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Oxytocin receptor gene polymorphism (rs53576) moderates the intergenerational transmission of depression

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Summary Maternal depression serves as a potent source of stress among offspring, greatly enhancing the risk of numerous adverse outcomes including youth depression. Several factors moderate the transmission of depression from mothers to offspring. However, the role of genetic characteristics in this process merits further exploration. Consistent with an interpersonal perspective on depression, the present study focused on a genetic polymorphism that has been shown to be relevant to social functioning, the rs53576 polymorphism of the oxytocin receptor gene (*OXTR*). In a community sample of 441 youth, *OXTR* genotype moderated the association between maternal depression in early childhood and youth depressive symptoms in adolescence, such that youth possessing at least one A allele of *OXTR* who also had a history of maternal depression exhibited the highest levels of depressive symptoms at age 15. In order to explore possible interpersonal mediators of this effect, conditional process analyses examined the role of youth social functioning in adolescence. Results suggest that *OXTR* genotype may partially account for the transmission of maternal depression to youth and support the role of dysfunctional social processes as a mechanism through which *OXTR* influences the development of depressive symptoms.

1. Introduction

Maternal depression is strongly associated with numerous adverse outcomes among offspring, with a particularly robust association between maternal and youth depression (Downey

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and Coyne, 1990; Beardslee et al., 1998). Estimates suggest that offspring of depressed mothers are three times more likely to experience depression than those without a depressed mother (Lieb et al., 2002). A history of maternal depression is also associated with characteristics of youth depression that reflect poorer prognosis, including earlier onset (Hammen et al., 2008), higher rates of recurrence (Lieb et al., 2002), and increased risk of comorbid conditions (Hammen and Brennan, 2001).

However, despite the enhanced risk conferred by maternal depression, half of all youth with a depressed mother remain free of psychopathology (Pilowsky et al., 2006). Various factors have been identified as moderators of the transmission of maternal depression, including youth gender (Davies and Windle, 1997), emotion regulation abilities (Silk et al., 2006), and self-esteem (Pargas et al., 2010). Consistent with an interpersonal perspective on depression (Joiner and Coyne, 1999), social factors such as parent—child relationship quality, interpersonal stress, and peer functioning have also been recognized as moderators (Hammen et al., 2004; Pargas et al., 2010).

Given the moderate heritability of depression (Sullivan et al., 2000) as well as some evidence supporting the interplay of genes and the environment in its development (Caspi et al., 2003), additional research is needed to explore the role of candidate genes in the intergenerational transmission of depression. To date, only two studies have examined offspring genetic characteristics as moderators of maternal depression's effect on youth (Thompson et al., 2011; Oppenheimer et al., 2013), offering preliminary support for the role of the serotonin transporter and oxytocin receptor genes. These findings suggest that genetic factors may influence individual vulnerability to the adverse effects of maternal depression. However, additional research is needed to explore the longitudinal influence of genetic moderators and establish potential mediators of this process.

Given the importance of interpersonal processes in the etiology of depression (Joiner and Coyne, 1999), identifying genetic polymorphisms that exhibit a strong association with social factors is a logical focus of research. Interpersonal functioning is particularly relevant to the association between maternal and youth depression because depressed mothers often exhibit problematic parenting behavior (e.g., hostility, disengagement) that may influence the development of youth depression (Lovejoy et al., 2000; Brennan et al., 2003). Research linking the oxytocin receptor gene (*OXTR*) with interpersonal processes in humans suggests that it is a promising candidate as one moderator of the intergenerational transmission of depression (Kumsta and Heinrichs, 2013). Oxytocin is a neurohormone that has been associated with a range of affiliative behaviors in humans including demonstrations of trust (Kosfeld et al., 2005), parental bonding (Gordon et al., 2008), and sensitivity to others' mental state (Domes et al., 2007).

An emerging body of literature supports an association between the rs53576 single nucleotide polymorphism (SNP) of *OXTR* and social processes, with most studies suggesting that the GG genotype is associated with prosocial behavior. Individuals who are homozygous for the G allele report higher levels of dispositional empathy and perform more accurately on a theory of mind task than A carriers (i.e., AG or AA genotype; Rodrigues et al., 2009). When interacting with a romantic partner, GG homozygotes exhibited more nonverbal affiliative behaviors (e.g., smiling, head nodding) than A carriers (Kogan et al., 2011). Individuals who are homozygous for the G allele also displayed more trust during an economics task than A carriers, controlling for personality factors and attachment style (Krueger et al., 2012). Parents with the GG genotype exhibited heightened sensitivity to their child's needs when helping them to complete a problem-solving task (Bakermans-Kranenburg and van IJzendoorn, 2008).

Evidence also suggests that the rs53576 polymorphism of *OXTR* may be associated with depressive symptoms and affect. Individuals carrying an A allele exhibited higher levels of depressive symptoms than GG homozygotes (Saphire-Bernstein et al., 2011), while males who are homozygous for the A allele demonstrated lower positive affect than G carriers (Lucht et al., 2009). In contrast, Costa et al. (2009) found evidence for an association between the GG genotype of *OXTR* and depression in a clinical sample. These results indicate that *OXTR* may be associated with depression, but additional research is needed to elucidate this relationship. Furthermore, the results of a meta-analysis by Bakermans-Kranenburg and van IJzendoorn (in press) suggest that findings purporting main effects of *OXTR* genotype on biological and psychological outcomes should be interpreted with caution. Thus, the present study explores the rs53576 polymorphism of *OXTR* as a moderator of the intergenerational transmission of depression in order to examine its interactive effects with environmental characteristics.

In addition to examining genetic moderation, the present study tests a potential mechanism of this effect by examining the mediating role of youth social functioning. Maternal depression is associated with youth deficits in interpersonal functioning (Goodman, 2007), with evidence suggesting that impaired social competence is a mediator of the intergenerational transmission of depression (Hammen et al., 2004). Given that *OXTR* has also been associated with social processes, the present study explores youth social functioning as a mechanism of the relationship between youth *OXTR* genotype and the intergenerational transmission of depression.

The single previous study that examined youth *OXTR* genotype and the transmission of maternal depression found that adolescents with the AG genotype of the rs2254298 SNP and a history of maternal depression exhibited the highest levels of depressive symptoms (Thompson et al., 2011). However, the study was limited by its entirely female sample, exclusion of AA homozygotes, and relatively small sample size ($N = 92$). The present study seeks to extend this research by examining the role of the more-studied *OXTR* rs53576 polymorphism on the transmission of maternal depression to offspring in a moderately large community sample of adolescents. Additional analyses explore youth social functioning as one possible mechanism of the impact of *OXTR* on the intergenerational transmission of depression. It is expected that (a) youth *OXTR* genotype will interact with maternal depression in early childhood to predict youth depressive symptoms at age 15, such that youth with a history of maternal depression who also possess at least one A allele of *OXTR* will exhibit the highest levels of depressive symptoms and (b) this association will be mediated by indicators of youth social functioning.

2. Methods

2.1. Participants

Participants were drawn from a community sample of women and their children participating in the Mater Misericordiae Mothers' Hospital-University of Queensland Study of Pregnancy (Keeping et al., 1989), a longitudinal study of a birth cohort in Brisbane, Queensland, Australia between 1981 and 1984. Of the more than 7000 participants in the original study, a subsample of 815 mother-child pairs were selected in order to examine the effects of maternal depression on youth, oversampling for maternal depression as determined by scores on the Delusions-Symptoms-States Inventory (DSSI; Bedford and Foulds, 1978) which was completed by mothers at four points between pregnancy and youth age 5, and confirmed through diagnostic assessment on the Structured Clinical Interview for DSM-IV (SCID-I; First et al., 1995) administered at youth age 15. Mean maternal DSSI score prior to youth age 5 was significantly associated with diagnoses of maternal depression based on the SCID-I ($B = 0.03$, SE = 0.01, $p < 0.001$).

Youth and their mothers completed follow-up interviews and questionnaires at youth age 15 and again at youth age 20. The 705 youth who were available for the age 20 follow-up were asked to provide a DNA sample for genetic analysis between ages 22 and 25. Youth who were genotyped for the rs53576 polymorphism of *OXTR* and completed all measures relevant to the present study ($N = 441$) did not differ from the remainder of the full sample ($N = 374$) in terms of race (χ^2 (1,793) < 0.01, $p = 0.965$) or maternal depression history (χ^2 (1,811) = 0.34, $p = 0.562$). However, youth included in the present study were less likely to be male (χ^2 (1,815) = 36.44, $p < 0.001$), suggesting that the results may be affected by sampling bias.

Of the 441 youth included in the present analyses, a total of 261 participants (59.2%) are female, and most are Caucasian ($N = 413$, 93.7%). A minority of participants identified as Asian ($N = 18$, 4.1%), Maori/Pacific Islander ($N = 5$, 1.1%), Aboriginal ($N = 2$, 0.5%), and other ($N = 1$, 0.2%). Data on race/ethnicity were not available for two participants. Race (Caucasian vs. other) was not associated with dichotomous (GG vs. AG/AA) genotype (χ^2 (1,440) = 2.72, $p = 0.099$).

2.2. Procedure

At youth age 15, youth and their mothers completed a battery of self-report questionnaires and participated in follow-up interviews. Separate interviewers assessed mothers and their offspring, and youth interviewers were blind to maternal depression status. Between youth ages 22 and 25, participants were re-contacted and asked to provide DNA samples for genetic analysis. Participants were mailed consent forms and blood collection kits. Blood samples were drawn at local medical facilities and subsequently returned by courier to the Genetic Epidemiological Laboratory at the Queensland Institute of Medical Research for storage. Samples were later shipped to UCLA and analyzed at the Social Genomics Core of the USC/UCLA Biodemography Center. All participants gave consent/assent at each data collection point, and all procedures were approved by the Institutional Review Boards of the University of Queensland, Emory University, and the University of California, Los Angeles.

2.3. Measures

2.3.1. Maternal depression

History of maternal depression was assessed by the SCID-I administered at youth age 15 (First et al., 1995). Mothers were considered to have a history of depression if they met criteria for a diagnosis of a major depressive episode or dysthymic disorder at any point in the first five years of the child's life. Research suggests that maternal depression experienced in early childhood exerts a particularly negative effect on youth outcomes, resulting in increased risk of childhood internalizing and externalizing problems (Kiernan and Huerta, 2008) as well as heightened rates of youth emotion dysregulation (Maughan et al., 2007). History of maternal depression was coded as a dichotomous variable (depressed/not depressed). A total of 65 participants (14.7%) met criteria for a history of maternal depression by youth age 5.

2.3.2. Youth depressive symptoms

Youth depressive symptoms at age 15 were measured by the Beck Depression Inventory-II (BDI-II; Beck et al., 1996). The BDI-II has demonstrated high internal consistency and convergent validity in clinical and community samples of adults (Beck et al., 1996), and the excellent psychometric properties of the BDI-II have been replicated in community samples of adolescents (Osman et al., 2008). In the present sample, the mean BDI-II score was 6.20 (SD = 6.19) with scores ranging from 0 to 32. The BDI-II demonstrated high internal consistency in the present sample with a Cronbach's alpha coefficient of 0.85.

2.3.3. Youth social functioning

Youth social functioning was assessed using the UCLA Life Stress Interview (LSI; Hammen and Brennan, 2001), which was administered by trained interviewers at youth age 15. This semi-structured interview measures the nature and quality of ongoing conditions in the participant's life as a measure of chronic stress and adaptive functioning in several relevant domains. Interviewers collect specific details about conditions experienced within the past six months in each of several roles typical of a person of that age (e.g., social life, family relationships, and academic performance). The interviewer then makes objective ratings of functioning using a 1 to 5 scale with factual, behavioral anchors at each level. A score of 5 represents extremely negative conditions/poor functioning, while scores of 1 or 2 are considered relatively high levels of functioning in the specified domain. This measure demonstrates high reliability as well as excellent concurrent validity (Hammen and Brennan, 2001; Hammen et al., 2008).

In the present study, social functioning was measured as a composite of youth functioning in three interpersonal domains of the LSI: close friendships, general peer relationships, and family relationships. Scores in each of the three domains were averaged to create a composite variable representing the level of youth social dysfunction in the six months prior to the age 15 assessment of depressive symptoms. The mean social func-

tioning score was 2.28 (SD = 0.38) and ranged from 1.50 to 3.67. Higher scores represent greater levels of youth social dysfunction.

2.4. Genotyping

The oxytocin receptor gene is located on the short arm of the third chromosome at 3p25, and the rs53576 polymorphism of *OXTR* is found on the third intron (Kumsta and Heinrichs, 2013). *OXTR* codes for the oxytocin receptor, a G protein-coupled receptor involved in reproductive processes including parturition and lactation as well as affiliative and affective processes as described above (Lee et al., 2009). Due to financial constraints, only one polymorphism of *OXTR* was genotyped as part of the present study. The rs53576 polymorphism was selected due to the preponderance of literature utilizing this SNP at the time the parent study was conducted as well as evidence suggesting a meaningful association between the rs53576 polymorphism and characteristics of human social functioning. However, the particular physiologic function of the rs53576 polymorphism is unknown.

Genotyping for the rs53576 polymorphism of *OXTR* was conducted using a commercial TaqMan Genotyping Assay (Applied Biosystems, Foster City, CA) performed on an iCycler real-time PCR instrument (BioRad, Hercules, CA). Test-retest reliability analyses based on duplicated samples yielded a total genotyping error rate of $<1\%$. In the present sample, the genotype frequencies were GG = 192 (43.5%), AG = 196 (44.4%), and AA = 53 (12.0%), and in Hardy-Weinberg equilibrium, χ^2 (2,441) = 0.08, $p = 0.784$. Consistent with the majority of prior OXTR literature reporting more negative social behaviors associated with the A allele (e.g., Thompson et al., 2011; Saphire-Bernstein et al., 2011), genotype was recoded as a dichotomous variable, GG ($N = 192$) vs. AG/AA ($N = 249$).

2.5. Statistical analysis

Univariate analysis of variance was used to explore the effect of *OXTR* genotype on the intergenerational transmission of depression. Due to the higher prevalence of depression among women (Kessler et al., 1993) as well as previous studies that reported interactions between *OXTR* genotype and gender (e.g., Lucht et al., 2009), gender was included in the analyses. Gender, history of maternal depression, dichotomous *OXTR* genotype, and their respective interactions were examined as predictors of youth depressive symptoms at age 15 in a single univariate ANOVA. The interaction between history of maternal depression and *OXTR* genotype served as the crucial test of *OXTR* as a moderator of the intergenerational transmission of depression. The simple effects of maternal depression history on youth depressive symptoms by *OXTR* genotype were examined by conducting two additional univariate analyses of variance among GG homozygotes and A carriers, respectively. The alpha level was set at 0.05 for all analyses, unless otherwise noted.

Conditional process analyses were employed in order to explore youth social functioning as a mediator of the effect. Gender was included as a covariate in these analyses. Conditional process analysis techniques are equivalent to mediated moderation analyses, but allow greater flexibility in interpreting the results according to the variable of interest (i.e., the mediator or the moderator). These analyses were conducted using the PROCESS procedure for SPSS (Hayes, 2012), which estimates direct and indirect effects by calculating bias-corrected 95% confidence intervals using bootstrapping techniques ($N = 5000$ samples). A significant indirect effect supports the variable of interest as a mediator. Significant effects are those in which the estimated 95% confidence interval does not include zero. Effect sizes were calculated by dividing the indirect effect by the total effect in order to estimate the proportion of the total effect mediated by youth social functioning.

Although race was not associated with genotype (reported above), the analyses of interest were repeated excluding non-Caucasian participants in order to examine the hypothesized associations independent of race/ethnicity.

3. Results

3.1. Descriptive statistics

Stratified by genotype group and maternal depression history, descriptive statistics for all study variables are presented in Table 1. *OXTR* genotype did not differ by gender (χ^2 (1,441) = 2.07, $p = 0.150$).

3.2. Gene-environment correlation

In order to ensure that any observed gene-environment interactions were not confounded by a correlation between genotype and environmental exposure, analyses were

Table 1 Descriptive statistics for all study variables, stratified by maternal depression history and dichotomous *OXTR* genotype.

Variable	GG		A carriers	
	No maternal depression	History of maternal depression	No maternal depression	History of maternal depression
N	168	24	208	41
Female gender (%)	107 (63.7%)	14 (58.3%)	121 (58.2%)	19 (46.3%)
Caucasian race (%)[a]	161 (96.4%)	23 (95.8%)	190 (91.8%)	39 (95.1%)
Mean (SD) BDI-II score at age 15	6.29 (6.32)	5.25 (5.24)	5.89 (5.87)	7.95 (7.53)
Mean (SD) social functioning score	2.25 (0.38)	2.28 (0.34)	2.26 (0.37)	2.51 (0.43)

Note.
[a] Values do not match the total number of participants due to missing race/ethnicity data ($N = 2$).

Table 2 Effects of maternal depression history, *OXTR* genotype, and gender on youth depressive symptoms.

Predictor	*F*	*p*	Partial η^2
Maternal depression history	0.37	0.545	0.001
OXTR genotype	2.86	0.092	0.007
Gender	7.78**	0.006	0.018
Maternal depression history × *OXTR* genotype	3.92*	0.048	0.009
Maternal depression history × gender	0.80	0.371	0.002
OXTR genotype × gender	1.31	0.253	0.003
Maternal depression history × *OXTR* genotype × gender	0.71	0.400	0.002

Note.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

conducted to explore the association between *OXTR* genotype and history of maternal depression. Results revealed that genotype did not differ by maternal depression history (χ^2 (1,441) = 1.36, p = 0.244).

3.3. *OXTR* genotype as a moderator of the intergenerational transmission of depression

Univariate analysis of variance revealed that consistent with the higher prevalence of depression among women (Kessler et al., 1993), there was a main effect of gender (F(1,433) = 7.78, p = 0.006, partial η^2 = 0.018), such that females exhibited significantly more depressive symptoms than males at age 15. There were no significant main effects of maternal depression history (F(1,433) = 0.37, p = 0.545, partial η^2 = 0.001) or *OXTR* genotype (F(1,433) = 2.86, p = 0.092, partial η^2 = 0.007) on adolescent depressive symptoms. Gender did not interact with other study variables, as summarized in Table 2.

As predicted, there was a significant interaction between history of maternal depression and *OXTR* genotype in the prediction of depressive symptoms at age 15 (F(1,433) = 3.92, p = 0.048, partial η^2 = 0.009). Post hoc calculations indicated that the power to detect the effect ($1 - \beta$) was 0.25. Tests of simple effects revealed that youth possessing at least one A allele exhibited a significant association between maternal depression in early childhood and depressive symptoms in adolescence (F(1,245) = 4.44, p = 0.036, partial η^2 = 0.018), such that individuals with a history of maternal depression demonstrated more depressive symptoms at age 15 than individuals without depressed mothers. Among individuals homozygous for the G allele, there was no significant difference between individuals with a history of maternal depression and those without (F(1,188) = 0.76, p = 0.384, partial η^2 = 0.004). In order to account for multiple tests (N = 2), a stringent correction to the alpha level was applied, so that the significance levels attained in the tests of simple effects were compared to an alpha level of 0.025. After applying this correction, the p value of 0.036 obtained in the test of the simple effect among A carriers exceeded the significance threshold. Thus, these results offer preliminary evidence that *OXTR* genotype and maternal depression history interact to predict youth depressive symptoms at age 15 such that the A allele of the rs53576 polymorphism of *OXTR* appears to be associated with higher levels of youth depressive symptoms among individuals with a history of maternal depression.

Excluding non-Caucasian participants from the analyses did not alter the direction or significance of these findings. Fig. 1 illustrates the significant interaction effect, adjusting for the main effect of gender.

3.4. Mediation by youth social functioning

Conditional process analyses examined whether adolescents' social functioning serves as a mechanism of the association between *OXTR* genotype and the intergenerational transmission of depression. We examined a model utilizing the composite measure of social functioning as a mediator of the interaction between maternal depression and *OXTR* genotype in the prediction of adolescent depressive symptoms (Fig. 2). Conditional process analyses revealed that the indirect effect of social functioning was significant, as demonstrated by a 95% bootstrap confidence interval that does not include zero (95% CI: 0.04, 1.92). Thus, social functioning over the past six months mediates the interaction between maternal depression history and *OXTR* genotype in

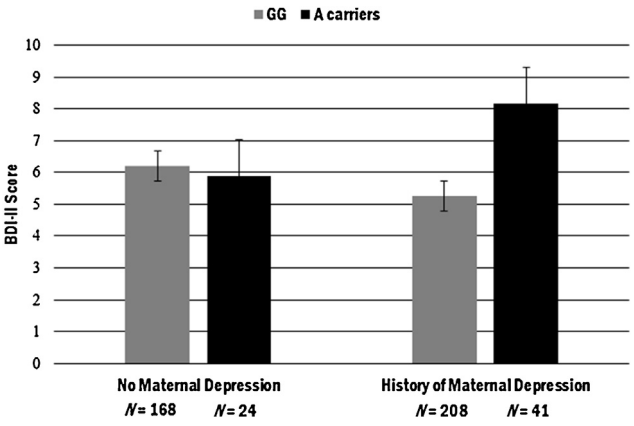

Fig. 1 Depressive symptoms at age 15 as a function of maternal depression history and *OXTR* genotype (adjusted by gender). Individuals carrying at least one A allele of the rs53576 polymorphism of *OXTR* who also have a history of maternal depression exhibit the highest levels of depressive symptoms at age 15. Error bars represent standard error. N = 441.

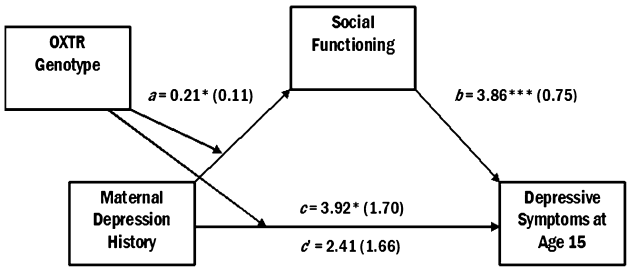

Fig. 2 Conditional process model of the association between maternal depression history, *OXTR* genotype, social functioning, and depressive symptoms. *OXTR* genotype moderates the association between maternal depression in early childhood and youth depressive symptoms at age 15. This interaction is mediated by youth social functioning in the six months prior to age 15. Unstandardized regression coefficients (with standard errors) are presented. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. $N = 441$.

the prediction of youth depressive symptoms. The ratio of the indirect effect to the total effect was 0.25, indicating that approximately 25% of the total effect was mediated by youth social functioning over the past six months. The r^2 value of 0.08 indicates that approximately 8% of the variance was explained by this model. These results are summarized in Table 3.

Examining the conditional indirect effects of maternal depression history on depressive symptoms by *OXTR* genotype revealed that youth social functioning significantly mediated this association among A carriers (95% CI: 0.39, 1.89), but not GG homozygotes (95% CI: −0.36, 0.82). The proportion of the total effect that was mediated by youth social functioning among A carriers was 0.41, while the proportion mediated by GG homozygotes was 0.12.

Repeating these analyses after excluding non-Caucasian participants revealed that youth social functioning continued to significantly mediate the association among maternal depression history, *OXTR* genotype, and youth depressive symptoms among A carriers (95% CI: 0.34, 1.96), but not among GG homozygotes (95% CI: −0.37, 0.93). The difference between the indirect effect among A carriers vs. that of GG homozygotes indicates that *OXTR* genotype continued to predict the strength of the indirect effect of youth social functioning on the intergenerational transmission of depression when the sample is restricted to Caucasian participants.

Table 3 Indirect effects of maternal depression history and *OXTR* genotype on youth depressive symptoms via youth social functioning.

Sample	Indirect effect		95% CI (lower, upper)
	Effect	SE	
Overall	0.82*	0.48	(0.04, 1.92)
GG	0.14	0.29	(−0.36, 0.82)
A carriers	0.97*	0.38	(0.39, 1.89)

Note.
* Significant indirect effect as evidenced by 95% confidence interval that does not include zero. CI, confidence interval.

The omnibus test of the role of *OXTR* genotype on the indirect effect of youth social functioning was only slightly reduced when excluding non-Caucasian participants (95% CI: −0.04, 1.98). This suggests that there is an effect of *OXTR* genotype on the indirect effect of youth social functioning that is independent of race/ethnicity, although the relatively small sample size of the present study may have prevented the omnibus test from attaining statistical significance in the Caucasian-only sample.

4. Discussion

The present study found that variations in the level of depressive symptoms among adolescent offspring of depressed women were significantly related to *OXTR* genotype. Youth carrying at least one A allele of the rs53576 polymorphism of *OXTR* who also have a history of early exposure to maternal depression displayed the highest levels of depressive symptoms in adolescence. Individuals with the GG genotype did not demonstrate an association between maternal depression in early childhood and later depressive symptoms. Thus, there is some evidence that certain youth appear to be protected from the negative influence of maternal depression as a result of *OXTR* genotype. These findings corroborate the results of the single previous study that explored the role of *OXTR* genotype in the intergenerational transmission of depression (Thompson et al., 2011), which suggested that the A allele of the rs2254298 polymorphism confers heightened risk for the transmission of maternal depression. The results also contribute to the limited extant literature examining the role of genetic variables in the intergenerational transmission of depression and offer one explanation for the variable transmission of depression from mothers to youth.

The oxytocin receptor gene was hypothesized to be relevant to youth depressive outcomes due to the association between interpersonal behaviors and *OXTR* genotype (see Kumsta and Heinrichs, 2013 for a review). This is consistent with the association between maternal depression and interpersonal dysfunction among offspring (Goodman, 2007), as well the association between youth interpersonal dysfunction and depression (Hammen et al., 2004). Accordingly, the present study tested one potential mechanism of the association between *OXTR* and the intergenerational transmission of depression, finding that youth social functioning serves as a mediator of the transmission of maternal depression, as moderated by *OXTR* genotype. Youth with a history of maternal depression who possess at least one A allele of the rs53576 polymorphism of *OXTR* appeared to exhibit deficits in peer and family functioning in young adolescence. These difficulties in social relationships predicted increases in depressive symptoms. Thus, the present findings are consistent with a model of intergenerational risk for depression that emphasizes social functioning, a process that is mediated by both psychosocial and genetic factors.

Despite support for a general pattern linking *OXTR* to depression via interpersonal dysfunction, the specific interpersonal processes that are affected by *OXTR* in the intergenerational transmission of depression remain to be identified. Existing research assessing the functions of oxytocin and the rs53576 polymorphism of *OXTR* suggests

several possible mechanisms that should be explored further, including empathic processes (Rodrigues et al., 2009), trust (Kosfeld et al., 2005; Krueger et al., 2012), and attachment (Costa et al., 2009). Alternative theories indicate that oxytocin may be associated with differences in the salience of social cues or with the regulation of approach and withdrawal behavior, rather than affiliative processes specifically (Kemp and Guastella, 2011; Olff et al., 2013). Thus, additional research is needed to elucidate the function of oxytocin and the oxytocin receptor gene in social interactions and to clarify the specific pathways through which *OXTR* affects social functioning and the experience of depressive symptoms.

OXTR genotype may also influence the ability of youth to adaptively respond to the stresses associated with having a depressed mother. Maternal depression serves as a potent source of stress in early childhood (Essex et al., 2002) and is also associated with a heightened risk of secondary stressors, including negative parenting practices and marital discord (Lovejoy et al., 2000; Hammen, 2009). Some research suggests that the rs53576 polymorphism of the *OXTR* genotype may confer sensitivity to the environment, such that individuals with a particular genotype exhibit increased physiological reactivity to environmental stressors (Rodrigues et al., 2009; Norman et al., 2011). Therefore, some youth may be particularly sensitive to the stresses associated with maternal depression, leading to more negative outcomes. *OXTR* genotype also appears to influence patterns of support seeking in response to stress (Kim et al., 2010) and moderates stress reactivity in the presence of supportive friend (Chen et al., 2011) based on studies utilizing the rs53576 SNP. These findings suggest a variety of possible mechanisms of the association between the intergenerational transmission of depression, *OXTR* genotype, and social functioning that warrant clarification through future research.

The present study has several strengths, including the use of both moderation and mediation analyses to elaborate on the processes through which genetic factors and social functioning affect the intergenerational transmission of depression, the use of comprehensive, detailed measures of social environmental characteristics, and the inclusion of a community sample of male and female adolescents examined during a critical developmental period. Further, the study expanded on the single previous study on this topic by utilizing the more-studied rs53576 polymorphism and extending the prior finding to males.

Nevertheless, important limitations must be acknowledged. First, although the present study was much larger (N = 441) than the single previous study on this topic (N = 92), future projects should utilize even larger samples in order to conduct a stronger test of the hypothesized associations. Large studies that broadly sample participants across racial and ethnic categories are particularly needed in order to elucidate the role of *OXTR* in human social functioning and the intergenerational transmission of depression. It is likely that idiosyncrasies of the present findings are largely due to issues of sample size. For example, it is probable that the alteration in the test of the simple effect among A carriers following the application of a stringent correction to the alpha level was strongly affected by limitations of sample size. Although some confidence in this effect may be gained from the strength of the effect among A carriers in the mediation analyses, future research should confirm these findings using larger samples. The present study provides preliminary findings to be explored and replicated in future large-scale studies of diverse participants that are better able to identify the true impact of the rs53576 polymorphism of *OXTR* on human functioning.

Additionally, although there was not a significant gene-environment correlation between *OXTR* genotype and maternal depression, it is likely that the effects observed in the present study to some extent reflect associations between maternal genetic characteristics, youth genetic characteristics, and parenting behaviors. Therefore, the possibility remains that the present results may be partially attributable to correlations between genetic characteristics and the environment. Given that maternal *OXTR* genotype was not measured, it is possible that interpersonal deficits exhibited in the offspring of depressed mothers may be attributable to maternal genetic characteristics, including the effect of candidate genes other than *OXTR*. Maternal depression was essentially treated as an environmental factor in the present study, although maternal depression's impact on offspring undoubtedly arises from the combined effects of genetic and environmental processes. Future research should examine both the environmental and genetic influence of maternal depression on youth outcomes as well as the effect of genetic and environmental characteristics that are shared by mothers and offspring.

Furthermore, the association between depressive symptoms and social functioning is likely bidirectional, and the choice to examine youth social functioning as a mediator in the present study does not preclude the possibility that the results could also be accounted for by a model in which youth depressive symptoms predict subsequent social functioning. The present study sought to reduce the probability of this alternate model by utilizing a measure of youth social functioning designed to capture functioning throughout the previous six months, while the measure of youth depressive symptoms evaluated symptoms during the previous two weeks. However, both measures were administered at the same assessment point. Therefore, the present findings should not be interpreted as offering a purely causal explanation for the association between the variables of interest. Future studies should seek to measure youth depressive symptoms and social functioning repeatedly across childhood and early adolescence in order to elucidate the timing and relative influence of these variables on one another.

The present analyses examined a relatively limited outcome (i.e., depressive symptoms among adolescents). Future research should attempt to explore the specificity of the observed results to depressive outcomes by incorporating broadband outcome measures of youth psychopathology and functioning (Seeley et al., 2011). Future studies should also extend this research to include more distal outcomes in adulthood and should examine other polymorphisms of *OXTR*. Due to financial constraints, the present study examined a single, commonly studied SNP of *OXTR* that had previously been associated with depressive symptoms and social functioning in humans, but additional research using a variety of polymorphisms is needed.

Despite growing interest in the role of oxytocin and *OXTR*, much additional research is needed in order to elucidate the specific functions associated with oxytocin and the gene that

codes for its receptor. The present study contributes to greater understanding of the role of *OXTR* in the development of depression among offspring of depressed mothers and identifies social functioning as a mediator of this association, but future research should continue to explicate mechanisms of this effect using large, ethnically diverse samples. By identifying the means through which *OXTR* genotype differentially contributes to mental health outcomes and social processes, the transmission of depression from mothers to youth can be better understood.

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Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Sarah M. Thompson designed the present study, completed the literature review, conducted the statistical analyses, and prepared the manuscript. Constance Hammen designed the parent study and assisted in the preparation of the manuscript. Lisa R. Starr contributed techniques for statistical analyses and assisted in the preparation of the manuscript. Jake M. Najman designed the parent study and was responsible for data collection. All authors contributed to and have approved the final manuscript.

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