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Differential susceptibility effects of oxytocin gene (*OXT*) polymorphisms and perceived parenting on social anxiety among adolescents

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Abstract

Social anxiety is one of the most commonly reported mental health problems among adolescents, and it has been suggested that parenting style influences an adolescent's level of anxiety. A context-dependent effect of oxytocin on human social behavior has been proposed; however, research on the oxytocin gene (*OXT*) has mostly been reported without considering contextual factors. This study investigated the interactions between parenting style and polymorphic variations in the *OXT* gene in association with social anxiety symptoms in a community sample of adolescents ($n = 1{,}359$). Two single nucleotide polymorphisms linked to *OXT*, rs4813625 and rs2770378, were genotyped. Social anxiety and perceived parenting style were assessed by behavioral questionnaires. In interaction models adjusted for sex, significant interaction effects with parenting style were observed for both variants in relation to social anxiety. The nature of the interactions was in line with the differential susceptibility framework for rs4813625, whereas for rs2770378 the results indicated a diathesis–stress type of interaction. The findings may be interpreted from the perspective of the social salience hypothesis of oxytocin, with rs4813625 affecting social anxiety levels along a perceived unsafe–safe social context dimension.

Social anxiety is one of the most commonly reported mental health problems among adolescents (Beesdo, Knappe, & Pine, 2009; Gren-Landell et al., 2009; Kessler et al., 2012; Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). This may not be surprising, as adolescence involves the fundamental task of developing autonomy, with immense biological changes as well as psychological and social developmental tasks, which can be challenging and stressful (Dick, Adkins, & Kuo, 2016; Eccles et al., 1991; Shaffer & Kipp, 2014). Adolescents certainly differ in their reactions to stressful periods, and conscious feelings of anxiety, a requisite for the feasibility of self-reports of anxiety (LeDoux, 2015), are not the only symptoms of stress in young people. Similarly, while heightened levels of anxiety are transient in most individuals, in others they are more persistent (Copeland, Angold, Shanahan, & Costello, 2014; Ginsburg et al., 2014; Kessler et al., 2012). Differences in the degree to which individuals develop mental health problems in response to stress have been attributed to resilient functioning, a concept first introduced in the 1970s (Garmezy, 1974; Rutter, 1979). The central idea is that some children and adolescents are more vulnerable to the environmental adversities they are exposed to, whereas others are more resistant to the same environment (Caspi et al., 2002). The conventional approach in studies of anxiety disorders in young people has been consistent with the diathesis–stress model of the interplay between biological and environmental risk variables, an approach predictive of a fan-shaped, ordinal form of interaction (Beesdo et al., 2009; Salum, Desousa, do Rosario, Pine, & Manfro, 2013; Widaman et al., 2012). A new way of understanding this interaction is to conceptualize certain genes as plasticity genes rather than vulnerability genes, a perspective predictive of a cross-over, disordinal form of interaction (Widaman et al., 2012). This approach is derived from the evolutionary–developmental perspective of differential susceptibility, a theory that proposes that individuals vary in their neurobiological sensitivity to both positive and negative environments, leading to a better than average outcome for carriers of plasticity gene variants in favorable environments (Belsky & Hartman, 2014; Belsky & Pluess, 2009, 2013; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011).

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The neuropeptide oxytocin has a key role in the regulation of human social behavior and the response to stress through its projections in a number of brain regions related to social and threat information processing, including the basal ganglia, the amygdala, and the hippocampus (Kirsch, 2015; Knobloch & Grinevich, 2014; Love, 2014; Wigton et al., 2015). Oxytocin has been shown to attenuate amygdala activation and the stress hormone response to social challenges and fearful stimuli, a stress-dampening and anxiolytic effect that is augmented in combination with social support (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kumsta & Heinrichs, 2013; McQuaid et al., 2016; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011; Tops, Van Peer, Korf, Wijers, & Tucker, 2007). Functional magnetic imaging studies have shown that, among individuals diagnosed with social anxiety disorder, intranasally administered oxytocin enhances connectivity between the amygdala and brain regions involved in socioemotional information processing (Dodhia et al., 2014; Gorka et al., 2015). In behavioral association studies, intranasally administered oxytocin has been shown to enhance face and emotional recognition and to increase eye region gazing, the ability to infer mental states from facial social cues and interpersonal trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Lee, Macbeth, Pagani, & Young, 2009), but these effects seem to be blunted or absent in individuals with adverse childhood experiences (Bakermans-Kranenburg & van IJzendoorn, 2013). High levels of blood plasma oxytocin have been associated with trust, positive interaction with a partner, and sensitive parenting (Feldman et al., 2012; Gordon, Martin, Feldman, & Leckman, 2011; Meyer-Lindenberg et al., 2011). A negative relationship between cerebrospinal fluid oxytocin concentrations and anxiety ratings has been observed in healthy women, with the lowest concentrations detected among those exposed to childhood emotional abuse (Heim et al., 2008). However, in response to a social stress test, higher mean levels of blood plasma oxytocin were observed among childhood cancer survivors compared to sexually abused and control subjects (Pierrehumbert et al., 2010). In pediatric patients, plasma oxytocin predicts both cerebrospinal fluid oxytocin concentrations and parent ratings of anxiety on the Spence Children's Anxiety Scale (SCAS; Carson et al., 2015).

Individual genetic variability in the oxytocin system in relation to social behavior and psychopathology has been investigated. Studies have primarily focused on single nucleotide polymorphisms (SNPs) located in the oxytocin receptor gene (*OXTR*; Ebstein, Knafo, Mankuta, Chew, & Lai, 2012; Feldman, Monakhov, Pratt, & Ebstein, 2016; Feldman et al., 2012; Heinrichs, von Dawans, & Domes, 2009; Onodera et al., 2015; Tost et al., 2010; Uzefovsky et al., 2015), with results showing support for polymorphic main effects on autism (LoParo & Waldman, 2015) and biological functioning outcomes (e.g., oxytocin levels and amygdalar volume; Bakermans-Kranenburg & van IJzendoorn, 2014). However, in their meta-analyses of two of the most widely studied *OXTR* SNPs, rs53576 and rs2254298, Bakermans-Kranenburg and van IJzendoorn (2014) found that these SNPs failed to explain individual differences in personality, psychopathology, social behavior, or autism, while also noting that few studies reported Gene × Environment (G × E) effects, precluding a meta-analysis of G × E interaction (Bakermans-Kranenburg & van IJzendoorn, 2014). In later reports, G × E interaction effects consistent with both the diathesis–stress and differential-susceptibility theories have been observed for rs53576 and rs2254298 in association with psychopathology, including social anxiety (Brune, 2012; Hammen, Bower, & Cole, 2015; Notzon et al., 2016).

Compared with research on *OXTR*, a limited number of studies have investigated the gene coding for oxytocin (*OXT*), with results also implicating a role for *OXT*-related variants in social behavior and psychiatric disorders (Feldman et al., 2016). Using positron emission tomography scans, Love et al. (2012) investigated associations between SNPs within *OXT* and stress-induced dopamine release. The *OXT* SNP rs4813625 was associated with greater dopamine responses in female C allele carriers relative to G homozygotes, with no difference found among male participants. Furthermore, among females, the C allele was related to lower emotional well-being and higher trait and attachment anxiety. Francis et al. (2016) reported significant associations between the rs4813625 C allele and social withdrawal scores and whole-blood serotonin levels in autistic children. A Swedish twin study investigated associations between four *OXT* SNPs and autistic-like behavior and found significant associations with rs2770378 in girls, with more symptoms of autistic behaviors consistently observed among homozygote major allele carriers than minor allele carriers (Hovey et al., 2014). Three *OXT* SNPs, rs274010, rs2770378, and rs4813627, were found to be related to childhood-onset mood disorders in a Hungarian family-based study; however, the associations did not remain significant after correction for multiple testing (Strauss et al., 2010). In a study of oxytocin variation effects on mothering, *OXT* SNPs rs274010 and rs4813627 were associated with differences in mothers' vocalization to their infants. Furthermore, these SNPs interacted with mothers' early life quality of care in predicting instrumental care of their infants and postpartum depression (Mileva-Seitz et al., 2013).

The parent–child relationship and a parental style of autonomy support and flexible guidance have been implicated as important factors in adolescents' healthy development toward self-reliance and independence (McElhaney, Allen, Stephenson, & Hare, 2009; Shaffer & Kipp, 2014), whereas excessive parental control, rejection, and overprotection have been associated with increased risk of developing anxiety disorders (Beesdo et al., 2009; Salum et al., 2013). In a systematic review of 22 studies examining the relationship between parental style and adolescent anxiety, Waite, Whittington, and Creswell (2014) found that 75% of the studies reported significant associations between anxiety and parental control, with effect sizes ranging from small to medium. In the same review, less consistent support was found for an association between adolescent anxiety and perceptions of parental lack of warmth, with 66%

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of the studies reporting a significant relationship with small to medium effect sizes. Cross-sectional studies investigating adolescent social anxiety found no significant relationship with parental control or warmth (Waite et al., 2014).

As outlined above, a limited body of research provides preliminary support for associations between variants in the *OXT* gene and the stress response, anxiety, social withdrawal, and parenting behavior. Likewise, reports of the role of parenting style in adolescent social anxiety provide preliminary, but not consistent, evidence for an association between parenting style and anxiety. The majority of studies in these two lines of research have conducted analyses either of the main effects of gene variants and parental behavior or from a risk perspective, without considering contextual factors or differential neurobiological sensitivity to the environment. In the presence of such G × E interaction effects, positive or negative parental behavior effects would be observable only among carriers of plasticity alleles, leading to lower or higher levels of anxiety in those individuals and not in carriers of nonplasticity alleles.

The primary aim of the present study was to investigate the potential interplay between aspects of parenting style and polymorphic variations in the *OXT* gene in association with social anxiety symptoms in a community sample of adolescents. A secondary aim was to explore the form of G × E interactions from the perspectives of the differential-susceptibility and diathesis–stress frameworks.

Methods

Recruitment of participants

Data for this study were collected from the Survey of Adolescent Life in Västmanland cohort study. The Survey of Adolescent Life in Västmanland study includes two birth cohorts (1997 and 1999) in the county of Västmanland, Sweden, and started in 2012. Västmanland is a medium-sized county located in the southwest of Sweden with approximately 264,000 inhabitants. Västmanland is representative of the larger Swedish society with regard to the distribution of urban and rural areas; educational, income, and employment levels; and ethnic backgrounds. The study group consisted of 1,359 adolescents (59.4% girls) with complete data on measures of anxiety symptoms, parenting style, and genotype, representing 93% of respondents who provided both saliva and questionnaire data (N = 1,456). Of the study group, 697 participants (51.3%) were born in 1997, and 662 (48.7%) in 1999. Participants were recruited by regular mail, and their informed written consent, saliva samples, and behavioral questionnaires were collected by mail in reply envelopes. Approval from the Ethical Review Board of Uppsala was obtained for the study.

Measures

Genotyping. DNA was extracted according to the kit manufacturer's guidelines from saliva samples collected using a DNA Self Collection Kit (Oragene®). Genotyping was performed using a fluorescence-based competitive allele-specific PCR (KASPar) assay (KBioscience®). Two common variants linked to the oxytocin gene, rs4813625 and rs2770378, were genotyped (Sherry et al., 2001). Allele discrimination was done using SNPviewer2®. The genotype calling was performed blind to psychosocial data. The genotypes were in Hardy–Weinberg equilibrium (Table 1). Genotypes were coded assuming an additive function and based on minor allele count: 0 = homozygous for the major allele, 1 = heterozygous, and 2 = homozygous for the minor allele.

Behavioral questionnaires.

Social anxiety symptoms. Self-reported symptoms of anxiety were measured using the SCAS (Spence, 1997), a 44-item (38 score-generating items and 6 positive filler items to reduce negative bias) Likert-type (0 = *never*, 3 = *always*) questionnaire designed to assess anxiety symptoms in children and adolescents. The SCAS provides a total score (range = 0–114 points) as well as scores on six subscales: panic/agoraphobia, separation anxiety, physical injury fears (specific phobia), social anxiety, obsessive compulsive, and generalized anxiety. The SCAS has been examined across multiple cultures, including in Sweden, and support for its six-factor structure and strong internal consistency have been found in the majority of studies (Olofsdotter, Sonnby, Vadlin, Furmark, & Nilsson, 2015; Orgiles, Fernandez-Martinez, Guillen-Riquelme, Espada, & Essau, 2015). In the current study, the 6-item subscale of social anxiety (range 0–18 points) was used. The internal consistency of the social anxiety subscale, measured as Cronbach α, was 0.79 in the current sample.

Parenting style. Aspects of parenting style were measured using the 24-item Parents as Social Context Questionnaire (PASCQ), adolescent version (Skinner, Johnson, & Snyder, 2005; Skinner, Wellborn, & Regan, 1986). The PASCQ was designed to measure parenting style in six dimensions, corresponding to six subscales: autonomy support, warmth, structure, coercion, chaos, and rejection. Adolescents rate how they perceive their parents on a scale ranging from 0 = *not at all true* to 3 = *very true*, with scores ranging from 0 to 12 on each subscale. Evaluation of the PASCQ has shown that (a) unipolar dimensions provide a better fit than bipolar dimensions (e.g., warmth–rejection) and (b) supportive and positive aspects of parenting may be captured by combining the three subscales of autonomy support, warmth, and structure, whereas unsupportive and negative aspects of parenting may be assessed by combining the three subscales of coercion, rejection, and chaos (Skinner et al., 2005). Thus, two composite, 12-item variables of parenting style, $PASCQ^{POS}$ and $PASCQ^{NEG}$, were computed by summing up individual participant scores on the three subscales corresponding to each composite variable. The scores on the $PASCQ^{POS}$ and $PASCQ^{NEG}$ ranged from 0 to 36 points. In the current sample, the internal consistency scores of the $PASCQ^{POS}$ and $PASCQ^{NEG}$ were 0.83 and

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Table 1. *Oxytocin gene single nucleotide polymorphism characteristics*

SNP	Chromosome Location	Molecular Consequence	Major/Minor Allele	MAF	Genotype Frequencies *N* (%)			HWE *p*
OXT rs4813625	chr20:3069074	Intron, noncoding variant	G/C	0.47	GG: 386 (28.4)	GC: 680 (50.0)	CC: 293 (21.6)	.84
OXT rs2770378	chr20:3072868	Downstream	G/A	0.37	GG: 535 (39.4)	GA: 29 (46.3)	AA: 195 (14.4)	.64

Note: SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium; *OXT*, oxytocin gene; chr20, chromosome 20.

0.85, respectively. The correlation between $PASCQ^{POS}$ and $PASCQ^{NEG}$ was –0.59.

Procedure

Statistical analyses. Statistical analyses were conducted using SPSS version 24 running on Windows 7. Descriptive statistics were obtained by computing chi-square (χ^2) tests for categorical data and *t* tests for continuous variables. Multiple linear regression and the PROCESS macro for SPSS version 2.16 were used to test and visualize interaction effects (Hayes, 2013). The PROCESS macro uses an ordinary least squares analytic framework for estimating conditional effects of the predictor on the outcome at different values of the moderator. The PROCESS output includes moderator values defining regions of significance (RoS), that is, where the effect of the predictor on the outcome transitions between statistically significant and not significant, or vice versa. These values define the region or regions of significance. Analyses of main effects of genotype and parenting style were conducted using regression models including only $PASCQ^{POS}$, $PASCQ^{NEG}$, or genotype and controlling for sex. Interaction models were controlled for sex and included three predictor variables: genotype, parenting style, and the Genotype × Parenting Style interaction term. Predictor, moderator, and outcome variables were all considered continuous. Because the assumption of equal variances was violated, the heteroscedasticity-consistent standard error estimator HC3 was used (Darlington & Hayes, 2017; White, 1980).

Analyses of missing data patterns showed that, among participants with genotype data, 5% had at least one missing item response on the PASCQ whereas 1% had missing item responses on the SCAS social anxiety scale. On both measures, less than 0.5% of all values were missing. Logistic regression analyses showed no significant relationships between missingness and genotype, mother's birthplace, sex, self-reported symptoms of social anxiety, depression, attention deficit hyperactivity disorder, and alcohol abuse.

Statistical power was estimated with Quanto (Gauderman & Morrison, 2006). The minor allele frequencies were 0.47 for rs4813625 and 0.37 for rs2770378. The power to detect a marginal coefficient of determination (R^2) interaction effect of 1%, typically seen in observational and genome-wide association studies (Dick et al., 2015; McClelland & Judd, 1993), was estimated to be 0.96 for each SNP in the current sample, assuming a significance level of 0.05 and a two-sided test.

Methods recommended by Roisman et al. (2012) for distinguishing between differential-susceptibility and diathesis–stress models were adopted in the evaluation of G × E interaction effects. These methods include three indices and a test for nonlinearity. The first index is a RoS test to demonstrate an association between social anxiety and genotype at both low and high scores of the $PASCQ^{POS}$ and $PASCQ^{NEG}$. The second index is the proportion of the interaction (PoI) index. This index is a measure of the proportion of the total area between the fitted regression lines in an interaction plot that is on the positive, that is, "for better," side of the cross-over point. Because existing differential susceptibility criteria for PoI values (i.e., values between 0.40 and 0.60) have been shown to produce false negatives, a revised index, PoI/*R*, was used where values between 0.20 and 0.80 suggest evidence for differential susceptibility, whereas values closer to 0 suggest evidence for the diathesis–stress model (Del Giudice, 2017). The third index, the proportion affected (PA) index, is designed to quantify the proportion of the total sample that falls above the crossover point. PA values equal to or greater than 0.16 have been suggested as evidence for differential susceptibility. As recommended by Roisman et al., the RoS and PoI indices were restricted to a range of interest ±2 *SD* from the mean of the $PASCQ^{POS}$ and $PASCQ^{NEG}$, although it must be noted that this boundary fell outside the observed range of scores on both parenting style variables. Finally, in order to test whether an apparent significant relationship was an artifact of imposing a linear model on a nonlinear phenomenon, quadratic terms of $PASCQ^{POS}$ and $PASCQ^{NEG}$ were included in additional regression models. The results of this model must show that the linear interaction term remains significant after controlling for nonlinear terms. Tests of nonlinearity were conducted with mean-centered parenting variables.

Results

Genotype and demographic characteristics of the study population are presented in Table 1 and Table 2. The mean par-

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Table 2. *Characteristics of the study population*

Variable	All ($N = 1,359$)	Girls ($N = 807$)	Boys ($N = 552$)	p
Sex,[a] *n* (%)				<.001
Girls	807 (59.4)			
Boys	552 (40.6)			
Age, mean (*SD*)	17.34 (1.04)	17.32 (1.03)	17.37 (1.04)	.378
Descent (mother's birth place), *n* (%)				.936
Sweden	1,113 (81.9)	661 (81.9)	452 (81.9)	
Nordic country	40 (2.9)	23 (2.9)	17 (3.1)	
Europe	56 (4.1)	32 (4.0)	24 (4.3)	
Outside Europe	135 (9.9)	83 (10.3)	52 (9.4)	
Anxiety symptoms, mean (*SD*)				
SCAS total score (range = 0–114)	22.41 (15.31)	27.72 (15.65)	14.65 (10.86)	<.001
SCAS social anxiety[a] (range = 0–18)	5.68 (3.89)	6.74 (3.89)	4.14 (3.32)	<.001
Dimensions of parenting				
$PASCQ^{POS,a}$ (range = 0–36)	28.45 (5.20)	28.58 (5.26)	28.25 (5.11)	.249
Autonomy support (range = 0–12)	9.81 (2.14)	9.84 (2.17)	9.77 (2.09)	.574
Warmth (range = 0–12)	10.75 (1.84)	10.79 (1.83)	10.71 (1.87)	.448
Structure (range = 0–12)	7.88 (2.44)	7.96 (2.43)	7.77 (2.47)	.165
$PASCQ^{NEG,a}$ (range = 0–36)	7.79 (5.73)	7.93 (5.89)	7.59 (5.47)	.267
Coercion (range = 0–12)	3.66 (2.47)	3.60 (2.51)	3.76 (2.41)	.233
Rejection (range = 0–12)	1.33 (2.10)	1.47 (2.22)	1.13 (1.88)	.002
Chaos (range = 0–12)	2.80 (2.37)	2.87 (2.41)	2.70 (2.31)	.205

Note: SCAS, Spence Children's Anxiety Scale; $PASCQ^{POS}$, Parents as Social Context Questionnaire composite variable of autonomy support, warmth, and structure subscales; $PASCQ^{NEG}$, PASCQ composite variable of coercion, rejection, and chaos subscales.
[a]Variables used in regression models.

ticipant age was 17, and a majority of the sample were female. Most were of Swedish, Nordic, or European descent as measured by mother's birthplace. No significant differences in genotype frequencies were found between participants of Swedish/Nordic/European and non-European descent. No significant associations were found between composite variables of parenting style and *OXT* variants. However, higher mean scores on the warmth subscale were observed among rs4813625 C allele carriers than among homozygous G allele carriers, $F\ (2, 1{,}356) = 2.92$, $p = .05$.

In main effect models adjusted for sex (not shown in tables), social anxiety was negatively associated with $PASCQ^{POS}$ ($B = -0.14$, $SE = 0.02$, $p < .001$, $\Delta R^2 = 3.5\%$) and positively associated with $PASCQ^{NEG}$ ($B = 0.18$, $SE = 0.02$, $p < .001$, $\Delta R^2 = 6.8\%$), whereas the main effects of both *OXT* variants were nonsignificant. In interaction models adjusted for sex, significant joint effects were observed for both *OXT* variants with $PASCQ^{POS}$ but only for rs2770378 with $PASCQ^{NEG}$. The interaction of $PASCQ^{POS}$ with rs4813625 was significantly and negatively associated with social anxiety with a significant marginal R^2 change due to the interaction of 1%. Unadjusted R^2 interaction effect sizes for the GG, GC, and CC genotypes in relation to social anxiety were 0.8%, 3.1%, and 9.5%, respectively. The interaction of $PASCQ^{POS}$ with rs2770378 was also significantly and negatively associated with social anxiety, but with a marginal R^2 change due to the interaction of only 0.3% and unadjusted R^2 interaction effect sizes for GG, GA, and AA of 1.6%, 3.2%, and 9.3%, respectively. A similar marginal R^2 change of 0.3% was also observed for the interaction of $PASCQ^{NEG}$ with rs2770378, which was positively associated with social anxiety. Unadjusted R^2 effect sizes for GG, GA, and AA genotypes were 4.0%, 8.7%, and 14.2%.

Covariate interactions were evaluated by adding three interaction terms, including sex, in additional models (*OXT* × Sex, $PASCQ^{POS/NEG}$ × Sex, and *OXT* × $PASCQ^{POS/NEG}$ × Sex). Results from these analyses showed that significant interactions between *OXT* variants and $PASCQ^{POS/NEG}$ from original models remained significant, whereas no significant effects of the interaction terms including sex were observed (results not shown in tables). Regression results for the interaction models are presented in Table 3.

Indices of differential-susceptibility or diathesis–stress forms of interaction

Supportive parenting style. Consistent with a differential susceptibility prediction of a crossover form of interaction, the RoS test showed that rs4813625 had an effect on social anxiety at both ends of the distribution of $PASCQ^{POS}$ scores, with lower and upper boundaries of the RoS within ±1 *SD* from the mean score of $PASCQ^{POS}$. Carriers of the C allele reported higher levels of social anxiety under low parental support and lower levels of anxiety under high parental support compared with G homozygote carriers. For every 1-point increase in $PASCQ^{POS}$ score, the effect on SCAS social anxiety score was a decrease of 0.15 points for carriers of one C allele and 0.26 points for carriers of two C alleles, whereas the

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Table 3. *Regression estimates and differential-susceptibility/diathesis–stress indices by two oxytocin gene variants and parental style among Swedish adolescents*

	Regression Estimates				Indices of Differential Susceptibility/Diatheses–Stress Models					
					RoS					
Model	Coefficient	*SE*	*t*	ΔR^2	Lower (*SD*) % Below	Upper (*SD*) % Above	Cross-over (*SD*)	PoI	PA	Test of Nonlinearity
rs4813625 × PASCQ^{POS}										
Sex (ref. cat.: boys)	2.68***	0.20	13.55							
rs4813625	3.00***	0.77	3.91							
PASCQ^{POS}	–0.05	0.03	−1.67							
rs4813625 × PASCQ^{POS}	–0.10***	0.03	−3.92	.010	25.94[a] (–0.5) 23.40	31.86[a] (+0.7) 30.91	28.94[a] (+0.1)	0.45[a]	0.58[a]	Passed
rs4813625 × PASCQ^{NEG}										
Sex (ref. cat.: boys)	2.54***	0.20	13.04							
rs4813625	–0.26	0.23	−1.15							
PASCQ^{NEG}	0.15***	0.03	5.54							
rs4813625 × PASCQ^{NEG}	0.03	0.02	1.41	.001	—	—	—	—	—	—
rs2770378 × PASCQ^{POS}										
Sex (ref. cat.: boys)	2.64***	0.20	13.30							
rs2770378	1.74*	0.79	2.20							
PASCQ^{POS}	−0.10***	0.03	−3.46							
rs2770378 × PASCQ^{POS}	–0.06*	0.03	−2.19	.003	8.37[b] (–3.9) 0.15	—	29.20[a] (+0.1)	0.43[a]	0.49[a]	Failed
rs2770378 × PASCQ^{NEG}										
Sex (ref. cat.: boys)	2.53***	0.19	12.97							
rs2770378	–0.42	0.24	−1.77							
PASCQ^{NEG}	0.13***	0.02	5.41							
rs2770378 × PASCQ^{NEG}	0.06*	0.02	2.31	.003	—	17.85[b] (+1.8) 7.21	7.46[a] (–0.1)	0.53[a]	0.43[a]	Passed

Note: Coefficient, unstandardized regression coefficient; ΔR^2, R^2 change due to the interaction; RoS, regions of significance on PASCQ$^{POS/NEG}$; % Below/Above, percentage of the sample below/above RoS values; Cross-over, PASCQ$^{POS/NEG}$ value where the regression lines cross over; PoI, proportion of interaction above the cross-over value; PA, proportion of the sample above the cross-over value; PASCQ^{POS}, Parents as Social Context Questionnaire supportive dimension; PASCQ^{NEG}, PASCQ unsupportive dimension.

[a]Support for the differential susceptibility model.

[b]Support for the diathesis–stress model.

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

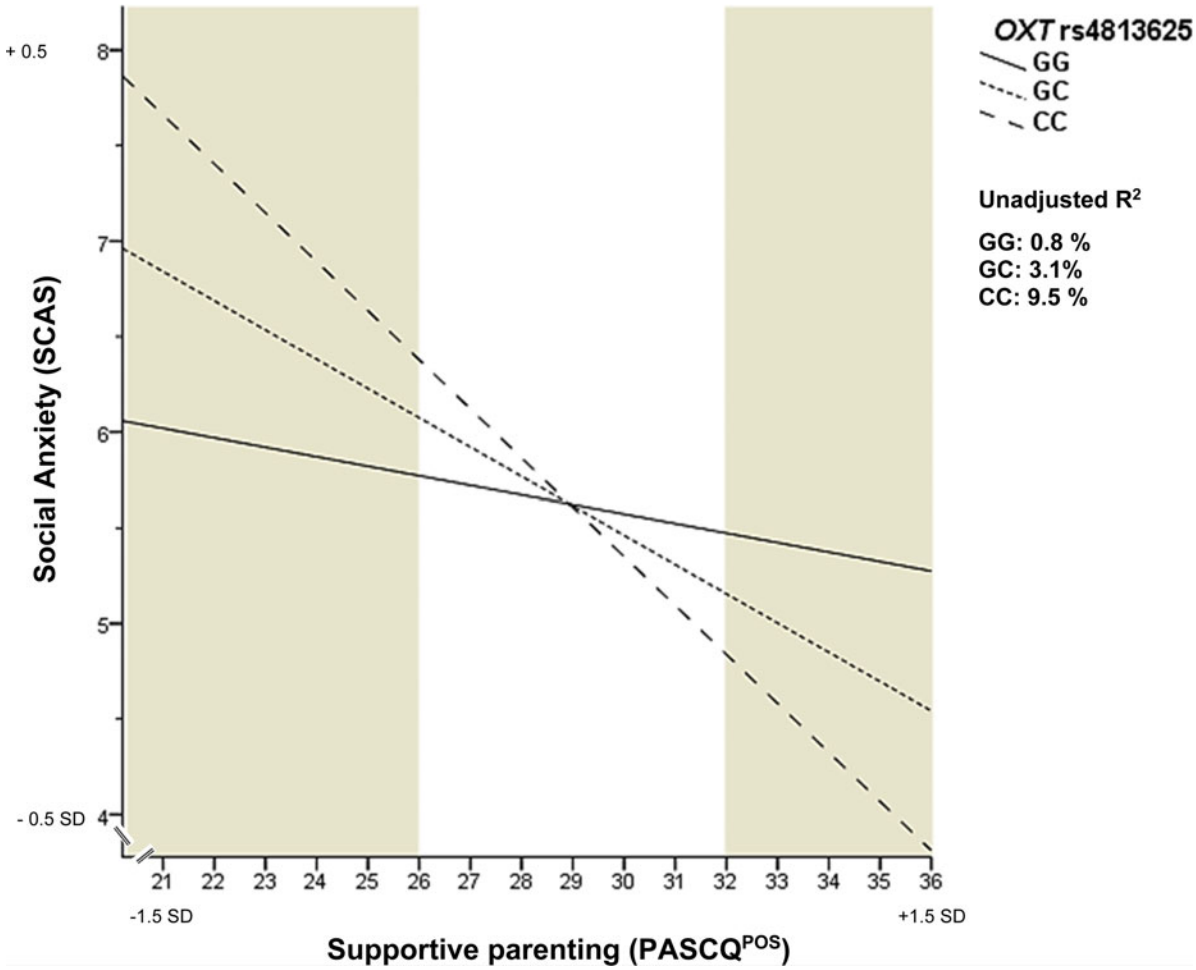

Figure 1. (Color online) Interaction effect of oxytocin gene (*OXT*) polymorphism rs4813625 and adolescent-reported supportive parenting on social anxiety scores. Model adjusted for sex. Shadowed areas represent regions of significance. SCAS, Spence Children's Anxiety Scale social anxiety subscale; $PASCQ^{POS}$, Parents As Social Context Questionnaire positive index (composite variable of parental warmth, structure, and autonomy support).

effect for G allele homozygotes, 0.05 points, was nonsignificant. Rs2770378 failed the RoS test of differential susceptibility, as only one value was identified corresponding to 3.9 *SD* below the mean on the $PASCQ^{POS}$. The RoS test indicates that rs2770378 is associated with social anxiety only at the lowest end of the $PASCQ^{POS}$ score distribution, with A allele carriers reporting higher levels of social anxiety than GG carriers. For both rs4813625 and rs2770378, evidence for differential susceptibility was observed both on the PoI index, with values close to 0.50, and on the PA index, with values above the proposed threshold of 0.16. Tests of nonlinearity revealed significant associations for the G×E interaction terms including the quadratic term of $PASCQ^{POS}$. However, when controlling for the nonlinear terms by adding them to the original model, the interaction between rs4813625 and $PASCQ^{POS}$ remained statistically significant ($B = –0.06$, $SE = 0.03$, $p = .049$). The interaction term including rs2770378 did not pass the test of nonlinearity. After controlling for the nonlinear terms in the model, the interaction between rs2770378 and $PASCQ^{POS}$ became nonsignificant. To summarize, evaluation of the form of interaction between *OXT* variants and supportive parenting style showed that rs4813625 passed all tests of differential susceptibility, whereas rs2770378 failed both the RoS test and the nonlinearity test. Indices of differential-susceptibility or diathesis–stress forms of interaction are presented in Table 3. The conditional effect of *OXT* rs4813625 on social anxiety scores at different values of adolescent-reported supportive parenting style is presented in Figure 1.

Unsupportive parenting style. Suggestive of a diathesis–stress form of interaction, the RoS test showed that rs2770378 was associated with social anxiety only at higher levels of unsupportive parenting style with a single RoS value identified, corresponding to 1.8 *SD* above the mean, with A allele carriers reporting higher levels of social anxiety than GG carriers. For every 1-point increase in $PASCQ^{NEG}$ score, the effect on SCAS social anxiety score was an increase of 0.14 points for G allele homozygotes, 0.18 points for carriers of one A allele, and 0.22 points for carriers of two A alleles.

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In contrast to the RoS test, the crossover value, PoI, and PA tests were indicative of a disordinal form of interaction. A test of nonlinearity revealed a significant and negative association for the quadratic term of $PASCQ^{NEG}$, whereas the $G \times E^2$ interaction term was nonsignificant. After controlling for nonlinear terms in the model, the interaction between rs2770378 and $PASCQ^{NEG}$ remained significant ($B = 0.07$, $SE = 0.03$, $p = .013$). Congruent with the nonsignificant interaction between rs4813625 and $PASCQ^{NEG}$, the RoS test yielded no statistically significant transition values within the observed range of the $PASCQ^{NEG}$. Indices of differential-susceptibility or diathesis–stress forms of interaction are presented in Table 3.

Discussion

The current study provides preliminary evidence for a modifying effect of supportive parenting style on the relationship between *OXT* SNP rs4813625 and social anxiety symptoms in adolescents, independent of sex. When supportive parenting behavior was perceived as low, carriers of the minor C allele reported higher than average levels of social anxiety compared with homozygote G allele carriers, whose levels of social anxiety were close to average. Likewise, at high perceived levels of supportive parental behavior, C allele carriers reported lower than average levels of social anxiety, again with homozygote G allele carriers remaining almost unaffected by parenting style. At average levels of parental support, rs4813625 was not associated with social anxiety. The nature of the modifying effect was in line with the differential susceptibility theory, which proposes that individuals differ in their neurobiological sensitivity to both favorable and less favorable environments, leading to a better than average outcome for carriers of plasticity gene variants in positive environments. Further support for a differential susceptibility model fit was provided by results from a series of tests suggested by Roisman et al. (2012). The interaction effects of rs2770378 with supportive and unsupportive parenting style were small but significant; however, only the interaction term including unsupportive parenting style remained significant in nonlinear models. The rs2770378 × $PASCQ^{NEG}$ effect was consistent with the diatheses–stress model.

Previous research has shown that oxytocin and social support interact to reduce stress (Heinrichs et al., 2003; Meyer-Lindenberg et al., 2011; Tops et al., 2007), and a supportive parenting style may act as a stress-reducing buffer against exposure to increasing demands for independent social functioning during adolescence, where the *OXT* variant rs4813625 influences the sensitivity to the social context of parental supportive behavior along a low to high continuum whereas rs2770378 influences sensitivity only to higher levels of unsupportive parenting. One theory about the mechanism by which oxytocin influences social behavior is the social salience hypothesis, which proposes that oxytocin increases attention to social information, such as safety or threat signals in the social context (Bartz, Zaki, Bolger, & Ochsner, 2011; Olff et al., 2013; Shamay-Tsoory & Abu-Akel, 2016). In line with the conditional joint effects of perceived parenting behavior and *OXT* variants on social anxiety in the current study, the social salience hypothesis specifies that prosocial behavior can be enhanced in positive, safe contexts, whereas negative or unsafe situations decrease prosocial behavior and increase anxiety (Shamay-Tsoory & Abu-Akel, 2016). Dopamine is a neurotransmitter that is vital in motivational processes, as it signals motivational value and the salience of events (Bromberg-Martin, Matsumoto, & Hikosaka, 2010). By way of projection into the mesolimbic pathway, oxytocin has been suggested to affect dopamine activity, further supporting the social salience hypothesis of oxytocin (Baskerville & Douglas, 2010; Love, 2014; Shamay-Tsoory & Abu-Akel, 2016). Corroborating proposed interactions between dopamine and oxytocin and variability in those interaction effects is the finding of greater stress-induced dopamine release observed in female rs4813625 C allele carriers than in G homozygotes (Love et al., 2012). However, similar to the main effect findings of the current study, Love et al. did not observe any differences between C allele carriers and GG carriers in self-reported state anxiety during the stressor condition. This observation further supports the idea of a contextual dependency of oxytocin effects, as suggested by a review of studies of experimentally manipulated levels of oxytocin, which found no main effect in 43% of studies, situational or personal moderating effects on social cognition or prosocial behavior in 63% of studies, and negative effects on prosocial behavior in 21% of studies (Bartz et al., 2011).

To our knowledge, this is the first study of joint associations of *OXT* variants and aspects of parenting style with social anxiety among healthy adolescents. The sample size provided adequate power for the detection of a 1% interaction effect on social anxiety outcome. However, conditional on the rs2770378 minor allele frequency, the power to detect the observed effect of 0.3% for the interaction terms including rs2770378 was only 0.52 in the study sample, which reduces the likelihood that statistically significant findings reflect a true effect (Button et al., 2013). With regard to parenting style, rs2770378 failed tests of differential susceptibility, with the implication of inconsistency in the form of interaction for rs4813625 compared with rs2770378. The explanation for this may be inadequate power or a difference in functionality between these variants; however, the inclusion of only two SNPs in this study precludes further analyses of their respective loci.

There are several limitations to this study. The cross-sectional design precludes interpretations of causal effects. In analyses of main effects in this study, associations of supportive and unsupportive parenting styles with social anxiety were significant, but any causal inferences about this relationship require different study designs. Parents trying to handle anxious adolescents who deviate from normal development toward autonomy may be perceived as unsupportive, and prior research suggests a reciprocal relationship between parenting style and social anxiety (Waite et al., 2014). By con-

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trast, maternal behaviors of warmth, autonomy support and hostility, and the quality of mother–child interactions have been shown to be fairly stable from infancy to adolescence (Else-Quest, Clark, & Owen, 2011). It must be stressed that PASCQ scores reported by adolescents cannot be equated with "true" parental behavior, as ratings may be influenced by a range of factors, including genetic effects on perceptions of parents (Moffitt, 2005), and this has implications for the level of agreement if parenting style scores are obtained from other informants. Apart from that, it has been argued that the assessment of adolescents' subjective understanding of parenting behaviors, rather than observations, can facilitate further understanding of the mechanisms by which parenting behaviors are related to adolescent outcomes (Powers, Welsh, & Wright, 1994). Our results suggest that rs4813625 affects social anxiety levels along a perceived unsafe–safe social context dimension, as reflected by $PASCQ^{POS}$ scores. By contrast, the joint effect of rs2770378 and unsupportive parenting style indicated that the $PASCQ^{NEG}$ captures only negative aspects of parenting. These results indicate that separating parenting behavior into negative and positive dimensions, rather than combining them in bipolar dimensions in order to achieve opposite ends of a construct, may be important for further understanding how parenting characteristics influence anxiety. The study design may also raise concerns of biased associations due to the use of a common method and a single respondent to assess social anxiety and parenting. However, because common method variance deflates rather than inflates interaction effects, findings of significant effects in the presence of shared variance should be taken as strong evidence that an interaction effect exists (Siemsen, Roth, & Oliveira, 2010).

One common critique of genetic association studies is the multiple comparisons problem, where the risk of Type I errors (i.e., mistakenly rejecting the null hypothesis of no association) increases with each additional test. Different statistical correction methods for this problem exist (Yi, Xu, Lou, & Mallick, 2014). However, reducing the risk of Type I errors reduces power and increases the risk of incorrectly stating that no relationship exists between the investigated factors (i.e., a Type II error; Nakagawa, 2004; Rothman, 1990). Instead, a thorough description and explanation of what has been done has been proposed as a better approach (Perneger, 1998). Nevertheless, using the most conservative correction method of standard Bonferroni for eight primary tests (four main effects models and four interaction models) would yield an adjusted significance level of 0.006 and thus retain significance for the interaction between rs4813625 and supportive parenting style. Because recommendations for $G \times E$ studies were followed (i.e., inclusion of covariate and quadratic interaction terms in the model), a number of additional models were tested (Dick et al., 2015; Roisman et al., 2012). The interactions between rs4813625 and $PASCQ^{POS}$ and rs2770378 and $PASCQ^{NEG}$ remained significant in these models, suggesting that the findings of the current study are robust. Finally, because the effect of rs4813625 and rs2770378 on oxytocin levels is still unknown, it is impossible to interpret results from this study in terms of higher or lower levels of central or peripheral oxytocin in minor allele carriers compared with homozygote major allele carriers.

In summary, our findings suggest that supportive and unsupportive parenting behaviors and *OXT* variants interact to influence social anxiety symptoms among adolescents. For rs4813625, this relationship was disordinal in nature, with nearly symmetric differences in anxiety scores between genotypes at both low and high levels of support. The nature of the interaction between rs2770378 and unsupportive parenting style was in line with the diathesis–stress model. Further investigations of the function of rs4813625, rs2770378, and colocalized *OXT* SNPs in other samples are warranted, as are studies of whether the function is context dependent in relation to social outcomes other than social anxiety.

References

Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2013). Sniffing around oxytocin: Review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. *Translational Psychiatry*, *3*, e258. doi:10.1038/tp.2013.34

Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2014). A sociability gene? Meta-analysis of oxytocin receptor genotype effects in humans. *Psychiatric Genetics*, *24*, 45–51. doi:10.1097/YPG.0b013e3283643684

Bartz, J. A., Zaki, J., Bolger, N., & Ochsner, K. N. (2011). Social effects of oxytocin in humans: Context and person matter. *Trends in Cognitive Sciences*, *15*, 301–309. doi:10.1016/j.tics.2011.05.002

Baskerville, T. A., & Douglas, A. J. (2010). Dopamine and oxytocin interactions underlying behaviors: Potential contributions to behavioral disorders. *CNS Neuroscience & Therapeutics*, *16*, e92–e123. doi:10.1111/j.1755-5949.2010.00154.x

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and anxiety disorders in children and adolescents: Developmental issues and implications for DSM-V. *Psychiatric Clinics of North America*, *32*, 483–524. doi:10.1016/j.psc.2009.06.002

Belsky, J., & Hartman, S. (2014). Gene-environment interaction in evolutionary perspective: Differential susceptibility to environmental influences. *World Psychiatry*, *13*, 87–89. doi:10.1002/wps.20092

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*, 885–908. doi:10.1037/a0017376

Belsky, J., & Pluess, M. (2013). Beyond risk, resilience, and dysregulation: Phenotypic plasticity and human development. *Development and Psychopathology*, *25*, 1243–1261. doi:10.1017/S095457941300059X

Bromberg-Martin, E. S., Matsumoto, M., & Hikosaka, O. (2010). Dopamine in motivational control: Rewarding, aversive, and alerting. *Neuron*, *68*, 815–834. doi:10.1016/j.neuron.2010.11.022

Brune, M. (2012). Does the oxytocin receptor (OXTR) polymorphism (rs2254298) confer "vulnerability" for psychopathology or "differential susceptibility"? Insights from evolution. *BMC Medicine*, *10*, 38. doi:10.1186/1741-7015-10-38

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafo, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*, 365–376. doi:10.1038/nrn3475

Carson, D. S., Berquist, S. W., Trujillo, T. H., Garner, J. P., Hannah, S. L., Hyde, S. A., . . . Parker, K. J. (2015). Cerebrospinal fluid and plasma oxytocin concentrations are positively correlated and negatively predict anxiety in children. *Molecular Psychiatry*, *20*, 1085–1090. doi:10.1038/mp.2014.132

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., . . . Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science*, *297*, 851–854. doi:10.1126/science.1072290

Copeland, W. E., Angold, A., Shanahan, L., & Costello, E. J. (2014). Longitudinal patterns of anxiety from childhood to adulthood: The Great Smoky Mountains Study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *53*, 21–33. doi:10.1016/j.jaac.2013.09.017

Darlington, R. B., & Hayes, A. F. (2017). *Regression analysis and linear models: Concepts, applications, and implementation*. New York: Guilford Press.

Del Giudice, M. (2017). Statistical tests of differential susceptibility: Performance, limitations, and improvements. *Development and Psychopathology*. Advance online publication. doi:10.1017/S0954579416001292

Dick, D. M., Adkins, A. E., & Kuo, S. I. (2016). Genetic influences on adolescent behavior. *Neuroscience and Biobehavioral Reviews*, *70*, 198–205. doi:10.1016/j.neubiorev.2016.07.007

Dick, D. M., Agrawal, A., Keller, M. C., Adkins, A., Aliev, F., Monroe, S., . . . Sher, K. J. (2015). Candidate gene-environment interaction research: Reflections and recommendations. *Perspectives on Psychological Science*, *10*, 37–59. doi:10.1177/1745691614556682

Dodhia, S., Hosanagar, A., Fitzgerald, D. A., Labuschagne, I., Wood, A. G., Nathan, P. J., & Phan, K. L. (2014). Modulation of resting-state amygdala-frontal functional connectivity by oxytocin in generalized social anxiety disorder. *Neuropsychopharmacology*, *39*, 2061–2069. doi:10.1038/npp.2014.53

Ebstein, R. P., Knafo, A., Mankuta, D., Chew, S. H., & Lai, P. S. (2012). The contributions of oxytocin and vasopressin pathway genes to human behavior. *Hormones and Behavior*, *61*, 359–379. doi:10.1016/j.yhbeh.2011.12.014

Eccles, J. S., Buchanan, C. M., Flanagan, C., Fuligni, A., Midgley, C., & Yee, D. (1991). Control versus autonomy during early adolescence. *Journal of Social Issues*, *47*, 53–68. doi:10.1111/j.1540-4560.1991.tb01834.x

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary–neurodevelopmental theory. *Development and Psychopathology*, *23*, 7–28. doi:10.1017/S0954579410000611

Else-Quest, N. M., Clark, R., & Owen, M. T. (2011). Stability in mother-child interactions from infancy through adolescence. *Parenting, Science and Practice*, *11*, 280–287. doi:10.1080/15295192.2011.613724

Feldman, R., Monakhov, M., Pratt, M., & Ebstein, R. P. (2016). Oxytocin pathway genes: Evolutionary ancient system impacting on human affiliation, sociality, and psychopathology. *Biological Psychiatry*, *79*, 174–184. doi:10.1016/j.biopsych.2015.08.008

Feldman, R., Zagoory-Sharon, O., Weisman, O., Schneiderman, I., Gordon, I., Maoz, R., . . . Ebstein, R. P. (2012). Sensitive parenting is associated with plasma oxytocin and polymorphisms in the OXTR and CD38 genes. *Biological Psychiatry*, *72*, 175–181. doi:10.1016/j.biopsych.2011.12.025

Francis, S. M., Kistner-Griffin, E., Yan, Z., Guter, S., Cook, E. H., & Jacob, S. (2016). Variants in adjacent oxytocin/vasopressin gene region and associations with ASD diagnosis and other autism related endophenotypes. *Frontiers in Neuroscience*, *10*, 195. doi:10.3389/fnins.2016.00195

Garmezy, N. (1974). Children at risk: The search for the antecedents of schizophrenia: Part II. Ongoing research programs, issues, and intervention. *Schizophrenia Bulletin*, *9*, 55–125.

Gauderman, W. J., & Morrison, J. M. (2006). Quanto 1.1: A computer program for power and sample size calculations for gene-epidemiology studies [Computer software]. Retrieved from http://hydra.usc.edu/gxe

Ginsburg, G. S., Becker, E. M., Keeton, C. P., Sakolsky, D., Piacentini, J., Albano, A. M., . . . Kendall, P. C. (2014). Naturalistic follow-up of youths treated for pediatric anxiety disorders. *JAMA Psychiatry*, *71*, 310–318. doi:10.1001/jamapsychiatry.2013.4186

Gordon, I., Martin, C., Feldman, R., & Leckman, J. F. (2011). Oxytocin and social motivation. *Developmental Cognitive Neuroscience*, *1*, 471–493. doi:10.1016/j.dcn.2011.07.007

Gorka, S. M., Fitzgerald, D. A., Labuschagne, I., Hosanagar, A., Wood, A. G., Nathan, P. J., & Phan, K. L. (2015). Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. *Neuropsychopharmacology*, *40*, 278–286. doi:10.1038/npp.2014.168

Gren-Landell, M., Tillfors, M., Furmark, T., Bohlin, G., Andersson, G., & Svedin, C. G. (2009). Social phobia in Swedish adolescents: Prevalence and gender differences. *Social Psychiatry and Psychiatric Epidemiology*, *44*, 1–7. doi:10.1007/s00127-008-0400-7

Hammen, C., Bower, J. E., & Cole, S. W. (2015). Oxytocin receptor gene variation and differential susceptibility to family environment in predicting youth borderline symptoms. *Journal of Personality Disorders*, *29*, 177–192. doi:10.1521/pedi_2014_28_152

Hayes, A. F. (2013). *Introduction to mediation, moderation and conditional process analysis*. New York: Guilford Press.

Heim, C., Young, L. J., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Molecular Psychiatry*, *14*, 954–958.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., & Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry*, *54*, 1389–1398. doi:10.1016/S0006-3223(03)00465-7

Heinrichs, M., von Dawans, B., & Domes, G. (2009). Oxytocin, vasopressin, and human social behavior. *Frontiers in Neuroendocrinology*, *30*, 548–557. doi:10.1016/j.yfrne.2009.05.005

Hovey, D., Zettergren, A., Jonsson, L., Melke, J., Anckarsater, H., Lichtenstein, P., & Westberg, L. (2014). Associations between oxytocin-related genes and autistic-like traits. *Social Neuroscience*, *9*, 378–386. doi:10.1080/17470919.2014.897995

Kessler, R. C., Avenevoli, S., Costello, E. J., Georgiades, K., Green, J. G., Gruber, M. J., . . . Merikangas, K. R. (2012). Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. *Archives of General Psychiatry*, *69*, 372–380. doi:10.1001/archgenpsychiatry.2011.160

Kirsch, P. (2015). Oxytocin in the socioemotional brain: Implications for psychiatric disorders. *Dialogues in Clinical Neuroscience*, *17*, 463–476.

Knobloch, H. S., & Grinevich, V. (2014). Evolution of oxytocin pathways in the brain of vertebrates. *Frontiers in Behavioral Neuroscience*, *8*. doi:10.3389/fnbeh.2014.00031

Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, *435*, 673–676. doi:10.1038/nature03701

Kumsta, R., & Heinrichs, M. (2013). Oxytocin, stress and social behavior: Neurogenetics of the human oxytocin system. *Current Opinion in Neurobiology*, *23*, 11–16. doi:10.1016/j.conb.2012.09.004

LeDoux, J. E. (2015). *Anxious: The modern mind in the age of anxiety*. London: Oneworld.

Lee, H. J., Macbeth, A. H., Pagani, J. H., & Young, W. S., III. (2009). Oxytocin: The great facilitator of life. *Progress in Neurobiology*, *88*, 127–151. doi:10.1016/j.pneurobio.2009.04.001

LoParo, D., & Waldman, I. D. (2015). The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: A meta-analysis. *Molecular Psychiatry*, *20*, 640–646. doi:10.1038/mp.2014.77

Love, T. M. (2014). Oxytocin, motivation and the role of dopamine. *Pharmacology, Biochemistry and Behavior*, *119*, 49–60. doi:10.1016/j.pbb.2013.06.011

Love, T. M., Enoch, M. A., Hodgkinson, C. A., Pecina, M., Mickey, B., Koeppe, R. A., . . . Zubieta, J. K. (2012). Oxytocin gene polymorphisms influence human dopaminergic function in a sex-dependent manner. *Biological Psychiatry*, *72*, 198–206. doi:10.1016/j.biopsych.2012.01.033

McClelland, G. H., & Judd, C. M. (1993). Statistical difficulties of detecting interactions and moderator effects. *Psychological Bulletin*, *114*, 376–390.

McElhaney, K. B., Allen, J. P., Stephenson, J. C., & Hare, A. L. (2009). Attachment and autonomy during adolescence. In R. M. Lerner & L. Steinberg (Eds.), *Handbook of adolescent psychology: Vol. 1. Individual bases of adolescent development* (3rd ed., pp. 358–403). Hoboken, NJ: Wiley.

McQuaid, R. J., McInnis, O. A., Paric, A., Al-Yawer, F., Matheson, K., & Anisman, H. (2016). Relations between plasma oxytocin and cortisol: The stress buffering role of social support. *Neurobiology of Stress*, *3*, 52–60. doi:10.1016/j.ynstr.2016.01.001

Meyer-Lindenberg, A., Domes, G., Kirsch, P., & Heinrichs, M. (2011). Oxytocin and vasopressin in the human brain: Social neuropeptides for translational medicine. *Nature Reviews: Neuroscience*, *12*, 524–538. doi:10.1038/nrn3044

Mileva-Seitz, V., Steiner, M., Atkinson, L., Meaney, M. J., Levitan, R., Kennedy, J. L., . . . Fleming, A. S. (2013). Interaction between oxytocin genotypes and early experience predicts quality of mothering and postpartum mood. *PlOS ONE*, *8*, e61443. doi:10.1371/journal.pone.0061443

Moffitt, T. E. (2005). The new look of behavioral genetics in developmental psychopathology: Gene-environment interplay in antisocial behaviors. *Psychological Bulletin*, *131*, 533–554. doi:10.1037/0033-2909.131.4.533

Nakagawa, S. (2004). A farewell to Bonferroni: The problems of low statistical power and publication bias. *Behavioral Ecology*, *15*, 1044–1045.

Notzon, S., Domschke, K., Holitschke, K., Ziegler, C., Arolt, V., Pauli, P., . . . Zwanzger, P. (2016). Attachment style and oxytocin receptor gene variation interact in influencing social anxiety. *World Journal of Biological Psychiatry*, *17*, 76–83. doi:10.3109/15622975.2015.1091502

Olff, M., Frijling, J. L., Kubzansky, L. D., Bradley, B., Ellenbogen, M. A., Cardoso, C., . . . van Zuiden, M. (2013). The role of oxytocin in social bonding, stress regulation and mental health: An update on the moderating effects of context and interindividual differences. *Psychoneuroendocrinology*, *38*, 1883–1894. doi:10.1016/j.psyneuen.2013.06.019

Olofsdotter, S., Sonnby, K., Vadlin, S., Furmark, T., & Nilsson, K. W. (2015). Assessing adolescent anxiety in general psychiatric care: Diagnostic accuracy of the Swedish Self-Report and Parent Versions of the Spence Children's Anxiety Scale. *Assessment*. Advance online publication. doi:10.1177/1073191115583858

Onodera, M., Ishitobi, Y., Tanaka, Y., Aizawa, S., Masuda, K., Inoue, A., . . . Akiyoshi, J. (2015). Genetic association of the oxytocin receptor genes with panic, major depressive disorder, and social anxiety disorder. *Psychiatric Genetics*, *25*, 212. doi:10.1097/YPG.0000000000000096

Orgiles, M., Fernandez-Martinez, I., Guillen-Riquelme, A., Espada, J. P., & Essau, C. A. (2015). A systematic review of the factor structure and reliability of the Spence Children's Anxiety Scale. *Journal of Affective Disorders*, *190*, 333–340. doi:10.1016/j.jad.2015.09.055

Perneger, T. V. (1998). What's wrong with Bonferroni adjustments. *British Medical Journal*, *316*, 1236–1238.

Pierrehumbert, B., Torrisi, R., Laufer, D., Halfon, O., Ansermet, F., & Beck Popovic, M. (2010). Oxytocin response to an experimental psychosocial challenge in adults exposed to traumatic experiences during childhood or adolescence. *Neuroscience*, *166*, 168–177. doi:10.1016/j.neuroscience.2009.12.016

Polanczyk, G. V., Salum, G. A., Sugaya, L. S., Caye, A., & Rohde, L. A. (2015). Annual Research Review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *Journal of Child Psychology and Psychiatry*, *56*, 345–365. doi:10.1111/jcpp.12381

Powers, S. I., Welsh, D. P., & Wright, V. (1994). Adolescents' affective experience of family behaviors: The role of subjective understanding. *Journal of Research on Adolescence*, *4*, 585–600.

Roisman, G. I., Newman, D. A., Fraley, R. C., Haltigan, J. D., Groh, A. M., & Haydon, K. C. (2012). Distinguishing differential susceptibility from diathesis–stress: Recommendations for evaluating interaction effects. *Development and Psychopathology*, *24*, 389–409. doi:10.1017/S0954579412000065

Rothman, K. J. (1990). No adjustments are needed for multiple comparisons. *Epidemiology*, *1*, 43–46.

Rutter, M. (1979). Protective factors in children's responses to stress and disadvantage. *Annals of the Academy of Medicine*, *8*, 324–338.

Salum, G. A., Desousa, D. A., do Rosario, M. C., Pine, D. S., & Manfro, G. G. (2013). Pediatric anxiety disorders: From neuroscience to evidence-based clinical practice. *Revista Brasileira de Psiquiatria*, *35*(Suppl. 1), S03–S21. doi:10.1590/1516-4446-2013-S108

Shaffer, D. R., & Kipp, K. (2014). *Developmental psychology: Childhood and adolescence* (9th ed.). Belmont, CA: Wadsworth Cengage Learning.

Shamay-Tsoory, S. G., & Abu-Akel, A. (2016). The social salience hypothesis of oxytocin. *Biological Psychiatry*, *79*, 194–202. doi:10.1016/j.biopsych.2015.07.020

Sherry, S. T., Ward, M. H., Kholodov, M., Baker, J., Phan, L., Smigielski, E. M., & Sirotkin, K. (2001). dbSNP: The NCBI database of genetic variation. *Nucleic Acids Research*, *29*, 308–311.

Siemsen, E., Roth, A., & Oliveira, P. (2010). Common method bias in regression models with linear, quadratic, and interaction effects. *Organizational Research Methods*, *13*, 456–476. doi:10.1177/1094428109351241

Skinner, E. A., Johnson, S., & Snyder, T. (2005). Six dimensions of parenting: A motivational model. *Parenting*, *5*, 175–235. doi:10.1207/s15327922par0502_3

Skinner, E. A., Wellborn, J. G., & Regan, C. (1986). *The "Parents as Social Context Questionnaire" (PASCQ): Parent-and child reports of parent involvement, structure, and autonomy support* (Tech. Rep.). Rochester, NY: University of Rochester.

Spence, S. H. (1997). Structure of anxiety symptoms among children: A confirmatory factor-analytic study. *Journal of Abnormal Psychology*, *106*, 280–297.

Strauss, J. S., Freeman, N. L., Shaikh, S. A., Vetró, Á., Kiss, E., Kapornai, K., . . . Kennedy, J. L. (2010). No association between oxytocin or prolactin gene variants and childhood-onset mood disorders. *Psychoneuroendocrinology*, *35*, 1422–1428. doi:10.1016/j.psyneuen.2010.04.008

Tops, M., Van Peer, J. M., Korf, J., Wijers, A. A., & Tucker, D. M. (2007). Anxiety, cortisol, and attachment predict plasma oxytocin. *Psychophysiology*, *44*, 444–449. doi:10.1111/j.1469-8986.2007.00510.x

Tost, H., Kolachana, B., Hakimi, S., Lemaitre, H., Verchinski, B. A., Mattay, V. S., . . . Meyer-Lindenberg, A. (2010). A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proceedings of the National Academy of Sciences*, *107*, 13936–13941. doi:10.1073/pnas.1003296107

Uzefovsky, F., Shalev, I., Israel, S., Edelman, S., Raz, Y., Mankuta, D., . . . Ebstein, R. P. (2015). Oxytocin receptor and vasopressin receptor 1a genes are respectively associated with emotional and cognitive empathy. *Hormones and Behavior*, *67*, 60–65. doi:10.1016/j.yhbeh.2014.11.007

Waite, P., Whittington, L., & Creswell, C. (2014). Parent-child interactions and adolescent anxiety: A systematic review. *Psychopathology Review*, *1*, 51–76. doi:10.5127/pr.033213

White, H. (1980). A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica*, *48*.

Widaman, K. F., Helm, J. L., Castro-Schilo, L., Pluess, M., Stallings, M. C., & Belsky, J. (2012). Distinguishing ordinal and disordinal interactions. *Psychological Methods*, *17*, 615–622. doi:10.1037/a0030003

Wigton, R., Radua, J., Allen, P., Averbeck, B., Meyer-Lindenberg, A., McGuire, P., . . . Fusar-Poli, P. (2015). Neurophysiological effects of acute oxytocin administration: Systematic review and meta-analysis of placebo-controlled imaging studies. *Journal of Psychiatry & Neuroscience*, *40*, E1–E22. doi:10.1503/jpn.130289

Yi, N., Xu, S., Lou, X. Y., & Mallick, H. (2014). Multiple comparisons in genetic association studies: A hierarchical modeling approach. *Statistical Applications in Genetics and Molecular Biology*, *13*, 35–48. doi:10.1515/sagmb-2012-0040