



## Salivary oxytocin in clinically anxious youth: Associations with separation anxiety and family accommodation



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### ABSTRACT

Clinical anxiety disorders in youth are common and associated with interpersonal behaviors including reliance on parents for family accommodation, or changes that parents make to their own behaviors to help the youth avoid anxiety related distress. The neuropeptide oxytocin is associated with the regulation of anxiety and of close interpersonal behavior leading to the hypothesis that oxytocinergic functioning plays a role in youth anxiety and its disorders, and the resulting family accommodation. To test this hypothesis salivary OT from 50 youth with primary DSM-5 anxiety disorders was assayed. A multi-source/multi-method anxiety assessment including semistructured interviews with youth and mothers, rating scales, and behavioral observations was used to assess anxiety disorders and symptoms, and family accommodation. Youth with separation anxiety disorder had significantly lower salivary OT levels than clinically anxious youth not diagnosed with separation anxiety disorder. Salivary OT levels were significantly negatively correlated with separation anxiety symptoms based on both youth- and mother-ratings. Anxious behavior displayed by youth during interactions with their mothers was associated with lower salivary OT levels in youth. Maternal ratings of family accommodation were negatively associated with salivary OT levels in youth. Results support the role of the oxytocinergic system in youth anxiety and its disorders and in parental involvement in youth anxiety through family accommodation. OT may be particularly important for diagnoses and symptoms of separation anxiety, which is inherently interpersonal in nature. Findings have potentially important implications for assessment and treatment of anxiety in youth.

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### 1. Introduction

Systems for threat detection and anxiety regulation overlap in the brain with systems for social attachment and affiliative behavior, with shared neurochemistry and overlapping circuitry (see MacDonald and Feifel, 2014 for a recent review). Social and attachment-related stimuli, as well as danger and threat-related stimuli activate shared neural circuitry, signaling the hypothalamic neuropeptide system, and producing behavioral responses of approach and avoidance, respectively (Damsa et al., 2009; LeDoux, 2003; Paulus and Stein, 2006). In infancy and childhood in particular, child–parent proximity and attachment behaviors provide

a safety signal, linking threat avoidance systems to attachment-related approach (Hofer, 1994; Porges, 2003).

Anxiety disorders in human youth are common (Costello et al., 2005; Messer and Beidel, 1994) and characterized by interpersonal behaviors such as heavy reliance on parents for help in regulating and avoiding feelings of anxiety, a process known as family accommodation (Benito et al., 2015; Lebowitz et al., 2013; Thompson-Hollands et al., 2014). Family accommodation helps to alleviate the anxious youth's distress in the short term but can maintain youth anxiety over time (Lebowitz et al., 2013; Peris et al., 2008). The neuropeptide oxytocin (OT) plays important roles for both the regulation of anxiety and the modulation of close interpersonal behaviors (Bethlehem et al., 2013; Carter, 2003; Feldman, 2015; Feldman et al., 2007; MacDonald and Feifel, 2014; Rilling and Young, 2014), suggesting that OT may be implicated in pediatric anxiety disorders and in family accommodation. Past work provides preliminary research evidence for a link between OT and

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anxiety symptoms but the current study is the first to examine peripheral OT levels in youth with anxiety disorders.

Carson et al. (2015) assayed cerebrospinal fluid (CSF) and plasma collected from ten youth (ages 6–18) who were undergoing CSF-related medical procedures (e.g., lumbar puncture) and examined their respective associations with parents' ratings of their children's trait anxiety symptoms. Youths' OT levels in both CSF and plasma were significantly negatively associated with the parents' ratings. Other investigative groups have also found significant negative correlations between anxiety symptoms and plasma OT levels in different segments of the adult population including women with fibromyalgia (Anderberg and Uvnas-Moberg, 2000), clinically depressed men and women (Scantamburlo et al., 2007), and nursing mothers (Stuebe et al., 2013). Weisman et al. (2013) examined plasma OT levels in 473 non-clinical adults (41.5% males), and found that males showed a significant negative correlation between plasma OT levels and trait anxiety.

Research linking peripheral OT levels to anxiety symptoms has generally focused on global symptom ratings (e.g., trait anxiety). Given OT's role in interpersonal behavior it may be fruitful to examine peripheral OT levels across different domains of youth anxiety and its disorders. Separation anxiety in particular straddles the line between anxiety and close interpersonal behavior, as separation from attachment figures is the primary trigger for the anxiety symptoms (American Psychiatric Association, 2013). Parental involvement is also more inevitable in separation anxiety disorder compared to other anxiety disorders, and youth and mothers report particularly high levels of family accommodation in cases of separation anxiety disorder (Lebowitz et al., 2014b, 2013). No studies have examined peripheral OT levels in youth or adults with separation anxiety disorder, but one study by Eapen et al. (2014) found that ratings of separation anxiety in 57 pregnant women were significantly negatively correlated with plasma OT levels from the same women 3 months post-partum.

The current study is the first to investigate peripheral OT levels in youth anxiety and its disorders, including family accommodation of the anxiety by mothers. The study used a multi-source/multi-method anxiety assessment strategy, including semi-structured diagnostic interviews, youth self-rating scales, mother-rating scales, and independent coded observer ratings of youth anxious behavior, to examine overall symptom severity and specific diagnoses and domains of anxiety.

The study hypotheses were that youth salivary OT levels would be negatively correlated with severity of youth anxiety symptoms, as assessed through the multi-source/multi-method anxiety assessment (Silverman and Ollendick, 2005). Youth salivary OT levels were also hypothesized to be negatively correlated with the degree family accommodation, as rated by mothers and youth. Higher levels of association were expected in youth with separation anxiety, compared to other anxiety disorders and symptoms, because of the interpersonal nature of separation anxiety disorder.

## 2. Materials and methods

### 2.1. Participants

Participants were 50 clinically anxious youth aged 7–16 years (mean age = 11.86 years; SD = 3.19; 55% females) and their mothers, who presented consecutively to a large specialty anxiety disorders research clinic. All youth met DSM-5 (American Psychiatric Association, 2013) criteria for a primary anxiety disorder. The primary diagnoses included: generalized anxiety disorder (GAD, 30%), social anxiety disorder (SoA, 28%), separation anxiety disorder (SAD, 22%), specific phobia (SP, 15%), and panic disorder (PD, 5%). Overall, including both primary and non-primary diagnoses, 68% of

youth had GAD ( $N = 34$  aged 7–17), 65% had SoA ( $N = 32$ , aged 7–17), 32% had SAD ( $N = 16$ , aged 7–15), 22% had SP ( $N = 11$ , aged 7–17), and 13% had PD ( $N = 7$ , aged 13–17). Psychiatric medications taken by youth included a typical antipsychotics ( $N = 3$ ), antidepressants ( $N = 6$ ), and stimulants ( $N = 1$ ).

Non-anxiety disorder comorbid diagnoses included attention deficit hyperactivity disorder (20.6%), major depression (10.3%), oppositional defiant disorder (5.9%), and conduct disorder (1.5%). All participants were enrolled in a regular educational setting. English was the primary language spoken in most (93.1%) of the homes with the remainder having Spanish as primary language. Youth were predominantly White (83.3%) and non-Hispanic (94.5%), with a minority being African American (6%), Asian (2%), or of mixed ethnic background.

The Institutional Review Board at the Yale University School of Medicine approved this study. Upon arrival, study procedures were explained and signed informed consents and assents were obtained from mothers and youth, respectively. Youth and mothers were then separately administered a semi-structured diagnostic interview and rating scales. Youth provided a salivary sample for analysis and then youth and mothers participated in a brief, four-minute dyadic interaction during which they planned a 'fun day' together, which was videotaped for subsequent behavioral coding. A second saliva sample was collected from the youth after the dyadic interaction.

### 2.2. Assessment of youth anxiety and family accommodation

The presence of a primary DSM-5 anxiety disorder diagnosis was established using the *Anxiety Disorders Interview Schedule—Children and Parent (ADIS-C/P)*, administered separately to the child and the mother (Silverman et al., 2001). Severity of youth anxiety symptoms was assessed using respective youth and mother versions of the *Multidimensional Anxiety Scale for Children (MASC2)*, a 50-item rating scale for anxiety in youth that contains subscales for particular domains of anxiety including: separation anxiety, social anxiety, physical symptoms, harm avoidance, generalized anxiety, and obsessive–compulsive symptoms (March, 2013). MASC has been shown to have good validity as a self-rated indicator of anxiety severity across the school age (March, 1997) and several studies have confirmed the factorial structure of the MASC and its ability to distinguish particular domains of anxiety (Baldwin and Dadds, 2007; Grills-Tauchel et al., 2008; March et al., 1999). Family accommodation was assessed using respective youth and mother versions of the *Family Accommodation Scale Anxiety (FASA)* that includes a total accommodation score based on 9 items and subscales for participation in symptom driven behavior (e.g., "How often did you assist your child in avoiding things that might make him/her more anxious"), and modification of family routines and schedules (e.g., "Have you modified your work schedule because of your child's anxiety") (Lebowitz et al., 2014b, 2013). The FASA also includes one additional item that assesses the degree to which the accommodations are distressing to the parent, and three items relating to negative child reactions to not being accommodated. Previous research demonstrated the validity of FASA a child-rated indicator of family accommodation for children between the ages of 6–17 (Lebowitz et al., 2015). Youth and mothers also participated in a brief videotaped interaction, which was independently coded for overt anxious youth behaviors using the child anxiety scale from the widely used Coding Interactive Behavior system (Feldman, 1998). Child anxiety was coded on a scale from 1 to 5 based on the presence, frequency, and severity of overt anxious behaviors (e.g., nail biting, excessive fidgeting, verbal expression of current fear or anxiety). As in previous research (Feldman, 2010), a uniform prompt was provided instructing the dyad to 'plan their

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