	0.16
Behavioral Sensitivity		10.98*	0.11	0.09		2.56	0.03	0.01
Engagement		7.86*	0.08	0.04		2.72	0.03	0.02
Positive Affect		0.17	0.00	0.01		0.43	0.01	0.00
Intrusiveness		12.43*	0.12	0.15		3.54	0.04	0.03
Hostility		2.72	0.03	0.01		8.81*	0.09	0.08
Anxiety		7.51*	0.08	0.03		0.27	0.00	0.01
Childhood Maltreatment	0.80	3.64*	0.20	0.14	0.76	3.99*	0.22	0.20
Behavioral Sensitivity		2.08	0.02	0.02		4.79	0.05	0.04
Engagement		8.67*	0.09	0.06		14.85*	0.14	0.11
Positive Affect		1.43	0.02	0.01		4.97	0.05	0.03
Intrusiveness		0.93	0.01	0.02		3.04	0.03	0.04
Hostility		2.66	0.03	0.01		5.08	0.05	0.03
Anxiety		8.30*	0.08	0.07		1.63	0.02	0.01
OXTR × Childhood Maltreatment	0.90	1.70	0.11	0.13	0.88	1.99	0.12	0.07
Behavioral Sensitivity		0.06	0.00	0.00		1.26	0.01	0.00
Engagement		0.04	0.00	0.00		0.96	0.01	0.00
Positive Affect		0.80	0.01	0.01		0.50	0.01	0.00
Intrusiveness		0.23	0.00	0.00		0.35	0.00	0.01
Hostility		0.03	0.00	0.00		0.05	0.00	0.00
Anxiety		9.57*	0.09	0.10		1.32	0.01	0.02
OXTR	0.907	2.36	0.09	0.10	0.96	0.54	0.04	0.04
Impaired Bonding		4.93	0.07	0.05		0.41	0.01	0.01
Rejection and Anger		4.05	0.05	0.03		0.88	0.02	0.02
Anxiety About Care		6.03	0.08	0.09		0.18	0.00	0.00
Childhood Maltreatment	0.979	0.50	0.02	0.02	0.97	0.41	0.03	0.03
Impaired Bonding		0.05	0.00	0.02		0.72	0.02	0.02
Rejection and Anger		0.53	0.01	0.02		1.18	0.03	0.03
Anxiety About Care		0.25	0.00	0.00		0.02	0.00	0.00
OXTR × Childhood Maltreatment	0.987	0.30	0.01	0.05	0.96	0.55	0.04	0.04
Impaired Bonding		0.60	0.01	0.00		0.00	0.00	0.00
Rejection and Anger		0.88	0.01	0.02		0.02	0.00	0.00
Anxiety About Care		0.09	0.00	0.01		1.29	0.03	0.03

*$p < .013$

[a] Analysis repeated among subsample of participants of European descent.