Depression in early adolescence: Contributions from relational aggression and variation in the oxytocin receptor gene

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Abstract:

Interpersonal stress arising from relational aggression (RA)—the intentional effort to harm others via rejection and exclusion—may increase risk for depression in youth. Biological vulnerabilities related to the hormone oxytocin, which affects social behavior and stress responses, may exacerbate this risk. In a community sample of 307 youth (52% female; age range = 10–14 years), we tested whether (1) the association between RA and subsequent depressive symptoms was mediated through social problems and (2) a single nucleotide polymorphism (rs53576) in the oxytocin receptor gene (OXTR) moderated this indirect association between RA and depression, where GG homozygotes are predicted to be more sensitive to the effects of social problems than A-allele carriers. Youth-reported RA and depressive symptoms were measured using a structured interview and a questionnaire, respectively. DNA was extracted from saliva collected with Oragene kits. Consistent with the interpersonal theory of depression, the association between relational aggression and subsequent depressive symptoms was mediated by social problems. This indirect effect was further moderated by rs53576 genotype, such that GG homozygotes showed a stronger mediation effect than A-carriers. These results suggest that rs53576 variants confer vulnerability for depression within the context of interpersonal risk factors, such that youth with the GG genotype may be particularly sensitive to the social consequences resulting from RA.

Keywords: depression | interpersonal stress | OXTR | oxytocin receptor gene | relational aggression | rs53576

Article:

1 INTRODUCTION

Relational aggression (RA)—the intentional effort to harm others via rejection and exclusion—may represent a behavioral catalyst for youth depression (Kawabata, Tseng, Murray-Close, & Crick, 2012). Specifically, perpetrators of RA may generate interpersonal problems that increase their own risk for depression. Biological vulnerabilities related to the neuropeptide oxytocin, which affects both social behavior and physiological responses to stress (Heinrichs, Chen, & Domes, 2013; Kumsta & Heinrichs, 2013), may further influence sensitivity to interpersonal problems, thereby partially accounting for the prospective effects of RA on depressive symptoms. Here we examined whether a single nucleotide polymorphism (SNP; rs53576) in the oxytocin receptor gene (OXTR) moderates the association between RA and depression in a community sample of youth.

2 INTERPERSONAL STRESS, RELATIONAL AGGRESSION, AND DEPRESSION

Stressful interpersonal experiences represent potent risk factors for depression (Hammen, 2005; Vrshek-Schallhorn et al., 2015). Among children and adolescents, several behavioral catalysts of interpersonal stressors have been identified, including solicitations of negative feedback (Borelli & Prinstein, 2006), excessive reassurance-seeking (Prinstein, Borelli, Cheah, Simon, & Aikins, 2005; Shih, Abela, & Starrs, 2009), co-rumination (Hankin, Stone, & Wright, 2010), and ineffective stress coping (e.g., disengagement; Flynn & Rudolph, 2011). Surprisingly, few studies have examined the influence of externalizing behavior (e.g., aggression, rule breaking) on the occurrence of interpersonal stressors (Gibb & Hanley, 2010; Kawabata et al., 2012), despite research suggesting that exposure to interpersonal problems and stressful life events is highest among youth with comorbid depression and externalizing psychopathology (Jensen, Shervette, Xenakis, & Richters, 1993; Rudolph et al., 2000).

Given its interpersonal nature, RA is a type of externalizing behavior that may particularly contribute to youth depression (Card, Stucky, Sawalani, & Little, 2008; Tackett, Daoud, De Bolle, & Burt, 2013). Meta-analytic evidence shows a robust cross-sectional association between RA and internalizing psychopathology, including depression and anxiety (Card et al., 2008). Longitudinally, RA predicts increases in internalizing problems in general (Murray-Close, Ostrov, & Crick, 2007), and depressive symptoms more specifically (Kawabata et al., 2012). RA is likely to provoke conflict in social contexts (Kawabata et al., 2012; Rose & Swenson, 2009; Rudolph et al., 2000), which may mediate the relationship between RA and depression. Nevertheless, RA shows considerable heterogeneity in trajectories and psychosocial consequences (Côté, Vaillancourt, Barker, Nagin, & Tremblay, 2007; Vaillancourt, Miller, Fagbemi, Côté, & Tremblay, 2007), raising the likelihood that other factors underlie vulnerability to RA-linked depressive symptoms (i.e., moderated mediation). No prior research has examined potential biological mechanisms accounting for the prospective associations between RA and depression.

3 VARIATION IN THE OXYTOCIN RECEPTOR GENE, SOCIAL SALIENCE, AND DEPRESSION

The oxytocin system may play an important role in the connection between social experiences and psychopathology (Lucas-Thompson & Holman, 2013; Olff et al., 2013), given its influence on social behavior (Heinrichs et al., 2013) and responses to stressors (Kumsta & Heinrichs, 2013). In particular, oxytocin is believed to influence the perception of social cues (i.e., social salience; Bartz, Zaki, Bolger, & Ochsner, 2011) and attenuate subjective and physiological reactivity to stressors (MacDonald & Feifel, 2013). A silent SNP, rs53576 (G/A), located in the third intron of the OXTR gene, on chromosome 3p25, has been linked to individual differences in sociality. Specifically, results from meta-analyses suggest that G-allele homozygotes are higher on sociality than A-allele carriers, although this effect may depend on the operationalization of sociality (e.g., general sociality vs. behavior in close relationships; Bakermans-Kranenburg & van Ijzendoorn, 2014; Li et al., 2015). The rs53576 genotype has also been linked to social behavior that may enhance coping efforts (e.g., emotional support seeking; Kim et al., 2010) as well as biological responses to interpersonal stressors and social supports (e.g., cortisol reactivity; Chen et al., 2011), consistent with a role for oxytocin in social salience. Specifically, GG homozygotes show greater responsiveness to social cues and engage in more prosocial behavior than AA and AG individuals (Kogan et al., 2011; Rodrigues, Saslow, Garcia, John, & Keltner, 2009; Tost et al., 2010). In contrast, a haplotype derived from the A allele (and another OXTR SNP) was over-represented in males with childhood-onset aggression compared to those without (Malik, Zai, Abu, Nowrouzi, & Beitchman, 2012). As such, GG homozygotes may be more sensitive to social cues, whereas A-allele carriers may be more prone to aggression; however, other studies have failed to replicate differences in youth aggression across oxytocinergic gene variants (Beitchman et al., 2012; Sakai et al., 2012). Further, studies performed with adult samples found no associations between rs53576 genotype and aggression and antisocial behavior (Hovey et al., 2016; Johansson et al., 2012). It is notable that prior investigations have focused exclusively on childhood physical aggression, to the exclusion of RA, which may be particularly relevant given its interpersonal nature.

Conceptualized as social salience, inter-individual differences in oxytocin functioning conferred by rs53576 may increase sensitivity to both positive and negative social cues, resulting in increased vulnerability to depression when exposed to interpersonal stressors (McQuaid, McInnis, Abizaid, & Anisman, 2014). For example, mothers with the GG genotype show more sensitive parenting than A-allele carriers (Bakermans-Kranenburg & van Ijzendoorn, 2008); however, GG homozygotes who experience severe maltreatment in childhood also exhibit greater emotional dysregulation and disorganized attachment in adulthood than A-carriers (Bradley et al., 2011). Moreover, depressive symptoms are more strongly associated with early-life maltreatment among G-carrier young adult than for AA homozygotes (McQuaid, McInnis, Stead, Matheson, & Hymie, 2013). In the context of childhood maltreatment, GG homozygotes show more alterations to the structure and function of brain regions implicated in the etiology of depression relative to A-allele carriers (Dannlowski et al., 2016). Despite the balance of studies showing an association between the GG genotype and greater social salience, this pattern is not without exceptions, even in the opposite direction (e.g., Thompson, Hammen, Starr, & Najman, 2014). Moreover, a recent meta-analysis found no support for an association between depression and rs53576 (Li et al., 2015). These mixed findings may be indicative of context-specific vulnerability conferred by different rs53576 variants, highlighting a need for research elucidating the inter-individual and

antecedent factors that may influence the developmental pathways linking oxytocin function to social behavior and adjustment (Bartz et al., 2011).

4 THE PRESENT STUDY

The current investigation constitutes the first research to examine the joint contributions from an OXTR SNP and RA to depression in a community sample of early adolescent youth. Based on prior research (Bradley et al., 2011; Kogan et al., 2011; McQuaid et al., 2013; Rodrigues et al., 2009; Sturge-Apple, Cicchetti, Davies, & Suor, 2012; Tost et al., 2010), we predicted that GG homozygotes would be more susceptible to depression in the context of social problems generated by their own relationally aggressive behavior. To this end, we tested whether (1) the association between RA and subsequent depressive symptoms 1 year later was mediated by social problems and (2) risk for depressive symptoms conferred by RA-linked social problems was moderated by the rs53576 genotype.

5 METHOD

Participants

Participants were 307 youth (51.5% female; mean age = 11.63, SD = 0.84) from the Child Personality and Behavior Study (CPBS), a four-wave longitudinal investigation of personality development and behavioral outcomes. At the outset of the larger longitudinal investigation, 346 children aged 9–10 years (M = 9.96, SD = 0.83) and their parents were recruited using a community-based participant pool maintained by the Department of Psychology and flyers posted throughout the community. Additional participants were recruited at later waves to increase the overall sample size and to account for attrition, resulting in an overall sample of 446 youth. Parents reported the following ethnicity breakdown for their children: 65.7% Caucasian, 9.4% Asian-Canadian, 3.6% African-Canadian, 0.4% Hispanic, 0.2% Pacific Islander, 18.2% other/multiracial, and 2.5% not reporting ethnicity. Inclusion criteria were fluency in English for both the caregiver and child; exclusion criteria were the presence of neurodevelopmental disorders, psychotic disorders, or intellectual disability in the child. Informed consent was obtained from parents and assent was obtained from participating youth. Ethics approval was obtained from the Institutional Review Board. A detailed description of recruitment, informed consent procedures, and demographic information for the larger longitudinal sample can be found in Tackett, Kushner, Herzhoff, Smack, and Reardon (2014).

Measures

5.2.1 Social Relations Questionnaire (SRQ; Lahey et al., 2004)

RA was measured using the youth-report version of the SRQ, a structured interview adapted from the Child and Adolescent Psychopathology Scale (Lahey et al., 2004). The SRQ consists of seven items that assess the frequency of relationally aggressive behavior (e.g., excluded others; teased others; spread rumors about others) within the past 12 months. Interviewers rated items on a 4-point scale (1 = not at all, 4 = very much). The SRQ generates a sum score for total RA. Internal consistency (Coefficient α) was 0.67 in the current sample.

5.2.2 Friendship Quality Questionnaire (FQQ; Parker & Asher, 1993)

Social problems were measured using an abbreviated version of the FQQ, a self-report questionnaire intended to assess friendship quality among middle childhood-aged youth. The abbreviated FQQ was developed for use in the National Institute of Child Health and Human Development (NICHD) Study of Early Child Care and Youth Development, and consists of 21 items that assess the target child's relationship with his or her best friend. The FQQ includes five subscales measuring positive friendship quality (Companionship and Recreation, Conflict Resolution, Help and Guidance, Intimate Exchange, and Validation and Caring), and one subscale measuring negative friendship quality (Conflict and Betrayal). Items were rated on a 5-point scale (1 = not at all true, 5 = really true). The present investigation used the Conflict and Betrayal scale as one contributor to a composite measure of Social Problems (e.g., get mad at each other a lot, argue a lot; fight); the remaining FQQ scales were not included because they do not measure interpersonal difficulties. Coefficient α was 0.75 in the current sample.

5.2.3 Youth Self-Report (YSR; Achenbach, 1991)

Social problems and depressive symptoms were measured using the YSR (Achenbach, 1991), a self-report questionnaire intended to assess psychopathology among 11–18-year-old youth. Items were rated on a 3-point scale (0 = not true, 2 = very true or often true). The YSR consists of 112-items that assess the frequency of emotional and behavioral problems within the past 6 months. The YSR generates broadband dimensional scores for internalizing problems, externalizing problems, and total problems, as well as syndrome and DSM-oriented scale scores. The present investigation used the Social Problems scale (e.g., feels lonely, gets teased, not liked by others; T-score M = 54.49, SD = 6.11) as a contributor to the composite measure of social problems (described below) and the DSM-oriented Affective Problems scale (e.g., enjoys very little, cries a lot, feels worthless or inferior; T-score M = 53.25, SD = 4.93). The Affective Problems scale shows high diagnostic accuracy for predicting depressive episodes in adolescents (Aebi, Metzke, & Steinhausen, 2009). Due to ethical constraints (some waves of data were collected by mail barring rapid follow-up), participating youth were not asked to respond to two items that assess self-harm behavior and suicidal ideation. Coefficient α was 0.72 for Social Problems and 0.71 for Affective Problems in the current sample.

Genotyping

DNA was extracted from saliva collected using Oragene DNA collection kits (OG-500; DNAGenotek, Inc., Ontario, Canada). OXTR SNP rs53576 was genotyped using Sequenom iPLEX technology (MassARRAY system, Sequenom, Inc., San Diego, CA) by the Mount Sinai Hospital Clinical Genomics Centre (http://clinicalgenomics.ca/). The genotype distribution for OXTR rs53576 (nAA = 37, nAG = 141, nGG = 129) was in Hardy–Weinberg equilibrium ($\chi 2$ (1) = .03, p = 0.862) and allele frequency was similar to previous reports (e.g., Chen et al., 2011; McQuaid et al., 2013; Thompson et al., 2014). Consistent with most prior investigations (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2008; Bradley et al., 2011; Sturge-Apple et al., 2012), rs53576 was coded as a dichotomous variable (AA/AG and GG) for the current analyses.

Procedure

Data were drawn from the final two yearly assessment waves of the CPBS, at which time self-reported data were collected on the YSR. The current investigation included 309 youth who provided saliva samples for DNA extraction and analysis during the final CPBS assessment wave (T2), when youth were primarily 12–13 years old (Mage = 12.65 years, SD = 0.86). Two saliva samples failed to produce sufficient quality DNA and, therefore, were omitted from the current investigation, resulting in viable data for 307 youth. RA and social problems were assessed approximately 1 year earlier (T1), when youth were primarily 11–12 years old (Mage = 11.63 years, SD = 0.84). During both waves, participating families were mailed informed consent and questionnaire packages containing the YSR to be completed at the participant's home. At T1, the YSR was returned either by mail (n = 14) or during a laboratory visit (n = 276), at which time the SRQ and FQQ were administered as part of a larger assessment battery. At T2, youth were also mailed Oragene DNA collection kits and instructions for their use; saliva samples and completed YSRs were returned to the lab by mail. Families received various combinations of monetary compensation and gifts for youth at different waves, depending on the extent of participation, with increasing compensation at each subsequent wave.

Statistical analysis

Missing data for all continuous variables (6.5–11.1%) were imputed using an expectation–maximization (EM) algorithm. We created a composite measure of social problems by subjecting items from the FFQ conflict and betrayal scale and YSR social problems scale to a principal component analysis and saving the regression-based factor score (item loadings ranged from 0.23 to 0.62). We first estimated a mediation model to test the assumption that the prospective effects of baseline RA on depressive symptoms at follow-up were mediated through social problems. We next tested for second stage moderation following the procedure outlined by Hayes (2015). This allowed us to examine whether OXTR rs53576 genotype moderated the path between social problems and depressive symptoms (i.e., path b; see Figure 1), thus testing for a potential gene–environment interaction. The mediation and moderated mediation models were estimated using Hayes' (2013) PROCESS modeling approach. Indirect effects were estimated using 5,000 bootstrap resamples (Preacher, Rucker, & Hayes, 2007). Confidence intervals (95%) were bound using the bias-corrected method. Confidence intervals that did not include "0" were considered to reflect effects that are significantly different from "0." Independent and moderator variables were mean-centered for products. Statistical power was adequate (0.80) to detect moderately small effects (d = 0.26; Fritz & MacKinnon, 2007), although evidence from genome-wide association studies suggests that effect sizes for complex phenotypes are considerably smaller (Dick et al., 2015). All analyses were conducted using SPSS 22.

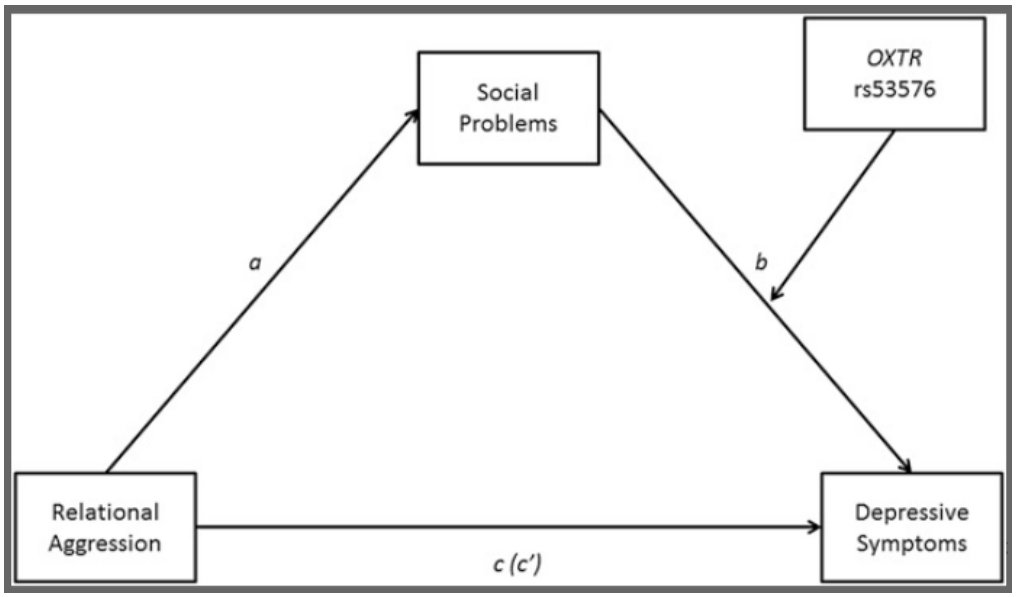

Figure 1. Mediation model displaying the impact of relational aggression on depressive symptoms at 1-year follow-up via associated social problems and second-stage moderation via the OXTR rs53576 genotype. Path a represent the relation of the independent variable to the mediator; path b represent the relation from the mediator to the dependent variable; path c′ represents the direct effect of the independent variable on the dependent variable after adjusting for the mediator; path c represents the total effect of the independent variable on the dependent variable.

6 RESULTS

Descriptive statistics

Tables 1 and 2 display descriptive statistics and Pearson correlation coefficients among RA, social problems, and depressive symptoms. Consistent with prior research and theory, all variables were positively correlated (all ps < .001). Independent-samples t-tests were computed to compare all variables across gender and the OXTR rs53576 genotype (AA/AG vs. GG). There were no significant gender differences (all ps > .05). Furthermore, there were no significant differences by OXTR rs53576 genotype (all ps > .05); thus, on average, there was no evidence for a gene–environment correlation between rs53576 and social problems.

Mediation and second stage moderation analyses

We predicted that the prospective effects of RA on depressive symptoms would be mediated through social problems. Unstandardized path coefficients of the direct and indirect effects tested at 95% bias corrected confidence intervals are displayed in Table 3 based on PROCESS model 4. Youth with higher levels of RA reported higher concurrent social problems, and more depressive symptoms at the 1-year follow-up. In addition, social problems positively predicted depressive symptoms at the 1-year follow-up. The indirect path from RA to depression via social problems was also significant, indicating that the direct effect of RA on depressive symptoms was attenuated when the indirect path through social problems was taken into account.1

Table 1. Descriptive statistics

	Total (N = 307) M (SD)	Males (n = 149) M (SD)	Females (n = 158) M (SD)	t(305)	AA/AG (n = 178) M (SD)	GG (n = 129) M (SD)	t(305)
T1 relational aggression	8.84 (1.97)	8.86 (2.08)	8.81 (1.86)	0.24	8.71 (1.97)	9.01 (1.95)	−1.34
T1 social problems	8.64 (4.26)	8.93 (4.34)	8.38 (4.18)	1.13	8.75 (4.37)	8.49 (4.11)	0.53
T1 depressive symptoms	3.14 (2.99)	3.54 (3.07)	2.75 (2.87)	2.33	3.15 (3.03)	3.11 (2.95)	0.11
T2 depressive symptoms	2.89 (2.84)	2.92 (2.67)	2.87 (3.00)	0.14	2.72 (2.69)	3.13 (3.03)	−1.25

Depressive symptoms were assessed approximately 1 year after relational aggression and social problems. Values for social problems reflect the sum of the Friendship Quality Questionnaire (FQQ; Parker & Asher, 1993) Conflict and Betrayal scale and the Youth Self-Report (YSR; Achenbach, 1991) Social Problems scale.

Table 2. Correlation coefficients

	1	2	3
1. Relational aggression	1.00		
2. Social problems	0.60***	1.00	
3. Depressive symptoms	0.44***	0.40***	1.00

Depressive symptoms were assessed approximately 1 year after relational aggression and social problems. Social Problems reflect the principal component score derived from the Friendship Quality Questionnaire (FQQ; Parker & Asher, 1993) Conflict and Betrayal scale and the Youth Self-Report (YSR; Achenbach, 1991) Social Problems scale.
N = 307. *** $p < .001$.

Table 3. Unstandardized path coefficients for direct and indirect effects in the mediation model of the associations among relational aggression (RA), social problems, and depressive symptoms

	B	SE_B	95% CI
Direct effects			
RA → depression (c)	0.63***	0.07	[0.49, 0.78]
RA → social problems (a)	0.28***	0.02	[0.24, 0.32]
Social problems → depression (b)	0.65**	0.19	[0.26, 1.03]
RA → depression (c′)	0.45***	0.09	[0.27, 0.63]
Indirect effects (mediation test)			
RA → depression via social problems (ab)	0.18**	0.06	[0.08, 0.31]

Values for a represents the relation of the independent variable to the mediator; values for b represent the relation from the mediator to the dependent variable; c represents the total effect of the independent variable on the dependent variable; c′ represents the direct effect of the independent variable on the dependent variable after adjusting for the mediator, and; ab represents the indirect effect of the independent variable on the dependent variable through the proposed mediator. 95% CIs are based on bootstrapping.
** $p < .01$. *** $p < .001$.

Table 4. Unstandardized path coefficients for second stage moderation effects of OXTR rs53576 genotype

	B	SE_B	95% CI
Direct effects			
RA → depression (c)	0.63***	0.07	[0.49, 0.78]
RA → social problems (a)	0.28***	0.02	[0.24, 0.32]
Social problems → depression (b)	0.71***	0.19	[0.33, 1.09]
OXTR → depression	0.33	0.29	[−0.24, 0.91]
Social problems × OXTR → depression	0.82*	0.32	[0.19, 1.45]
RA → depression (c′)	0.44***	0.09	[0.26, 0.62]
Indirect effects (mediation tests)			
RA → depression via social problems			
A-carriers	0.10	0.07	[−0.02, 0.24]
GG genotype	0.33*	0.08	[0.18, 0.51]

Second stage moderation of the associations among relational aggression, social problems, OXTR rs53576 genotype, and depressive symptoms. 95% CIs are based on bootstrapping.
* $p < .05$. *** $p < .001$.

To partial out the potentially confounding effects of gender and ethnicity, we re-estimated models including covariate-environment and covariate-gene interaction terms following Keller's (2014) recommendations. Results for these models were estimated using PROCESS model 18. Covariation of gender, its two-way interactions with social problems and OXTR rs53576 genotype, and the three-way gene × environment interaction with gender were not significant (all ps > 0.475), but critically, the interaction between social problems and rs53576 genotype remained significant (B = 0.81, SEB = 0.33, 95% CI = [0.15, 1.47], t(298) = 2.42, p = .016). Likewise, covariation of ethnicity, its two-way interactions with social problems and OXTR rs53576 genotype, and the three-way gene × environment interaction with ethnicity were not significant (all ps > 0.446), whereas the interaction between social problems and rs53576 genotype remained significant (B = 0.79, SEB = 0.33, 95% CI = [0.14, 1.43], t(296) = 2.40, p = .017). This evidence strongly reduces the likelihood that the observed interaction between social problems and rs53576 genotype were driven by gender or ethnicity. The full results of these analyses are available upon request.

7 DISCUSSION

The present investigation is the first to examine whether the OXTR rs53576 genotype interacts with RA-linked interpersonal problems in predicting depressive symptoms among early adolescent youth. Two main findings emerged. First, the prospective association between RA and depressive symptoms 1 year later was mediated by social problems. Second, depressive vulnerability to social problems was unique to GG homozygotes. The current results thus provide a novel examination of a genetic marker of interpersonal sensitivity in the context of externalizing behavior.

With few exceptions (e.g., Gibb & Hanley, 2010; Kawabata et al., 2012), the potential impact of RA on subsequent depressive symptoms have seldom been incorporated in studies of stress-generation. The current results implicate RA as a behavioral catalyst for youth depression, at least partly via associated social problems. Specifically, youth may experience interpersonal stress (i.e., conflict) as a result of their relationally aggressive behavior, contributing to social conditions that increase risk for depression (Hammen, 2005; Vrshek-Schallhorn et al., 2015). These findings represent the first to directly test the hypothesis that interpersonal stress generation may account for the prospective association between RA and depression (Kawabata et al., 2012).

Based on substantial heterogeneity in trajectories and psychosocial consequences of childhood RA (e.g., Côté et al., 2007; Vaillancourt et al., 2007), we predicted that the prospective association between RA and depressive symptoms might be moderated by individual differences such as underlying biological vulnerabilities. To this end, we examined the OXTR rs53576 genotype, which has previously been implicated in both the perception of social cues (i.e., social salience; Bartz et al., 2011) and reactivity to stressors (MacDonald & Feifel, 2013). Consistent with prior research, the current results revealed no evidence for significant main effects of the rs53576 genotype on RA, social problems, or depression (Bakermans-Kranenburg & van Ijzendoorn, 2014; Hovey et al., 2016; Johansson et al., 2012; Li et al., 2015). As such, we did not find evidence for a gene–environment correlation, whereby the rs53576 genotype influences exposure to social problems. Rather, the current results indicate a gene–environment interaction, whereby the OXTR rs53576 genotype moderates the impact of social problems related to their own relationally aggressive behavior, increasing susceptibility to depressive symptoms in GG homozygotes.

By enhancing the perception of social salience (Bartz et al., 2011), the rs53576 GG variant may represent a genetic marker of vulnerability to depression in the context of interpersonal

stressors. These findings corroborate prior findings showing that the rs53576 GG variant confers vulnerability for negative outcomes (e.g., emotional dysregulation, disorganized attachment, and depression) in the context of negative social cues (e.g., maltreatment; Bradley et al., 2011; McQuaid et al., 2013). Nevertheless, the rs53576 GG variant may also increase sensitivity to positive social cues (i.e., social salience), and has been associated with more positive outcomes (e.g., sensitive parenting) than A-allele carriers (Bakermans-Kranenburg & van Ijzendoorn, 2008). Consistent with the differential susceptibility hypothesis (Belsky & Pluess, 2009), the rs53576 GG genotype may better represent a plasticity factor rather than a strict vulnerability factor for depression. That is, GG homozygotes may be particularly susceptible to social influences, whether they are negative (e.g., interpersonal conflict) or positive (e.g., interpersonal support). Although differential susceptibility may represent a plausible explanation for the current results, tests of differential susceptibility require both the concurrent assessment of adversity and environmental support, as well as a range of outcomes, spanning from maladjustment to competence (Belsky & Pluess, 2009).

8 LIMITATIONS AND FUTURE DIRECTIONS

The current investigation is subject to several limitations. Notably, our mediation model examined the prospective association between RA-linked social problems and depression; however, there are important limitations to our measurement of social problems. In particular, our measures of RA and social problems were completed concurrently. Accordingly, we did not assess whether social problems were the direct result of youth's RA, or if youth exposed to more social problems were more likely to respond with RA. There may also be important bidirectional associations between RA, social problems, and depression. Consistent with the stress-generation theory of depression (Hammen, 1991, 2005), individuals with a history of depression generate stressful life events (i.e., interpersonal stressors, such as conflict arising from RA), which may serve to aggravate or maintain their depressive symptoms. Future longitudinal studies may aim to directly assess the social and contextual antecedents and consequences of RA to disentangle these effects. It is also unclear whether sensitivity conferred by the GG variant may be equally triggered by self-generated and independent (i.e., occurring outside of one's control) stressors. Elucidating specific contexts in which the rs53576 genotype confers vulnerability for depression represents an exciting direction for future research. The rs53576 genotype may represent a distal vulnerability factor for depression via its influence on more proximal vulnerabilities (e.g., personality traits; Kushner, 2014). For example, low agreeableness—a trait describing tendencies toward compliance and empathy versus antagonism—may contribute to interpersonal conflict via its association with RA (Tackett et al., 2014). Despite observed associations between OXTR rs53576 and characteristics of agreeableness (Kogan et al., 2011), no prior research has jointly examined their contributions to depression vulnerability. Future studies would also do well to investigate the functional biological mechanisms underlying associations between OXTR rs53576, social behavior, stress reactivity, and adjustment, given that this SNP is a putatively silent marker.

Another limitation of the current study is that that we did not evaluate the impact of positive social cues and their impact on positive emotional functioning. Future studies may include the concurrent assessment of adversity and environmental support, as well as a range of positive and negative outcomes in order to fully test the differential susceptibility hypothesis (Belsky & Pluess, 2009). Exploring these effects represents a promising direction for future research.

The current results are subject to the composition of the current sample and may, therefore, not generalize to other populations (e.g., clinical samples) or developmental periods (e.g., later adolescence, adulthood). Replication is, therefore, needed. Although the current sample size is similar to the median sample size for published genetic research on candidate gene-by-environment interactions (N = 345; Duncan & Keller, 2011), it may not be adequately powered to detect the complexity of the associations between oxytocin, social behavior, and vulnerability to depression. Future research will require larger samples to elucidate the impact of the rs53576 genotype on associations among RA, social problems, and depressive symptoms. In particular, no existing research has tested gender specificity in the moderating effects of the rs53576 genotype (although see Thompson et al., 2014). This is particularly relevant, as adolescent females typically show higher sensitivity to interpersonal stressors and vulnerability for depression than males do (Rudolph et al., 2000).

9 CONCLUSION

Results from the present investigation support evidence that perpetrators of RA are at greater risk for subsequent depressive symptoms in an early adolescent community sample. Consistent with the stress-generation hypothesis for depression, this association was mediated through associated social problems. Moreover, the current results demonstrated support for a significant gene-by-environment interaction, wherein the rs53576 genotype moderated the association between RA-linked social problems and subsequent depressive symptoms. In particular, the GG genotype was uniquely associated with depressive symptoms within the context of RA-linked social problems.

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CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest in the conduct or reporting of this research.

ENDNOTE

1 Results for the mediation model and second stage moderation were replicated using residualized difference scores derived from the T1 versus T2 depressive symptoms. Specifically, the simple mediation effect, social problems × OXTR interaction effect, and the index of moderated mediation (test of equality of the indirect effects for each rs53576 variant) remained significant; however, tests of simple effects revealed two noteworthy differences: (1) the direct effect of social problems (path b) and the indirect effect of relational aggression via social problems (path ab) on depressive symptoms are now negative and (2) in conditional indirect effect is now significant for A-allele carriers, but not for GG homozygotes. Given the documented problems resulting from attempts to partial out the effects of related variables (i.e., Sleep, Lynam, Hyatt, & Miller, in press),

we opted to present results for the simpler model. The results of these analyses are available upon request.

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