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Amygdala responses to salient social cues vary with oxytocin receptor genotype in youth

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ABSTRACT

Depression, anxiety, and posttraumatic stress disorder are linked to altered limbic morphology, dysregulated neuroendocrine function, and heightened amygdala responses to salient social cues. Oxytocin appears to be a potent modulator of amygdala reactivity and neuroendocrine responses to psychosocial stress. Given these stress regulatory effects, there is increasing interest in understanding the role of oxytocin in vulnerability to stress-related clinical disorders. The present study examines the impact of a common functional variant within the oxytocin receptor (*OXTR*) gene (rs2254298) on structure and function of the amygdala in a high-risk sample of urban, low-income, minority youth with a high incidence of early life stress (ELS). Compared to G/G homozygotes, youth carrying the *OXTR* A-allele showed increased amygdala volume, reduced behavioral performance, and heightened amygdala response during two functional magnetic resonance imaging (fMRI) tasks that involved viewing socially-relevant face stimuli. Higher amygdala response was related to ELS in A-allele carriers but not G/G homozygotes. These findings underscore a series of relations among a common oxytocin system gene variant, ELS exposure, and structure and function of the amygdala in early life. Heightened amygdala response to salient social cues in *OXTR* A-allele carriers may elevate risk for emotional psychopathology by increasing amygdala involvement in disambiguating environmental cues, particularly for individuals with ELS.

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1. Introduction

In addition to its well-known role in promoting pro-social behavior, the neuropeptide oxytocin is increasingly recognized for its ability to attenuate anxiety and stress reactivity. Oxytocin administration reduces self-reported anxiety (Bartz and Hollander, 2006) and levels of cortisol (Heinrichs et al., 2003), the hormonal end product of the hypothalamic-pituitary-adrenal (HPA) axis. Thus, there is a growing interest in understanding the role of oxytocin in stress-related clinical disorders, such as anxiety, depression, and posttraumatic stress disorder (PTSD).

Variation in the oxytocin system may be an important factor in predicting risk for the development of psychiatric disorders, particularly in the context of early adversity. For example, children and adolescents exposed to early life stress (ELS), one of the most significant predictors of psychiatric illness (Green et al., 2010), exhibit lower levels of peripheral oxytocin following physical contact with their mothers (Wismer Fries et al., 2005). Further, a common variant in the oxytocin receptor gene (*OXTR*; rs2254298) has been found to interact with ELS to predict symptoms of anxiety and depression in young participants (Thompson et al., 2011). Given that sensitivity of the oxytocin system appears to be set in early life (Meinlschmidt and Heim, 2007), there is a critical need to better understand the role of oxytocin in mediating psychiatric risk during childhood and adolescence, when stress-

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related clinical disorders frequently emerge.

In the brain, oxytocin has marked inhibitory effects on the amygdala (Bale et al., 2001; in adult males), a limbic region that plays a critical role in biasing information processing by orienting attention to salient, emotionally-laden, and biologically-relevant stimuli in the environment (Le Doux, 1998). The amygdala is also posited to govern the processing of potentially-relevant but ambiguous information, such as faces lacking interpretable emotional content (Wright and Liu, 2006). Higher amygdala response to ambiguous faces is thought to reflect a greater tendency to perceive these cues as threatening (Forbes et al., 2011), and heightened amygdala responses to ambiguous faces are reported in individuals with anxiety (Cooney et al., 2006) and in youth at risk for depression (Dearing and Gotlib, 2009). These findings suggest that altered sensitivity of the amygdala to socially-relevant cues might contribute to the functional pathophysiology of these conditions (LeDoux, 1998).

Neuroimaging studies report that intranasal oxytocin administration dampens amygdala reactivity and reduces coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear (Domes et al., 2007; Kirsch et al., 2005; in adult males but not females). Thus, it is possible that individual variation in the oxytocin system may impact amygdala sensitivity, which may, in turn, alter the way information in the environment is processed. Consistent with this notion, adult (Inoue et al., 2010) and adolescent (Furman et al., 2011) carriers of the rs2254298 *OXTR* A-allele variant are reported to have increased amygdala volume, a neural marker thought to confer elevated emotional reactivity and anxiety (Holmes et al., 2012). These findings highlight the amygdala as an important neural substrate for *OXTR*-mediated risk for emotional psychopathology. However, it is unknown whether there is an association between oxytocin and amygdala function in early life. It is possible that increased sensitivity of the amygdala in childhood may contribute to larger amygdala volumes observed in individuals carrying the rs2254298 *OXTR* A-allele.

The present study tests the effects of the *OXTR* polymorphism rs2254298 on amygdala volume and functional responses in youth. We evaluated amygdala function using two tasks that involve processing socially-relevant face stimuli to examine the generalizability of effects across tasks. Amygdala responses to social ambiguity and during conditions of varying cognitive load were evaluated. We predicted that A-allele carriers would show heightened amygdala responses to ambiguous social cues and a lower ability to dampen amygdala responses during higher cognitive load. We also predicted that A-allele carriers would show increased amygdala volume, as observed in prior work.

Current theory suggests that A-allele carriers may be more sensitive to environmental exposures and thus more vulnerable to the harmful effects of ELS (Brune, 2012). Emerging empirical data in youth support this notion, showing greater increases in anxiety and depressive symptoms in *OXTR* rs2254298 A-alleles than in youth with a G/G genotype following exposure to ELS (Thompson et al., 2011). Given research showing that ELS is associated with enhanced amygdala reactivity (e.g., Marusak et al., in press), we evaluated the hypothesis that young A-allele carriers are more sensitive to the effects of ELS on amygdala function. Here, we investigate interactive effect of ELS and *OXTR* genotype on amygdala activity. We do so in a sample of high-risk (i.e., urban, low-income, minority) youth with a high prevalence of ELS. This demographic was selected for several reasons. First, prior research shows not only that trauma frequency is more extreme in African Americans living in impoverished urban areas, but also that the negative consequences of trauma may be more severe (Alim et al., 2006). For instance, African American urban residents who experience trauma are nearly two times more likely to develop PTSD than their lower risk counterparts (Goldmann et al., 2011). Lower income is also a significant predictor of more severe emotional psychopathology following trauma (Lowe et al., 2014). Thus, the present sample is considered high-risk due to additive effects of trauma frequency and stress burden.

2. Material and methods

2.1. Participants

The present study reports on 55 children and adolescents, ages 7–15, recruited through classified advertisements posted on Craigslist (Metro Detroit), printed flyers, Wayne State University (WSU) community postings, and area pediatric mental health clinics/service providers. Although 61 participants were initially included, 6 were excluded due to image artifacts that prohibited analysis of gray matter volume (GMV), as described below. Study exclusion criteria included history of neurological injury, significant learning disorder, English as a second language, or presence of magnetic resonance imaging (MRI) contraindications. Prior to the scan session, participants and parents were shown a brief video to prepare them for their MRI scan (available at: www.brainnexus.com/links). Full-Scale IQ was determined using the Kaufman Brief Intelligence Test, Second Edition (Kaufman and Kaufman, 2004). Written informed consent and child/adolescent assent were obtained for all participants and their parents as approved by the WSU Institutional Review Board.

2.2. Early life stress and internalizing symptomology

ELS was measured using the 24-item Traumatic Events Screening Inventory (TESI; Ippen et al., 2002), a parent report of potential stressors experienced by the child (e.g., assault, witnessing violence, family member arrested). Number of early life stressors was calculated by summing the positively endorsed items on the TESI. Anxiety and depressive symptoms were assessed using the 41-item Screen for Child Anxiety Related Emotional Disorders (SCR; Birmaher et al., 1997) and the 10-item Children's Depression Inventory (CDI; Kovacs, 1992), respectively. A visual analog scale (VAS) was used to obtain an average rating of fear/anxiety during the MRI visit (repeat measures at 30 minute intervals) as previously described (Thomason et al., 2013).

2.3. Pubertal development

Pubertal development was assessed with the self-report Tanner stages questionnaire (Marshall and Tanner, 1968). Following prior work (Forbes et al., 2011), participants were categorized as pre/early (Tanner stages 1–2) or mid/late (stages 3–5) pubertal.

2.4. OXTR polymorphism genotyping

Details of genotyping methods are provided in the Supplemental Material. Of the 55 total participants, 34 were carrying two G alleles (G/G homozygotes), 17 were carrying one A and one G allele (A/G), and four were carrying two A-alleles (A/A). Individuals heterozygous and homozygous for the A-allele were combined into an 'A-allele carrier' group ($n=21$). Genetic distribution across the sample was in Hardy–Weinberg equilibrium, $\chi^2=1.163$, $p=0.56$ (www.ncbi.nlm.nih.gov/snp).

2.5. MRI data acquisition

MRI data were acquired with a Siemens 3.0T MRI scanner (MAGNETOM Verio system, Siemens Medical Solutions) equipped with a 12-channel head coil (WSU School of Medicine MR Research Facility). Blood-oxygen level dependent (BOLD) fMRI data were acquired using a T2*-weighted echo-planar imaging sequence with the following parameters: TR: 2000 ms, TE: 25 ms, 29 axial slices, field of view: 220×220 (whole brain coverage), flip angle: 90°, voxel size: $3.44 \times 3.44 \times 4$ mm^3. High-resolution anatomical images were acquired using a three-dimensional T1 magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following parameters: TR: 1680 ms, TE: 3.51 ms, 176 axial slices, field of view: 256×256 (whole brain coverage), flip angle: 9°, voxel size: $0.7 \times 0.7 \times 1.3$ mm^3.

2.6. Structural image processing

Prior to analysis, T1-weighted anatomical images were screened for motion artifacts (ghosting, blurring). Individual participant whole-brain intracranial masks were generated and manually corrected for $N=61$ anatomical images by a trained rater (N.K.) using the interactive editing tools in the BrainSuite software package (v.13a4; Shattuck and Leahy, 2002; http://brainsuite.org/). Intrarater reliability was

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