Journal of Personality Disorders, 29(2), 177–192, 2015

OXYTOCIN RECEPTOR GENE VARIATION AND DIFFERENTIAL SUSCEPTIBILITY TO FAMILY ENVIRONMENT IN PREDICTING YOUTH BORDERLINE SYMPTOMS

Constance Hammen, PhD, Julienne E. Bower, PhD, and Steven W. Cole, PhD

Oxytocin appears to be centrally involved in socioemotional functioning, and is hypothesized to be relevant to the severe disruption in close relationships characteristic of borderline personality pathology. We examined whether a polymorphism of the oxytocin receptor gene (*OXTR* rs53576) interacts with quality of family functioning to predict borderline personality disorder (BPD) symptomatology in a sample of youth at age 20. A total of 385 youth from a longitudinal study of offspring of depressed or nondepressed mothers who were well characterized with respect to their family conditions and BPD symptomatology provided DNA for genotyping. Analyses revealed a significant moderation of the link between early family quality and later BPD symptoms by *OXTR* rs53576, and the pattern was consistent with differential susceptibility (plasticity). Whereas A-allele carriers had high levels of BPD symptoms under negative family conditions and low levels under positive conditions, GG homozygotes had average levels of BPD symptoms regardless of their family quality.

Most types of psychological disorder are characterized in part by dysfunctions in close relationships, but perhaps nowhere are interpersonal disruptions more central to defining and diagnosing the psychopathology

This article was accepted under the editorship of Robert F. Krueger and John Livesely.

From Department of Psychology at the University of California, Los Angeles (C. H., J. E. B.); and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, and the Cousins Center for Psychoneuroimmunology, Geffen School of Medicine, University of California, Los Angeles (S. W. C.).

This research was supported by NIMH R01MH052239 and a grant from the UCLA Cousins Center for Psychoneuroimmunology. We are also grateful for the assistance of the Social Genomics Core of the USC/UCLA Biodemography Center. Special thanks to the Australian research teams and project coordinators Robyne Le Brocque, Cheri Dalton Comber, and Sascha Hardwicke, and to the parents and youth in the Mater Cohort for their participation in this study; thanks also to Christopher Conway and Elizabeth Dalton for statistical assistance. The cooperation of Patricia Brennan, Emory University, and Jake Najman of the University of Queensland and head of the MUSP program are gratefully acknowledged.

Address correspondence to Constance Hammen, Department of Psychology, University of California, Los Angeles (UCLA), Los Angeles, CA 90095-1563; E-mail: hammen@psych.ucla.edu

than in borderline personality disorder (BPD). Symptoms of BPD include characteristically disturbed relationships, such as conflictual and unstable close relationships, perceptual distortions of the feelings, behaviors, and intentions of others, intense desire for closeness, and pathological fear of abandonment. BPD affects about 1–3% of the U.S. adult population (e.g., Trull, Jahng, Tomko, Wood, & Sher, 2010), but is considerably more common among treatment-seeking populations. It is known to complicate treatment, course, and outcome of co-occurring disorders, such as depression, anxiety, and substance use, and hence is disproportionately costly in services and resources as well as associated with more clinical and psychosocial disability than most other personality disorders (e.g., Zimmerman et al., 2012; Zimmerman, Rothschild, & Chelminski, 2005). Thus, investigation of the etiological mechanisms of BPD has important theoretical and treatment implications. The current study addresses the interplay of genetic and family environment factors as contributors to borderline personality pathology.

The etiology of BPD is currently unknown, although retrospectively reported traumatic childhood experiences such as child sexual abuse have often been linked to BPD and assumed to have causal significance. Recent research has suggested a more refined position, broadly implicating discordant family relationships. For example, Paris (2009) reviewed and noted the limitations of BPD research on early childhood trauma, reporting that severe abuse occurs in only a minority of BPD patients, and also noted that studies of childhood maltreatment have generally indicated nonspecific increased risk for diverse forms of psychopathology. Indeed, as Kessler and colleagues (2010) report, adversities associated with maladaptive family functioning are among the strongest predictors of psychopathology in general. Zanarini (2000) reported that the majority of BPD patients recall adverse childhood family experiences. It is likely that family dysfunction, therefore, may be a contributory factor in many cases. Consistent with this possibility, Trull (2001) found that childhood sexual abuse was not predictive of borderline psychopathology in a large community sample, but parental mental illness was a significant contributor, likely operating through unstable family and marital environments and dysfunctional parenting associated with parental mental illness (see also Tackett, Balsis, Oltmanns, & Krueger, 2009).

Direct biological research on BPD is limited, although genetic effects have long been suspected. Indeed, a recent twin study indicated that an underlying latent trait of borderline pathology was about 51% heritable and 49% due to unique environmental effects (Distel et al., 2010; see also Distel et al., 2011; Distel, Hottenga, Trull, & Boomsma, 2008). It is assumed that particular heritable traits, such as impulsivity and affect instability, contribute to BPD phenomena, but it is not yet clear what other trait markers may be relevant (Paris, 2009). Gunderson (2007; see also Gunderson & Lyons-Ruth, 2008) hypothesized that "disturbed relatedness," such as interpersonal hypersensitivity, may

serve as an (heritable) endophenotype for BPD, but empirical tests are needed.

There has been a recent surge of interest in the neural processes and genetic factors that influence human social functioning, and in identifying alterations in such processes that might underlie different forms of psychopathology (e.g., Meyer-Lindenberg & Tost, 2012). One line of research in this context has focused on the peptide hormone oxytocin, with findings indicating that increased oxytocin levels reduce reactivity to social stress and promote trust, sociability, empathy, and sensitive perceptions of the states of minds of others (e.g., Bartz & Hollander, 2006; Meyer-Lindenberg & Tost, 2012). Other researchers have also called for gene-environment studies of BPD in the context of *OXTR* (e.g., Bartz & Hollander, 2006; Heinrich & Domes, 2008; Stanley & Siever, 2010).

In their recent review, Kumsta and Heinrichs (2013) identified two single nucleotide polymorphisms (SNPs) located on the third intron of the gene coding for the oxytocin receptor (*OXTR*) as especially intriguing candidate loci associated with social behavior. The current study focuses on *OXTR* rs53576. The *OXTR* gene codes for oxytocin receptors by which oxytocin exerts a range of effects throughout the body and the brain. A number of earlier studies reported links between a heterogeneous array of interpersonal behaviors, traits, and disorders. However, a recent meta-analysis incorporating many of these and more recent studies of *OXTR* failed to confirm a significant main effect of the genotypes associated with diverse social, clinical, and personality behaviors, but left open the question of moderators, especially gene by environment interactions (Bakermans-Kranenburg & van IJzendoorn, 2014). Intriguingly, Bakermans-Kranenburg and Van IJzendoorn (2013) also completed a meta-analysis on studies of the effects of intranasally administered oxytocin (OT) on prosocial outcomes in clinical and healthy groups. They found that effects were modified significantly by context, including childhood exposure to adverse experiences. While healthy groups generally showed positive changes in prosocial outcomes or neurobiological functioning following OT administration, the authors reported that, "positive OT effects were . . . lowered or absent in individuals with negative caregiving experiences." In the small borderline personality disorder samples, they similarly found comparatively less trust and cooperativeness associated with OT administration.

Together these findings encourage pursuit of *OXTR* gene × adverse childhood environment interactions associated with borderline symptomatology. We propose that the effects of *OXTR* polymorphisms on borderline pathology are moderated by quality of the family environment. Study of the genetically shaped sensitivity to the environment as modeled by gene-environment interactions involving the serotonin transporter gene (*5-HTTLPR*) and stress (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010) presents a valuable parallel (e.g., Karg, Burmeister, Shedden, & Sen, 2011; Risch et al., 2009) for studying effects of the oxytocin receptor SNP. More-

over, we propose to test a "differential susceptibility" effect rather than the prevalent diathesis-stress approach. Consistent with van IJzendoorn, Belsky, and Bakermans-Kranenburg (2012) in their meta-analysis of 5-HTTLRP and evidence of differential susceptibility, and also in keeping with Brune's (2012) hypotheses specifically about the likelihood that *OXTR* polymorphisms likely display differential susceptibility patterns, we propose that quality of childhood family relationships will differentially affect the A-allele carriers who might be described as more susceptible to effects of environmental characteristics. The differential susceptibility model (also called "plasticity") attempts to explain the persistence of maladaptive characteristics in the gene pool, and hypothesizes that allelic variation that leads to psychopathological outcomes under adverse environmental conditions could lead to enhanced, positive outcomes with the same genetic factor under favorable environmental conditions. We test whether individuals who express the "risk" (A) alleles actually experience better than typical outcomes on borderline personality pathology under conditions of positive family relationships compared to those with more negative family quality, while G-allele homozygotes are relatively unaffected by variation in family environment. Hence, whereas GG carriers are relatively unaffected in terms of BPD symptoms by differences in quality of the family environment, the A carriers are more responsive "for better or for worse," such that they will do better than GG homozygotes under positive conditions and worse under negative conditions.

The goal of the present study was to examine how family environment and *OXTR* status on rs53576 interact to predict BPD symptomatology in a community sample of 20 year olds in families originally recruited as at risk for psychopathology due to maternal depression and then followed longitudinally since childhood. It is generally accepted that borderline psychopathology emerges in childhood and adolescence (e.g., Reich & Zanarini, 2001; Tackett et al., 2009), and by definition the disorder must be evident by early adulthood. In the present study, a dimensional measure of BPD symptomatology was derived from a standard personality disorder interview (*Structured Clinical Interview for DSM Axis II Personality Disorders* [SCID II]; First, Spitzer, Gibbon, Williams, & Benjamin, 1994). It provides a continuous measure of severity of symptomatology that is more sensitive in gene-environment interaction analyses than would be possible with the limited sample size of those who met full criteria for diagnostic classification. Moreover, numerous studies have shown that even mild borderline symptomatology in nonclinical populations is associated with significant impairment of functioning (e.g., Trull, Useda, Conforti, & Doan, 1997). Additionally, while controversies reign in the question of the utility of dimensional versus categorical (diagnostic) assessment of BPD and other personality disorders, a review of phenotypic and genetic studies generally supports the use of dimensional approaches (Trull, Distel, & Carpenter, 2011). Depression is highly comorbid with borderline personality disorder (Trull et al., 2010), and the present study controls for co-occur-

ring depression at the time of BPD assessment. The measure of family environment is a well-characterized composite variable of contemporaneously obtained information about marital and parental quality ongoing at age 15; it is based on multiple methods including interviews, and multiple informants; it provides scores on a dimension of "family discord" ranging from exceptionally positive interactions across family relationships to exceptionally negative, and it has sound psychometric qualities. Thus, the primary hypothesis is that A carriers of *OXTR* SNP rs53576 will be more likely to show high levels of BPD symptoms under chronically negative family conditions compared to low levels of BPD among those exposed to positive environmental conditions, and will be more likely to differ from GG carriers raised in either environment. Analyses will control for depressive symptoms at the time of assessment of BPD symptoms. No specific gender differences are predicted but gender patterns will be explored. Ethnicity is also taken into account given differences in allele frequencies and behavioral correlates of *OXTR* reported in the literature (e.g., Bakermans-Kranenburg & van IJzendoorn, 2014).

METHOD

PARTICIPANTS

The current sample consisted of 385 youth (235 females, 150 males) who provided genetic samples between the ages of 22 and 25, and who participated in a longitudinal study of children of depressed or never-depressed mothers, with the original goal of studying risk predictors and outcomes in the youth. A total of 815 families were initially identified and studied at age 15, drawn from the Mater University Study of Pregnancy (MUSP) birth cohort study of health and development in families with children born between 1981 and 1984 at the Mater Misericordiae Mother's Hospital in Brisbane (Queensland), Australia (Keeping et al., 1989). The 815 families were selected from women who had a probable history of depression during the child's early life, based on multiple testings with a depression questionnaire between pregnancy and child age 5, and a random sample of never-depressed women. Depression status was later confirmed by diagnostic evaluation. A total of 706 of the 815 were followed up at age 20, and all available youth were recontacted when they were between 22 and 25 to obtain biological samples for genetic analyses. A total of 444 provided blood samples, but the current study is based on the 385 who also had participated in both the age 15 study and age 20 follow-up, and who completed depression questionnaires and personality disorder interviews at age 20, as described below.

The sample was 92.5% Caucasian, 4.2% Asian, and 3.3% Other, with participants raised in largely working/lower middle class families; 67% of mothers were married to the fathers of the children at age 15. There were no differences between the youth participating in the current borderline

gene-environment analyses and those not participating on youth depression status by 15, $\chi^2(1, 815) < 1$, $p = .67$, maternal depression status by 15, $\chi^2(1, 815) < 1$, $p = .72$, borderline symptomatology at 20, $t(697) = .23$, $p = .82$, or the family discord variable at 15 (described below), $t(814) = 1.31$, $p = .19$. The only difference was that females were more likely to participate in the genetic sampling than males, $\chi^2(1, 815) = 39.29$, $p < .001$.

PROCEDURES

Participants, their mothers, and their fathers (if available) completed interviews and questionnaires separately and independently in their homes when the youth turned 15. All interviews were conducted blind to the mothers' diagnostic history. Subsequently, participants and mothers were again studied when the youth turned 20, and youth were re-contacted for the DNA collection between the ages of 22 and 25. All interviewers were graduate students in psychology, trained in interview protocols to high standards of reliability. Participants gave written informed consent for each procedure, and all protocols were approved by the institutional review boards of the University of Queensland, University of California, Los Angeles, Emory University, and (for the genetic study) the Queensland Institute of Medical Research Genetic Epidemiology Laboratory. Maternal depression (major depression and dysthymic disorder during the child's lifetime to age 15) was diagnosed using the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995). Further details of the original sampling ascertainment and mothers' diagnoses are reported in Hammen and Brennan (2001).

MEASURES

Youth Borderline Personality Disorder (BPD) Symptomatology. BPD criteria were assessed at age 20 using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders, Version 2.0 (SCID-II; First et al., 1994). The SCID-II is a semi-structured interview containing 140 items organized by Axis II diagnosis. Following the First and colleagues' (1994) recommended administration procedures, the interview was preceded by administration of the corresponding SCID-II self-report questionnaire (yes/no), which features items included in the SCID-II interview. Interviewers thus probed only those items that participants had endorsed on the self-report form (First et al., 1994), and rated each item as absent (0) present-subthreshold; (1) present-threshold; or (2) depending on their judgment of whether the examples provided by participants met full or subthreshold criteria. Across the entire age 20 sample and all personality disorder symptoms, inter-rater reliabilities based on a randomly selected sample of 34 respondents yielded kappa coefficients ranging from .76 to 1.0 (median = .96).

For BPD, the SCID-II interview dimensional (total numeric) score for the genotyped sample was 2.36 ($SD = 4.05$). Seventeen individuals (4.4% of

the sample) met full diagnostic criteria for BPD (e.g., met at least five *DSM* criteria).

Youth Depressive Symptoms. Current self-reported depressive symptoms at age 20 were assessed using the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). The BDI has excellent psychometric properties and is highly sensitive and specific for the detection of depressive disorders (e.g., Lasa, Ayuso-Mateos, Vazquez-Barquero, Diez-Manrigue, & Dowrick, 2000).

Family Relationship Quality at Age 15. A multi-method, multi-informant index of ongoing family environment quality in early adolescence was created using information from 11 measures of ongoing marital and parental relationship quality obtained at the age 15 assessment from mothers (n = 4), fathers (n = 2), and youth (n = 5). All measures characterized conditions ranging from highly positive to highly negative. Three variables were interviewer-rated scores from the youth and mother versions of the UCLA Chronic Stress Interview (Hammen et al., 1987) covering quality of family relationships in at least the past six months: mother's intimate/romantic relationship, her relationship with the youth, and the youth's relationship with immediate family members. Interviewers assigned ratings ranging from exceptionally positive to highly negative conditions on a 5-point scale, with specific behavioral anchors indicating objective features (e.g., mother-youth relationship quality score of 4: "poor parent-child relationship, lacking in most quality factors such as closeness, communication, problem-resolution; significant conflict; poor monitoring or control"). Reliabilities based on ratings by independent raters yielded intraclass correlations of .82 for the mother–child relationship, .88 for mother's intimate relationship, and .76 for youth's report of family relationship quality. Validity data for adults and youth have been reported elsewhere (e.g., Hammen et al., 1987; Hammen, Brennan, & Keenan-Miller, 2008).

The family environment index also included four questionnaire measures of parents' relationship quality, including items from the 7-item subscale of the Dyadic Adjustment Scale (DAS; Spanier, 1976), each rated from *all the time* to *never* and administered to women currently in relationships and to partners who were available. The scale has good levels of reliability and validity and is useful as a measure of overall relationship quality (Hunsley, Best, Lefebvre, & Vito, 2001). Additionally, mothers and fathers completed a self-report well-validated version of the Modified Conflict Tactics Scale (MCTS; Pan, Neidig, & O'Leary, 1994) covering frequency (rated *often* to *never*) of seven items of psychological or physical coercion (argued heatedly; yelled/insulted; sulked and refused to talk; threw something; pushed, grabbed or shoved partner; hit partner). Four questionnaire measures of youth-rated quality of parent–child interactions included two subscales of the revised Children's Report of Parental Behavior Inventory (CRPBI; Schludermann & Schludermann, 1988), parental acceptance versus rejection (e.g., "gives me a lot of care and attention") and psychological control versus psychological autonomy (e.g., "tells me all of

the things she has done for me"), completed for each parent separately, with each item rated "not like," "somewhat like," or "a lot like." Coefficient αs ranged from .77 to .91. Measures of the CRPBI have been shown to have good reliability and validity (e.g., Safford, Alloy, & Pieracci, 2007).

Each of the 11 family discord scores was standardized across the entire age 15 sample, and averaged across each participant in the current sample to form an overall summary score for family relationship quality (α = .78), which ranged from –1.25 (highly positive conditions) to 1.99 (highly negative conditions) (M = –.01, SD = .57). Evidence that family relationship quality is relatively stable is supported by significant correlations between this measure at age 15 and both an interview-based rating of family relations at age 20 (r = .31, p < .001) and an early family adversity composite that included a measure of marital quality (Hazel, Hammen, Brennan, & Najman, 2008) based on data in the first five years of the youth's life (r = .23, p < .001).

GENOTYPING

Participants who agreed to the blood collection study in 2006–2007 were mailed consent forms, a blood collection pack, and questionnaires, and were instructed to have their blood drawn at a local pathology lab. The blood samples were picked up by courier from the individual and transported to the Genetic Epidemiological Laboratory of the Queensland Institute of Medical Research, where they were stored. For the current study, aliquots of DNA were shipped to UCLA for processing at the Social Genomics Core of the USC/UCLA Biodemography Center. Financial constraints resulted in genotyping a single SNP of *OXTR* selected from prior research as a promising candidate for studies of differences in social cognition and social behavior (e.g., Kumsta & Heinrichs, 2013). The *OXTR* rs53576 polymorphism was assayed by a commercial TaqMan Genotyping Assay (Applied Biosystems, Foster City, CA) performed on an iCycler real-time PCR instrument (BioRad, Hercules, CA) following the manufacturer's specified protocol. Test-retest reliability of duplicated specimens yielded a total genotyping error rate < 1%. Genotype distributions were in Hardy-Weinberg equilibrium, $\chi^2(2, 385) = 0.13$, $p > 0.05$, and were distributed as follows: GG, n = 170 (44.5%); AG, n = 167 (43.4%); and AA, n = 48 (12.5%). There were no significant Caucasian versus Asian differences in distribution of the genotype, χ^2 (2) = 2.52, p = .28. In keeping with the majority of studies reporting more negative social behaviors associated with the A-allele, individuals were recoded into two groups: GG(n = 170) and A/G or AA (n = 215).

RESULTS

Descriptive information is presented in Table 1. There were no significant differences in the distributions of genetic groups by gender or by history of

TABLE 1. Comparison of AG/AA and GG Groups

	AG/AA (*n* = 215)	GG (*n* = 170)	Comparison
Gender (%)			$\chi^2 = 2.32$, $p = .128$
Female	52.8	47.2	
Male	60.7	39.3	
Maternal Depression by 15 (%)	56.7	43.3	$\chi^2 < 1$, $p = .76$
Borderline Symptom Total *M* (*SD*)	2.33 (4.25)	2.46 (3.80)	$t < 1$, $p = .858$
BDI Score *M* (*SD*)	7.43 (8.74)	7.49 (8.04)	$t < 1$, $p = .949$
Family Discord Score *M* (*SD*)	.001 (0.56)	–.012 (0.57)	$t < 1$, $p = .779$

maternal depression in the youth's childhood to age 15. Also, there were no significant differences in the genetic groups on borderline symptom scores, family quality composite scores, or current BDI scores. Borderline symptom scores were strongly correlated with current BDI scores, $r = .55$, $p < .001$; we thus included participants' BDI scores in all main analyses. Gender and maternal depression status made no additional significant contribution to borderline symptoms. Also, analyses were conducted testing Gender × *OXTR*, Gender × Family Quality, and Gender × *OXTR* × Family Quality on BPD symptoms, and none of the gender interaction effects were significant. Therefore, gender was not included in the analyses that follow.

The presence of a gene-environment interaction effect predicting BPD symptoms was tested in an ordinary least squares multiple regression analysis. BDI symptoms at age 20 were entered in Step 1 to control for their effects on borderline symptoms, followed by the main effects of *OXTR* genotype (GG vs. AA/AG) and the family relationship quality composite in Step 2, and the interaction term in Step 3, all relevant variables mean-centered. The overall regression model was significant, $F(4, 380) = 46.17$, $p < .001$, $R^2\text{Adj} = .32$. In the final model, the effect of BDI on borderline symptoms was significant, $B = .25$, $SE = .021$, $p < .001$. There were no main effects of *OXTR* genotype or family quality on BPD symptoms, but family quality and *OXTR* genotype did interact to predict borderline symptoms, $B = 1.55$, $SE = .61$, $p = .011$, R^2 change = .012, $p = .011$. As illustrated in Figure 1, decomposition of this significant interaction revealed a significant, positive association between family quality and borderline pathology for those with AA/AG genotypes while adjusting for BDI, ($B = 1.59$, $SE = .45$, $p < .001$), and a non-significant association for GG participants ($B = -.15$, $SE = .45$, $p = .74$). Supporting the differential susceptibility hypothesis, there were significant differences between the two genetic groups on BPD symptoms at values of Family Discord of –.58 and greater on the positive relationship end of the spectrum and at .80 and above on the negative family relationship end, as illustrated in Figure 2 (graph of regions of significance showing confidence interval bands).

Analyses were repeated as above controlling for maternal depression diagnoses, and the results for the interaction of family quality and *OXTR* genotype were unchanged ($B = 1.59$, $SE = .61$, $p = .009$, R^2 change = .012, $p = .009$). Similarly, analyses were repeated on the sample of Caucasians

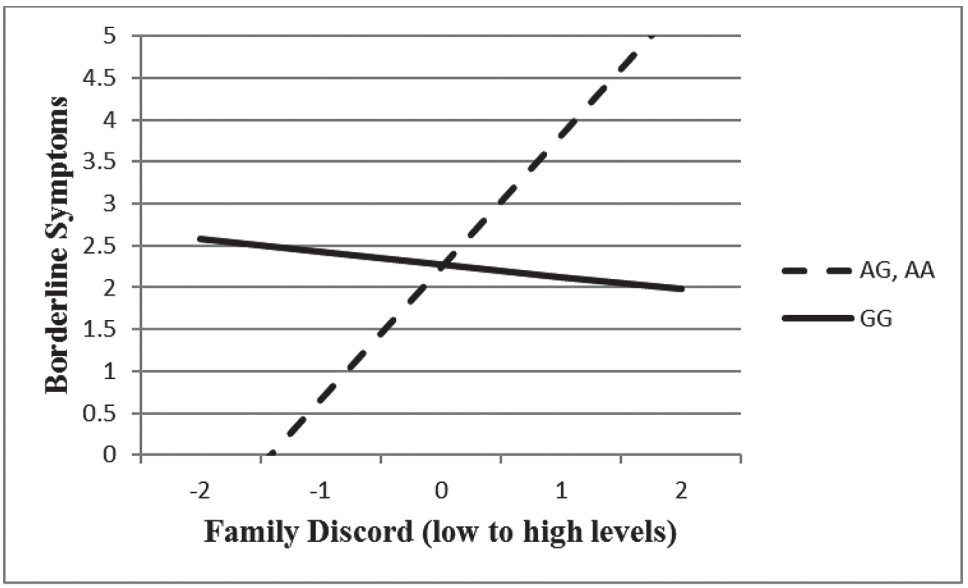

FIGURE 1. Borderline personality disorder symptom level as a function of family discord (ranging from extremely low levels of discord (positive relationships) to extremely high levels of discord (negative relationships)) and GG versus AA/AG genotype of the oxytocin receptor gene, *OXTR* rs53576, controlling for BDI scores.

only, and the results were unchanged (interaction of family quality and *OXTR* genotype, $B = 1.43$, $SE = .63$, $p = .01$, R^2 change = .01, $p = .02$).

DISCUSSION

Interpersonal discord and instability in close relationships are central features of borderline personality pathology, and have been hypothesized to be related in part to the neuromodulator, oxytocin. We explored the relationship of the oxytocin receptor gene (AA and AG genotypes compared to GG genotype) polymorphisms of the rs53576 SNP in interaction with family discord as a predictor of borderline personality symptomatology. The results were consistent with predictions of differential susceptibility, showing that the effects of the *OXTR* rs53576 A-polymorphisms are strongly affected by whether the early family experiences are nurturant and harmonious or discordant and harsh, with no association between borderline symptoms and family discord for GG homozygotes. Analyses ruled out the effects of concurrent depressive symptoms, maternal depression, and gender on the gene-environment interactions predicting BPD.

The findings are generally consistent with clinical and largely retrospective findings of abusive or adverse early environments in BPD patients on

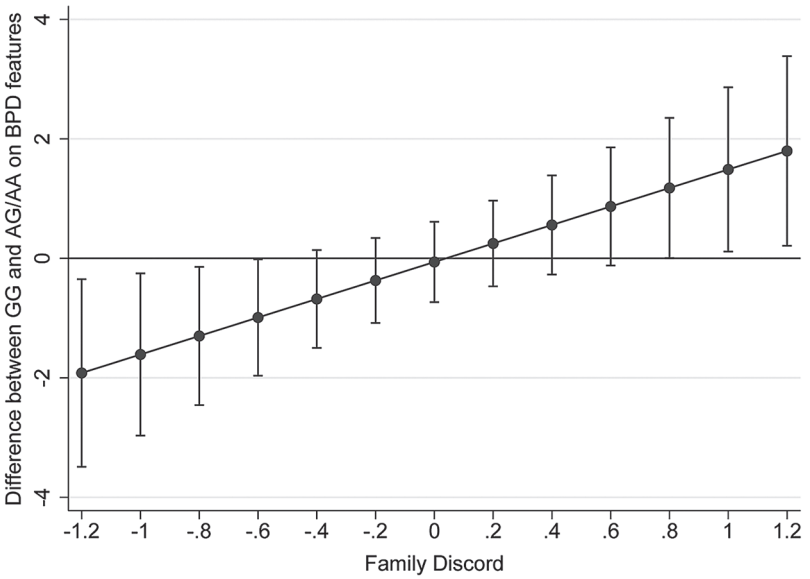

FIGURE 2. Regions of significance of the difference between the GG and AA/AG groups on BPD features are indicated by the vertical confidence interval bands at steps .20 family discord units apart on the x-axis. A confidence interval that does not overlap with the horizontal reference line (0 difference between groups) indicates a statistically significant difference between the genetic groups.

the one hand, and with research suggestive of genetic and neurobiological contributions on the other. However, results dispute a simple "double risk" diathesis-stress hypothesis and suggest that A-allele carriers of this SNP are highly susceptible to the family environment "for better or for worse." However, considerable additional research is needed to identify precise mechanisms, likely both learning/attachment and neurobiological factors, which account for different outcomes under different family quality conditions.

In contrast to the A-carriers of the *OXTR* rs53576 SNP, G homozygotes were largely unaffected by quality of the family relationships in terms of expression of borderline symptoms, with levels in the average range. Future research will be needed to clarify the significance of this pattern, whether it reflects adaptive imperviousness to family quality more generally, or specifically in relation to borderline symptomatology.

The results speak to some of the recent developments in the voluminous body of research on oxytocin and *OXTR.* It must be acknowledged that research on the behavioral effects of exogenous oxytocin has documented a wide variety of social effects from autism to optimism, but reviews indicate considerable variability and inconsistency across studies (e.g., Bartz, Zaki, Bolger, & Ochsner, 2011). Similarly, according to a recent meta-analysis by Bakermans-Kranenberg and van IJzendoorn (2014), many

previously reported main effects of genetic polymorphisms of *OXTR* have not been replicated. Considerable refinement and sharpening of the specific relevant sociobehavioral phenotypes will be needed to more fully understand the relevance of *OXTR* to psychopathology. Also, as Bartz and colleagues have pointed out, inconsistencies in the oxytocin research literature require careful consideration of effects of personal and situational factors that shape oxytocin-related effects (Bartz et al., 2011; see also Bakermans-Kranenburg & van IJzendoorn, 2013). Such disparate patterns may reflect in part operation of gene-environment interactions. In addition, environmental modulation of genetic effects also may extend to the genetic plasticity effects in which positive environments lead to good outcomes for so-called "risk" genotypes.

BPD as currently diagnosed is a complex amalgamation of several facets—not just interpersonal instability, but also negative affect instability particularly around dysphoria, anger, and self-hatred, as well as self-identity disturbances and impulsivity. The focus of this study was a proposed link between social dysfunction and *OXTR* as moderated by family interaction quality, and the results are consistent with formulations of BPD that emphasize the centrality of impaired functioning in intimate relationships (e.g., Stanley & Siever, 2010; see also Bender & Skodol, 2007; Clarkin, Lenzenweger, Yeomans, Levy, & Kernberg, 2007). However, it cannot be determined whether the effects were specific to maladaptive close relationships as such, rather than to related elements of the syndrome of BPD. It will remain for future research to more precisely evaluate the specificity of *OXTR* to the disturbed relationships of those with BPD symptoms. Additionally, it is important to consider that many other genetic variants are likely to be relevant to borderline symptomatology. Carpenter, Tomko, Trull, and Boomsma (2013), for example, reviewed preliminary results from diverse candidate genes in gene-environment interaction analyses of BPD, most of which may be relevant to impulsivity and emotional sensitivity to the environment. These authors also underscore the importance of gene-environment correlation (rGE), and we acknowledge that what is modeled as "environment" in the present study in fact likely reflects, in part, parents' genetically moderated interaction styles, although rs53576 was itself not associated with the family discord composite.

It is noted that the present study found that patterns of *OXTR* × family quality interactions were independent of gender, consistent with Distel and colleagues (2010) in their multivariate genetic models in a twin sample. Although women are far more likely to seek treatment for borderline personality disorder, recent community epidemiology studies suggest equal prevalence among women and men.

In addition to the empirical and conceptual issues that this study cannot resolve, as noted, several significant methodological limitations need to be acknowledged. Foremost among them is the reliance on a single SNP of the oxytocin receptor gene, selected due to its promise in publications in the past few years (e.g., Kumsta & Heinrichs, 2013). Emerging research

makes it clear that not only is the specific functionality of this SNP not known, but also that even multiple SNPs in the same region may not yield the same results (e.g., Walum et al., 2012). Similarly, G × E studies have been controversial (e.g., Karg et al., 2011; Risch et al., 2009), and investigators are warned that extremely and possibly prohibitively large samples are needed to detect and have confidence in findings, and require excellence in measurement and statistical methods, as well as replication in order to be credible. The present study has a moderately large sample, conceptual and biological plausibility supporting its credibility, and high quality measurement of family environment. However, replication is essential, as are extensions that include multiple SNPs of the *OXTR* gene.

The current sample was 20 years of age and was at risk for disorders, especially depression, due to oversampling of maternal depression. Thus, it is possible that results would differ in an unselected community sample, or in an older sample in which borderline symptoms might be more stable and perhaps less affected by the emotional turmoil and changing life conditions that are developmentally prevalent in the transition to adulthood. On the other hand, by clinical definition, this age group is truly at risk for the emergence of various forms of personality disorders—and indeed, most major forms of disorder. It is likely that a high risk sample improved our ability to detect the predicted gene-environment patterns associated with BPD, because of the increased frequency of parenting dysfunction which likely promotes increased BPD levels (and other forms of psychopathology) in genetically susceptible offspring. Of note, maternal depression was itself unrelated to youth BPD symptoms in the present study. Maternal depression does increase the risk of youth depression which is highly comorbid with BPD, but the results for BPD symptoms were robust even while adjusting for depressive symptoms, suggesting that similar results might be likely to be seen in less depressive, less high risk samples as well, provided ample variability in parenting quality. The possibility of gene-environment correlations due to mothers' own possible BPD symptoms affecting family discord is an intriguing question, but genotyping was not carried out for mothers, and this issue remains for future studies. By the same token, it is possible that youths' borderline symptoms may have contributed to family turmoil, although it is likely that marital and parenting dysfunction largely preceded emergence of features of the borderline syndrome, and probably in most cases represented chronically stressful conditions dating from the child's early life.

A further potential limitation is the use of dimensional scores of BPD rather than diagnostic classification. However, this study noted, as have others, that subclinical levels of BPD symptoms are problematic in close relationship functioning and other areas. A subgroup of youth in the current sample have already attained sufficient symptomatology for BPD diagnoses, but the diagnosis sample size is too small to yield meaningful gene-environment results, and it is expected that many high scorers will eventually be diagnosed with borderline personality disorder.

On the positive side, the study employed a relatively large longitudinal sample that was well characterized with respect to family quality, based on contemporaneous rather than retrospective, and multi-method, multi-informant measures of family processes, representing a range from very positive and nurturant relationships to harsh and unsupportive patterns. In addition, the main results for borderline symptom outcomes were independent of co-occurring depressive symptoms. The results suggest that family conditions present a potent factor that interacts with a genetic characteristic presumably tied to affiliative and socioemotional motives and functioning. The findings shed some light on risk factors for the enormously impairing syndrome of borderline pathology, and contribute both to further clarification of the origins of the disorder and also to the future prospect of social cognitive, family process, and emotional regulation interventions that might fruitfully address the treatment or even prevention of BPD.

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*(2), 45–51. doi:10.1097/YPG.0b013e3283643684

Bartz, J. A., & Hollander, E. (2006). The neuroscience of affiliation: Forging links between basic and clinical research on neuropeptides and social behavior. *Hormones and Behavior*, *50*(4), 518–528.

Bartz, J.A., Zaki, J., Bolger, N., & Ochsner, K. (2011). Social effects of oxytocin in humans: Context and person matter. *Trends in Cognitive Sciences, 15*, 301309.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *The Beck Depression Inventory—Second Edition.* San Antonio, TX: Psychological Corporation.

Bender, D. S., & Skodol, A. E. (2007). Borderline personality as a self-other representational disturbance. *Journal of Personality Disorders*, *21*, 500–517.

Brune, M. (2012). Does the oxytocin receptor polymorphism (rs2254298) confer "vulnerability" for psychopathology or "differential susceptibility"? Insights from evolution. *BMC Medicine*, *10*, 38–46.

Carpenter, R., Tomko, R., Trull, T., & Boomsma, D. (2013). Gene-environment studies and borderline personality disorder: A review. *Current Psychiatry Reports, 15*, 336.

Caspi, A., Hariri, A., Holmes, A., Uher, R., & Moffitt, T. (2010). Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry*, *167*, 509–527.

Clarkin, J. F., Lenzenweger, M. F., Yeomans, F. E., Levy, K. N., & Kernberg, O. F. (2007). An object relations model of borderline pathology. *Journal of Personality Disorders*, *21*, 474–499.

Distel, M. A., Hottenga, J. J., Trull, T. J., & Boomsma, D. I. (2008). Chromosome 9: Linkage for borderline personality disorder features. *Psychiatric Genetics*, *18*(6), 302–307.

Distel, M. A., Middledorp, C. M., Trull, T. J., Derom, C. A., Willemsen, G., & Boomsma, D. I. (2011). Life events and borderline personality features: The influence of gene-environment interaction and gene-environment correlation. *Psychological Medicine*, *41*, 849–860.

Distel, M. A., Willemsen, G., Ligthart, L., Derom, C. A., Martin, N. G., Neale, M. C., … Boomsma, D. I. (2010). Genetic covariance structure of the four main features of borderline personality disorder. *Journal of Personality Disorders*, *24*(4), 427–444.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1995). *Structured clinical interview for DSM–IV Axis I disorders.* Washington, DC: American Psychiatric Press.

First, M. B., Spitzer, R. L., Gibbon, M., Williams, J. B. W., & Benjamin, L. (1994). *Structured clinical interview for DSM-IV Axis II personality disorders (SCID-II) (Version 2.0).* New York, NY: Biometrics Research, New York State Psychiatric Institute.

Gunderson, J. G. (2007). Disturbed relationships as a phenotype for borderline personality disorder. *American Journal of Psychiatry*, *164*(11), 1637–1640.

Gunderson, J. G., & Lyons-Ruth, K. (2008). BPD's interpersonal hypersensitivity phenotype: A gene-environment-developmental model. *Journal of Personality Disorders*, *22*(1), 22–41.

Hammen, C., Adrian, C., Gordon, D., Burge, D., Jaenicke, C., & Hiroto, D. (1987). Children of depressed mothers: Maternal strain and symptom predictors of dysfunction. *Journal of Abnormal Psychology*, *96*, 190–198.

Hammen, C., & Brennan, P. (2001). Depressed adolescents of depressed and nondepressed mothers: Tests of an interpersonal impairment hypothesis. *Journal of Consulting and Clinical Psychology*, *69*, 284–294.

Hammen, C., Brennan, P., & Keenan-Miller, D. (2008). Patterns of adolescent depression to age 20: The role of maternal depression and youth interpersonal dysfunction. *Journal of Abnormal Child Psychology*, *36*, 1189–1198.

Hazel, N., Hammen, C., Brennan, P., & Najman, J. (2008). Early childhood adversity and adolescent depression: The mediating role of continued stress. *Psychological Medicine*, *38*(4), 581–589.

Heinrichs, M., & Domes, G. (2008). Neuropeptides and social behaviour: Effects of oxytocin and vasopressin in humans. *Progress in Brain Research*, *170*, 337–350.

Hunsley, M., Best, M., Lefebvre, D., & Vito, J. (2001). The seven-item short form of the Dyadic Adjustment Scale: Further evidence for construct validity. *American Journal of Family Therapy*, *29*, 325–335.

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of General Psychiatry, 68*, 444–454.

Keeping, J. D., Najman, J. M., Morrison, J., Western, J. S., Andersen, M. J., & Williams, G. M. (1989). A prospective longitudinal study of social, psychological, and obstetrical factors in pregnancy: Response rates and demographic characteristics of the 8,556 respondents. *British Journal of Obstetrics and Gynecology, 96*, 289–297.

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., … Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *British Journal of Psychiatry*, *197*(5), 378–385.

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

Lasa, L., Ayuso-Mateos, J., Vazquez-Barquero, J., Diez-Manrique, F., & Dowrick, C. (2000). The use of the Beck Depression Inventory to screen for depression in the general population: A preliminary analysis. *Journal of Affective Disorders*, *57*, 261–265.

Meyer-Lindenberg, A., & Tost, H. (2012). Neural mechanisms of social risk for psychiatric disorders. *Nature Neuroscience*, *15*(5), 663–668.

Pan, H., Neidig, P. H., & O'Leary, K. D. (1994). Male-female and aggressor-victim differences in the factor structure of the Modified Conflict Tactics Scale. *Journal of Interpersonal Violence*, *9*, 366–382.

Paris, J. (2009). The treatment of borderline personality disorder: implications of research on diagnosis, etiology, and outcome. *Annual Review of Clinical Psychology*, *5*, 277–290.

Reich, D. B., & Zanarini, M. C. (2001). Developmental aspects of borderline personality disorder. *Harvard Review of Psychiatry*, *9*, 294–301.

Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., …Merikangas (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression. *Journal of the American Medical Association*, *301*, 2462–2471.

Safford, S. M., Alloy, L. B., & Pieracci, A. (2007). A comparison of two measures of parental behavior. *Journal of Child and Family Studies*, *16*, 375–384.

Schludermann S., & Schludermann E. (1988). *Shortened Child Report of Parent Behavior Inventory (CRPBI-30): Schludermann revision*. Unpublished manuscript, University of Manitoba, Winnipeg, Canada.

Spanier, G. B. (1976). Measuring dyadic adjustment: New scales for assessing the quality of marriage and similar dyads. *Journal of Marriage and the Family*, *38*, 15–28.

Stanley, B., & Siever, L. J. (2010). The interpersonal dimension of borderline personality disorder: Toward a neuropeptide model. *American Journal of Psychiatry*, *167*(1), 24–39.

Tackett, J., Balsis, S., Oltmanns, T., & Krueger, R. (2009). A unifying perspective on personality pathology across the life span: Developmental considerations for the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders. Development and Psychopathology, 21*, 687–713.

Trull, T. J. (2001). Relationships of borderline features to parental mental illness, childhood abuse, Axis I disorder, and current functioning. *Journal of Personality Disorders, 15*(1), 19–32.

Trull, T. J., Distel, M. A., & Carpenter, R. W. (2011). DSM-V borderline personality disorder at the border between a dimensional and a categorical view. *Current Psychiatry Reports*, *13*, 43–49.

Trull, T.J., Jahng, S., Tomko, R. L., Wood, P. K., & Sher, K. J. (2010). Revised NESARC personality disorder diagnoses: Gender, prevalence, and comorbidity with substance dependence disorders. *Journal of Personality Disorders, 24*, 412–426.

Trull, T. J., Useda, J. D., Conforti, K., & Doan, B. T. (1997). Borderline personality disorder features in nonclinical young adults: Two-year outcome. *Journal of Abnormal Psychology*, *106*, 307–314.

Van IJzendoorn, M.H., Belsky, J., & Bakermans-Kranenburg, M.J. (2012). Serotonin transporter genotype 5HTTLPR as a marker of differential susceptibility? A meta-analysis of child and adolescent gene-by-environment studies. *Translational Psychiatry, 2*, e147. doi:10.1038/tp.2012.73

Walum, H., Lichtenstein, P., Neiderhiser, J., Reiss, D., Ganiban, J., Spotts, E., … Westberg, L. (2012). Variation in the oxytocin receptor gene is associated with pair-bonding and social behavior. *Biological Psychiatry*, *71*, 419–426.

Zanarini, M. C. (2000). Childhood experiences associated with the development of borderline personality disorder. *Psychiatric Clinics of North America*, *23*, 89–101.

Zimmerman, M., Chelminski, I., Young, D., Dalrymple, K., Martinez, J., & Morgan, T. A. (2012). Which DSM-IV personality disorders are most strongly associated with indices of psychosocial morbidity in psychiatric outpatients? *Comprehensive Psychiatry*, *53*(7), 940–945.

Zimmerman, M., Rothschild, L., & Chelminski, I. (2005). The prevalence of DSM-IV personality disorders in psychiatric outpatients. *American Journal of Psychiatry*, *162*(10), 1911–1918.