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Oxytocin-related single nucleotide polymorphisms, family environment, and psychopathic traits

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Abstract

Multiple studies have linked oxytocin to social behavior and affiliation-attachment. This research would suggest that oxytocin function may relate to the absence of loving kindness and empathy in psychopathy. The current study examined the associations of three oxytocin-related single-nucleotide polymorphisms (SNPs) and participant-reported childhood invalidating environment with psychopathic traits in community adults, predicting that alleles associated with higher empathy in the literature would relate to lower levels of psychopathic affective traits in particular. Results showed that the *rs53576* SNP on OXTR and cumulative risk alleles across the three SNPs were associated with psychopathic traits, and the interaction between cumulative risk and emotionally-invalidating environment was associated especially with affective deficits of psychopathy. Although this study requires replication in larger samples, results lend support to the role of attachment-related processes in psychopathy.

Keywords

Psychopathy; Oxytocin; Empathy; Affective facet; Genes; Attachment

The clinical construct of psychopathy contains a diverse set of characteristics, including serious empathy deficits, egocentricity, deceitfulness, impulsivity, and antisocial behavior (Hare, 2003). Although there continue to be disagreements as to exactly which traits should define psychopathy (e.g., Lilienfeld et al., 2012; Miller & Lynam, 2012), most models and perspectives similarly emphasize empathy deficits (e.g., meanness; Patrick, Fowles, Krueger, 2009). Furthermore, there are strong conceptual and empirical connections between the primary affective psychopathic traits and empathy deficits in childhood reflected in “callous-unemotional” (CU) traits in children, which are viewed by many as a prevalent developmental predecessor of psychopathy (Frick & Marsee, 2008). From nearly all

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perspectives, empathy deficits and lack of loving kindness loom large in the psychopathy construct.

For generations of researchers, there has been an interest in the possibility that psychopathy may be heavily genetic in nature (e.g., Karpman, 1941) and appears to be heritable (e.g., Larsson, Andershed, & Lichtenstein, 2006), especially its core affective traits (Dhanani et al., 2017). However, relationships between individual genes and traits related to psychopathy (e.g., antisocial behavior) are less robust (see Duncan, Pollastri, & Smoller, 2014 for a review). It now seems extremely unlikely that there is a specific "gene for" psychopathy (cf. Kendler, 2005); however, individual genes may nonetheless be directly related to some of the core features of psychopathy. As such, the current study tested a priori hypotheses that (1) psychopathic traits linked to low empathy relate to three oxytocin-related single-nucleotide polymorphisms (SNPs; OXTR *rs53576* and *rs2254298*, CD38 *rs3796863*) and (2) childhood family emotional invalidation moderates relationships between these genetic variants and psychopathy.

Oxytocin, Empathy, and Psychopathy

Oxytocin is a neurohormone that is synthesized in hypothalamic cells and released into the bloodstream. Researchers have, in recent years, compiled a large body of findings regarding oxytocin's relationship to interpersonal functioning across many domains, such as autism (e.g., LoParo & Waldman, 2015); empathic functioning (e.g., Gong et al., 2017); and perceptions of harm to crime victims (Krueger et al., 2013). In consort, the examination of oxytocin-related SNPs has expanded recently, with many studies reporting a link to affective empathic function and/or prosociality (e.g., Schneiderman, Kanat-Maymon, Ebstein, & Feldman, 2014). One of the SNPs explored in the present study, on the oxytocin receptor (OXTR) gene, *rs53576*, has been especially linked to empathy deficits in prior research. A number of studies (e.g., Huetter et al., 2016) have reported that G carriers are more emotionally empathic than AA carriers, a conclusion which has been meta-analytically confirmed across many studies (Gong et al., 2017).

Two other SNPs, specifically OXTR *rs2254298* and *rs3796863* on the CD38 gene, have been less heavily studied. A small number of studies of OXTR *rs2254298* indicate that carriers of the A allele have higher levels of empathy (Montag et al., 2012; Schneiderman et al., 2014) or higher levels of plasma oxytocin (Feldman et al., 2012). The third SNP of interest, *rs3796863*, has very limited research, although extant studies support the role of the CD38 gene in social and attachment behavior and oxytocin function (Feldman et al., 2012; Higashida et al., 2012). Unfortunately, no data exist on the level of co-segregation of these SNP's, nor whether these SNPs serve overlapping functions in regard to social behavior.

Given oxytocin links to empathy, authors have hypothesized that functioning of oxytocin might be associated with core psychopathic traits (e.g., Moul, Kilcross, & Dadds, 2012). This hypothesis is especially fueled by the fact that psychopathy is strongly characterized by empathy deficits. Within a four-facet model of psychopathy (e.g., Hare & Neumann, 2008), empathic deficits are best captured within the affective facet, characterized by low empathy, lack of remorse, and failure to take responsibility for one's antisocial behaviors. In fact, a

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small number of studies involving children with CU traits have shown relationships with the OXTR gene. For instance, high levels of CU traits have been associated with increased methylation of OXTR (Dadds et al., 2014a; also see Levy et al., 2015) and polymorphisms of OXTR *rs237885* and *rs1042778* (Beitchman et al., 2012; Dadds et al., 2014b). Only one study has examined oxytocin and psychopathic traits in adults (Mitchell et al., 2013) but this study relied upon oxytocin levels in urine, which have been repeatedly found to correlate poorly with central oxytocin function as observed in the bloodstream (e.g., Francis, Kirkpatrick, Wit, & Jacob, 2016). Overall, the empirical support for the role of genetic variation in oxytocin and psychopathy is preliminary.

Oxytocin Gene by Environment Interaction in Psychopathy

A number of studies have indicated that the pro-social and other effects of oxytocin are moderated by attachment dynamics and emotional validation by caregivers (e.g., Bakermans-Kranenburg et al, 2012). Likewise, there is a growing body of research indicating that less emotionally supportive childhood environments are associated with high levels of CU traits and antisocial outcomes in children (Gao et al., 2010; Hawes et al., 2011; Pasalich et al., 2012). Given this background, work has begun to examine the moderating role of oxytocin genes on childhood environment effects. These studies have shown that the "protective" allele (G allele) of OXTR *rs53576* moderates relationships between parental caregiving quality and social/mental health functioning in children and adults (McDonald, Baker, and Messinger, 2016; Reiner, Frieling, Beutel, and Michal, 2016). In contrast, Hygen et al. (2017) observed that change in a child's parenting quality only predicted changes in the child's relationships with teachers if the child was an AA (not G) carrier on OXTR *rs53576*. This emerging inconsistency and the lack of gene-environment studies involving adult psychopathy suggests more research is needed.

Current Study

This study is the first to report oxytocin-related genetic variation across three polymorphisms, and gene by environment effects, in relation to specific facets of psychopathy in an adult sample of community participants with histories of externalizing behaviors. An advantage of our study, over larger scale studies, is more precision in the measurement of the phenotype. Due to replicability concerns in the area of candidate gene studies, hypotheses were generated that explicitly predicted which SNP variants would be associated with specific psychopathic traits. For OXTR *rs53576* and *rs2254298*, we predicted that G and A allele carriers, respectively, would shower lower psychopathy, as per previous empathy study findings on these alleles. For CD38 *rs3796863* SNP, based on very limited evidence (e.g., Feldman et al, 2012), we tentatively predicted that G allele carriers would have higher affective psychopathic traits. We also used a procedure similar to Schneiderman, Kanta-Maymon, Ebstein, and Feldman (2014) to create a cumulative risk score representing the number of identified risk alleles across the three SNPs in relation to psychopathic traits, especially the affective traits. Finally, we explored gene by environment interactions, such that reports by adult participants of poorer emotional support by parents would relate to higher levels of psychopathic traits, especially affective traits, among those with higher risk alleles.

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Method

Participants

The data for this study were collected as part of a larger study on substance use, violence, and psychopathy. The three hundred and twelve participants (134 women) were recruited from the community and legal or treatment agencies (e.g., parole, substance use treatment) and ranged in age from 18 to 62 (M = 34.70; SD = 11.82), although most were in their 30s and 40s. Approximately half (n = 150; 48%) identified as African-American, 36% (n = 112) as Caucasian, 7% as "mixed ethnicity," and another 8% as either Asian, Hispanic, Native American, or other. The overwhelming majority of the participants (85%) had been incarcerated in jail or prison at some point in their lives. All participants provided consent, and all procedures were approved by the Institutional Review Board of the governing institution.

Measures

Psychopathic traits—Psychopathy was assessed according to the Psychopathy Checklist-Screening Version (PCL-SV; Hart, Cox, & Hare, 1995) based on information from a life history interview conducted by trained graduate student interviewers and a review of public of criminal records. We focused on the four-facet model, which breaks the PCL-SV into interpersonal traits (α = .62); affective traits (α = .68); impulsivity and irresponsible lifestyle traits (α = .55); and antisocial behaviors (α = .65). Secondary raters were available for a subset of interviews (n = 184, 57%). Interrater reliability was high for total scores and facets (*ICC*s ranged from .83–.95).

Childhood emotional invalidation—Childhood environment was measured with the Childhood Trauma Questionnaire (CTQ; Bernstein et al, 2003). Participants rated 28 items on a 5-point Likert scale (1= *never true*, 5= *always true*) in relation to experiences and feelings participants had as they were "growing up," across five subscales (sexual abuse, physical abuse, physical neglect, emotional abuse, and emotional neglect). Based on our hypotheses, we combined the emotional neglect and emotional abuse subscales into an "emotional support" variable (α = .89; see Bresin, Finy, & Verona, 2013 for a similar procedure). We summed across items such that higher (relative to lower) scores indicate emotionally invalidating environments.

Genotyping—Genomic DNA was collected from saliva deposited into cryovials, which were quickly placed into a Fisher Scientific low temperature freezer. Once all samples were collected, they were packed with dry ice in an appropriate shipping container and sent to Salimetrics (www.salimetrics.com) for genotyping of the three selected polymorphisms. A TaqMan SNP Genotyping Assay from Applied Biosystems was used to amplify and evaluate the two alleles at *rs53576, rs2254298*, and *rs3796863*. The amplification of a target region on the DNA occurs in the presence of sequence-specific primers and is performed using an Applied Biosystems 7500 Real-Time PCR System.

The breakdown of the OXTR *rs53576* genotypes was 55% G/G, 35% A/G, and 8% A/A, which were in Hardy-Weinberg equilibrium, χ^2 = 2.27, p = .131. As was the breakdown of

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the OXTR *rs2254298* genotypes (69% G/G, 27% A/G, and 2% A/A), $\chi^2 = .01$, $p = .892$, and CD38 *rs3796863* genotypes (25% G/G, 45% G/T, and 29% T/T), $\chi^2 = 2.08$, $p = .149$. None of the allelic distributions significantly differed by gender or ethnicity (all p's > .192), with distributions provided by gender and ethnicity in supplemental materials.

Data Analytic Plan

Our first aim was tested using ANCOVAs, with one SNP (*rs53576, rs2254298, or rs3796863*) included as the between-subject variable (in separate analyses). Age, gender, and ethnicity contrasts (White = 1, African American = 0, and other =−1; White = 0, African American = 1, and other =−1]) were entered as covariates, due to their relationship with the dependent measures. To create cumulative risk scores, we coded the alleles similar to prior research (e.g., Feldman et al., 2012; Montag et al., 2012), such that for *rs53576,* GG = 0, AG = 1, AA = 2; for *rs2254298*: AA/AG = 0, GG = 2; and for *rs3796863*, TT = 0, GT = 1, GG = 2. These scores were added together to create a cumulative risk score variable, with higher scores representing more genetic risk for empathy deficits.

Our second aim, investigating a gene by environment interaction, was tested in multiple regression. Cumulative genetic score along with the family emotional support variable (mean-centered) and their interaction (partialled product term) were entered as independent variables. We followed up significant interactions with simple slopes tests (Aiken & West, 1991). We focused not only on statistical significance but also on effect size estimates (partial η^2, Cohen's d) and their 95% confidence interval (Cumming, 2013).

Results

See Supplemental Table 1 for descriptive statistics. For main effects of oxytocin genes, significant results were found for total and affective psychopathy facet scores (see Supplemental Table 2 for mean scores on psychopathy facets by SNPs, and full regression results). First, there was a significant and small effect of OXTR *rs53576* for total scores, $F(2, 304) = 3.45$, $p = .030$, partial $\eta^2 = .022$, and the affective facet, $F(2, 304) = 4.30$, $p = .014$, $\eta^2 = .027$. Consistent with hypotheses, AA carriers had higher total and affective traits than AG (total: $d = .36$, 95% CI [−.06, .78]; affective: $d = .43$, 95% CI [.01, .85]) and GG carriers (total: $d = .49$, 95% CI [.08, .89]; affective: $d = .56$, 95% CI [.15, .96]), with small to medium effect sizes. Second, the effect of OXTR *rs2254298* was not significant, with almost zero mean difference for total ($d = .03$) and affective facet ($d = -.08$). Third, the effect of CD38 *rs3796863* was small and not significant for total, $F(2, 304) = 2.84$, $p = .060$, partial $\eta^2 = .018$, and affective, $F(2, 304) = 2.68$, $p = .070$, $\eta^2 = .010$, although the mean differences were in the expected direction (GT/GG vs TT, total: *d's* = .22 and .28, affective: *d's* = .27 and .27). Finally, there was a significant small effect of cumulative risk for total scores, $F(1, 304) = 5.32$, $p = .021$, partial $\eta^2 = .013$, and marginal for affective traits, $F(1, 304) = 3.72$, $p = .054$, $\eta^2 = .012$, with more risk alleles relating to higher PCL total and affective scores.[1] Very few significant effects were found for the psychopathy facets besides affective, with the exception of two effects. OXTR *rs53576* was related to the lifestyle facet, $F(2, 304) = 4.25$, p

[1]Analyses conducted separately by ethnicity category yielded the same pattern of results, with similar allele effect sizes and in the same direction for each ethnic group (e.g., for total scores, *rs53576* partial $\eta^2 = .02–.04$; *rs3796863* partial $\eta^2 = .02–.05$).

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= .015, η^2 = .027. AA carriers had higher lifestyle traits than AG (*d* =.53, 95% CI [.16, .98]) and GG carriers (*d* = .57, 95% CI [.16, .98]), but AG and GG did not differ, *d* = .04, 95% CI [−.19, .28]. For the antisocial facet, there was a small and significant effect for the cumulative risk score, with higher cumulative risk related to higher antisocial behavior, $F(1, 304) = 7.59$, $p = .006$, $\eta^2 = .024$.

For the second set of analyses involving cumulative alleles by environment interactions, results were consistent with predictions. We found significant interactions between cumulative risk score and childhood family emotional invalidation for psychopathy total, *b* = .04, *t*(303) = 2.08, *p* = .038, *partial* η^2 = .014, and affective facet, *b* = .01, *t*(303) = 2.11, *p* = .035, *partial* η^2 = .014. Figure 1 displays the estimated regression lines for these interactions.[2] For total PCL scores and affective traits, the results showed that there was a small, non-significant negative relationship between cumulative risk scores and psychopathy at low emotional invalidation, *b* = −.49, *t*(303) = −1.03, *p* = .304, *partial r* = −.058; *b* = −.17, *t*(303) = −1.19, *p* = .234, *partial r* = −.068, and a small significant positive relationship at high emotional invalidation, *b* = 1.37, *t*(303) = −2.77, *p* = .005, *partial r* = .157; *b* = .40, *t*(303) = 2.68, *p* = .007, *partial r* = .152. Thus, being a carrier of combinations of oxytocin-related alleles represented risk for the affective deficits of psychopathy when combined with reports of an invalidating family environment.[3]

Discussion

Ours is the first study to provide early support for associations between oxytocin-related SNPs and psychopathic traits in an at-risk adult sample. In regard to the individual effects of the selected SNPs, our hypotheses were generally supported for *rs53576*, the SNP with the most evidence in the literature in regard to empathy. The G allele was associated with lower total psychopathy scores, affective facet scores, and lifestyle facet scores. Our hypotheses were not supported, however, for OXTR *rs2254298*, and results for CD 38 *rs3796863* generally followed expected patterns, although most did not reach conventional levels of significance. Thus, the findings for the individual SNPs are considered preliminary and less reliable; they also require replication. Given the small effects attributable to individual genotypes in regard to any psychological attribute, the combined presence of risk alleles, relative to individual genotypes, is more likely to influence phenotype expression.

And indeed, most consistent was the cumulative risk effect of these three SNPs, for which our hypotheses were generally supported. The cumulative risk score was associated with heightened psychopathic traits, specifically the affective and antisocial behavior facet. The results with these two psychopathy facets in particular are not surprising, as there is a clear conceptual link between (a) low empathy and (b) engaging in antisocial/violent behaviors. The robustness of results for the cumulative risk score across outcomes may explain why it,

[2]Analyses of moderation were conducted with the *rs53576* SNP instead of the cumulative risk score as moderator; it did not interact with invalidating environment for PCL total (*p* = .402) or affective traits (*p* = .736).

[3]We conducted a number of additional analyses to determine the robustness of the significant interactions (e.g., Dick et al., 2015). Both interactions were significant when including quadratic terms for gene and environment. Additionally, both interactions were also still significant when including all covariate by gene and covariate by environment interactions. These results provide further support for the interactions. Finally, the interaction was very similar across ethnic groups, as were the simple effects of genotype at high levels of emotional invalidation.

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but not individual SNPs, moderated the effects of invalidating childhood environment on total and affective psychopathy traits. The gene by environment interaction supported our hypothesis that affective psychopathic traits are correlated with, and perhaps shaped by, poor parent-child attachment dynamics among those with a combination of oxytocin alleles linked to low empathy. It should be noted that this connection could be due to a passive or evocative gene-by-environment correlation, which needs to be ruled out. Importantly, the pattern of results for individual SNPs, cumulative risk score, and interaction was similar across ethnic groups, suggesting that the functional significance of the alleles generalize across ethnic groups.

Given that oxytocin is implicated in a host of social behaviors, its potential role in psychopathy likely stems from its influence on bonding, attachment, and empathy. Alterations in oxytocin functioning and genetic coding related to oxytocin can influence the ways in which individuals relate others, including those individuals expressing other traits (e.g., impulsivity, fearlessness) that, combined, can manifest as psychopathic.

Compared to some other small sample candidate gene studies, this study has a number of strengths. For example, the participant sample was characterized by much higher rates of (a) psychopathic traits and behaviors and (b) childhood emotional adversity than are typically found in research samples. Well-validated instruments were used for both. This gave us greater power to be able to evaluate the connection between these kinds of elements and variation in oxytocin-related SNPs. The main limitation of the study involved the focus on individual SNPs in a relatively small sample. Individual SNP-based genetic studies are limited, due to the very small variance that, at best, can be accounted for by any particular polymorphism. As a result, high levels of caution should be exercised when placing confidence in small candidate gene studies like the current study and replication is needed before these results are confirmed. In an attempt to somewhat account for such issues, we supplemented significance testing with effect sizes and confidence intervals.

In sum, the current analysis revealed support for the role of certain oxytocin SNPs, particularly *rs53576* on the OXTR gene and combination alleles, in regard to affective deficits in psychopathy. Although the effects were mostly small in size, the study of oxytocin may lead to valuable insights regarding empathic deficits and callous-unemotional traits, including the role of childhood attachment dynamics. This study's results encourage further exploration of this intriguing line of research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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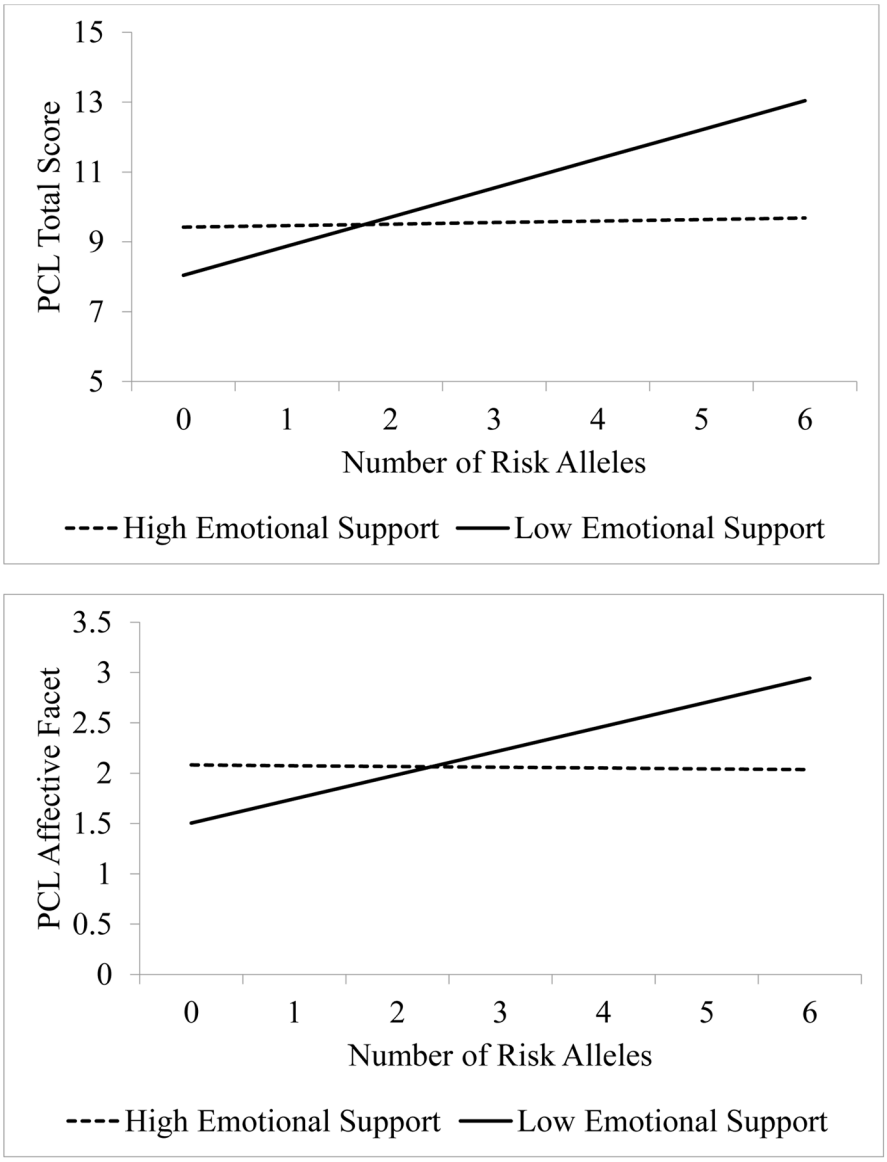

Figure 1.
Psychopathy-Checklist Total Score (Top Panel) and Affective Facet (Bottom Panel) as a function of Emotional Environment and Cumulative Risk Alleles