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# 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.



## 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-Taquechel 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

best day together.' Coders were trained to reliability and blind to all clinical information. Inter-rater reliability was $r = 0.79$.

### 2.3. Sample preparation and immunoassay

Salivary OT provides an easy and non-invasive method of examining peripheral OT levels, although the coordination between various peripheral measure remains an area of research (Weisman et al., 2012). Earlier research has demonstrated the link between salivary and plasma measures of OT (Feldman et al., 2011), and salivary OT is elevated after intranasal OT administration (Weisman et al., 2012).

Saliva was collected using Salivettes (Sarstedt, Rommelsdorf, Germany). Saliva samples were collected between 4PM and 6PM. Participants did not eat for 2 h and did not drink for 30 min, prior to the saliva collection. Two samples were collected from each participating youth, 7 min apart. Samples were stored at −20 °C until centrifuged twice, 2 days apart, at 4 °C at 1500 × g for 20 min. Liquid samples were kept at −80 °C, lyophilized for 10 days, and stored at −20 °C. On the assay day, the dry samples were reconstituted in water and concentrated ×4 before immunoassay.

In numerous past research studies we measured peripheral OT levels using an ELISA kit from Assay Designs® (Feldman et al., 2010a, 2011, 2012; Gordon et al., 2008; Weisman et al., 2013). That kit is no longer available (Assay Designs having been purchased by Enzo®). The Enzo® (NY, USA) OT kit used in the current study is less sensitive to small concentrations of OT, necessitating careful sample preparation with the following modifications relative to our previous procedure: samples were centrifuged twice; delicate lyophilization maintaining constant refrigeration to slow the drying; and reconstitution of the samples in water prior to assay. No standard OT concentration values exist as yet for the new kit and caution must be exercised in interpreting absolute values.

Measurements were performed in duplicate and the concentrations of samples were calculated using Matlab-7 according to relevant standard curves. The intra-assay and inter-assay coefficients of variability are less than 14.7%.

### 2.4. Statistical analysis

Study data were managed and analyzed using SPSS20. Comparison of mean salivary OT concentrations across anxiety disorder diagnoses was determined using independent sample *t*-tests, controlling for the multiple tests using Holms Bonferroni (Holm, 1979). Because of the high comorbidity between anxiety disorders which is common in clinically anxious samples (Costello et al., 2005; Walkup et al., 2008) *t*-tests compared those with and without each disorder, regardless of whether the disorder was the primary diagnosis or a secondary anxiety diagnosis.

Associations between salivary OT levels and parent and child ratings of overall anxiety and MASC2 subscales for the various anxiety domains, as well as ratings of family accommodation were determined using Pearson bivariate correlations. We also conducted a hierarchical linear regression with salivary OT levels as the dependent variable to determine the relative contribution of the various predictors including demographic variables, anxiety measures, and family accommodation.

## 3. Results

Table 1 presents clinical sample characterization, as well as relations between study variables. Mother and youth ratings of youth anxiety and family accommodation were consistent with those found in other clinical samples of anxious youth reflecting the clinical nature of the sample (RUPP Anxiety Study Group, 2002). Salivary OT levels ranged from 6 pg/ml to 64 pg/ml with a distribution that was not significantly different from normal (K–S test = 0.15, $p > 0.05$) though with moderate positive skewness (1.2, SEM = 0.34) and kurtosis (1.4, SEM 0.68). Male and female youth did not differ significantly on mean salivary OT levels or on any of the study variables, and use of psychiatric medications was not associated with salivary oxytocin levels. Child age was significantly positively correlated with child salivary OT levels ($r_{48} = 0.40$, $p < 0.01$). Salivary OT levels were measured twice, before and after a brief 4 min mother–youth dyadic interaction, and the two samples were significantly positively correlated ($r = 0.51$, $p < 0.001$) and did not differ significantly. Six youth did not produce enough saliva for analysis the second time due to dry mouth. Because of this, and because the mother–youth dyadic interaction has potentially direct bearing on upward or downward regulation of the OT system, in particular in the context of separation anxiety, we used the first measurement (before the dyadic interaction) in the study analyses.

### 3.1. Salivary oxytocin levels and youth anxiety symptoms

#### 3.1.1. Group comparisons by anxiety disorder diagnosis

Youth with separation anxiety disorder had significantly lower mean salivary OT levels (16.7 pg/ml, SD = 7.6) than anxious youth not meeting criteria for separation anxiety disorder (26.8 pg/ml, SD = 15.6) ($t_{48} = 2.61$, $p < 0.01$). No other anxiety or non-anxiety diagnosis was associated with significant differences in child salivary OT levels. Youth with separation anxiety were predictably younger than anxious youth without separation anxiety ($t = 2.9$, $p < 0.01$) and youth age was thus included as a predictor of youth salivary OT levels in the subsequent multivariate regression model.

#### 3.1.2. Youth self-rated anxiety

Salivary OT levels were significantly negatively correlated with child MASC2 ratings of separation anxiety symptoms ($r_{48} = -0.38$, $p < 0.01$; 95% CI: 0.11–0.59; partial correlation controlling for age: $r_{partial} = -0.30$, $p < 0.05$), but not significantly associated with other domains of youth self-rated anxiety or total MASC scores (see Fig. 1).

#### 3.1.3. Mother-rated youth anxiety

Child salivary OT levels were significantly negatively associated with overall child anxiety and several indices of anxiety domains (separation anxiety; generalized anxiety; social anxiety). However, after correcting for the multiple correlations, only separation anxiety scores were significantly associated with youth salivary OT levels ($r_{48} = -0.40$, $p < 0.01$; 95% CI: 0.14–0.61; partial correlation controlling for age: $r_{partial} = -0.29$, $p < 0.05$; see Fig. 2).

#### 3.1.4. Coded behavioral observation of child anxiety

Child anxiety, as coded by independent blinded raters, was significantly negatively associated with child salivary OT levels ($r_{48} = -0.447$, $p < 0.01$; 95% CI: 0.20–0.65; partial correlation controlling for youth age $r_{partial} = -0.37$, $p < 0.05$). Table 1 summarizes the association between youth's salivary OT levels and the various clinical measures.

### 3.2. Salivary oxytocin levels and family accommodation of child anxiety

#### 3.2.1. Mother-rated family accommodation

Youth salivary OT levels were significantly negatively associated with overall level of mother-rated family accommodation on FASA ($r_{48} = -0.34$, $p < 0.05$; 95% CI: 0.07–0.56) and the participation subscale of FASA ($r_{48} = -0.44$, $p < 0.01$; 95% CI: 0.18–0.64). Youth salivary OT levels were not significantly associated with maternal ratings of distress associated with the accommodation or with negative youth consequences if not accommodated. Total

**Table 1**
Clinical characteristics of anxious youth ($N = 50$) and correlations with salivary oxytocin levels, with significance and 95% confidence intervals.

| | Mean | SD | Correlation with youth salivary oxytocin | $p$ (95% CI) |
|---|---|---|---|---|
| Youth salivary oxytocin (pg/ml) | 22.9 | 14.0 | – | – |
| Youth Anxiety: Mother-Report (MASC[a]) | | | | |
| Total | 62.6 | 22.6 | −0.30* | 0.04 (0.02–0.53) |
| Separation | 11.1 | 6.1 | −0.40** | 0.006 (0.14–0.61) |
| Generalized | 15.4 | 5.3 | −0.31* | 0.03 (0.03–0.54) |
| Social | 15.9 | 6.3 | −0.34* | 0.02 (0.07–0.56) |
| Obsessive–compulsive | 5.7 | 6.3 | −0.18 | 0.21 |
| Physical/somatic | 10.7 | 6.6 | −0.1 | 0.52 |
| Harm avoidance | 16.5 | 4.0 | −0.03 | 0.85 |
| Youth Anxiety: Self-Report (MASC[a]) | | | | |
| Total | 71.4 | 26.9 | −0.09 | 0.55 |
| Separation | 11.5 | 5.5 | −0.38** | 0.009 (0.11–0.59) |
| Generalized | 14.8 | 6.0 | −0.12 | 0.41 |
| Social | 14.1 | 7.1 | 0.04 | 0.77 |
| Obsessive–compulsive | 12.1 | 6.9 | −0.9 | 0.54 |
| Physical/somatic | 14.6 | 8.1 | 0.03 | 0.83 |
| Harm avoidance | 16.2 | 4.4 | −0.06 | 0.69 |
| Youth anxiety-behavioral coding[b] | 2.3 | 0.9 | −0.45** | 0.006 (0.20–0.65) |
| Family Accommodation Mother-Report (FASA[c]) | | | | |
| Total | 15.6 | 8.2 | −0.34 | 0.19 (0.07–0.56) |
| Participation | 10.5 | 4.9 | −0.44 | 0.002 (0.18–0.64) |
| Modification | 5.1 | 4.0 | −0.17 | 0.26 |
| Distress | 1.4 | 1.0 | −0.12 | 0.44 |
| Consequences | 4.9 | 3.6 | −0.26 | 0.85 |
| Family Accommodation Youth-Report (FASA-CR[c]) | | | | |
| Total | 11.4 | 7.0 | −0.05 | 0.76 |
| Participation | 8.3 | 4.7 | 0.04 | 0.78 |
| Modification | 3.1 | 3.0 | 0.17 | 0.26 |
| Distress | 1.1 | 1.2 | −0.50** | <0.001 (0.26–0.68) |
| Consequences | 5.8 | 3.4 | −0.33* | 0.02 (0.06–0.56) |

[a] Multidimensional Anxiety Scale for Children.
[b] Behavioral coding of youth anxiety during mother–youth dyadic interaction was on a scale of 1–5.
[c] Family Accommodation Scale Anxiety (Child Report).
* $p < 0.05$.
** $p < 0.01$.

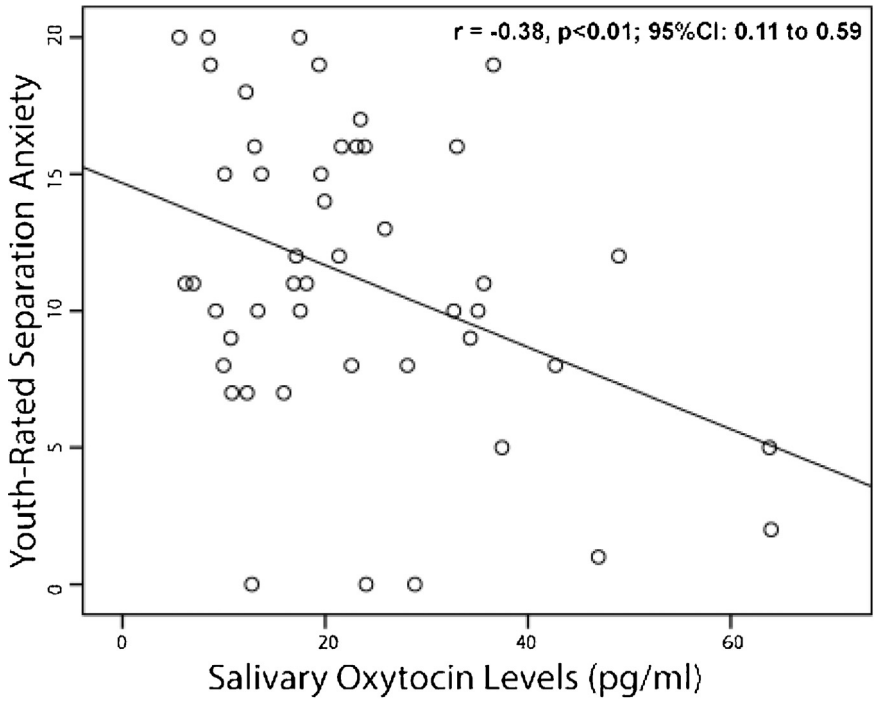


**Fig. 1.** Youth ratings of youth separation anxiety, and youth salivary oxytocin levels ($N = 50$).

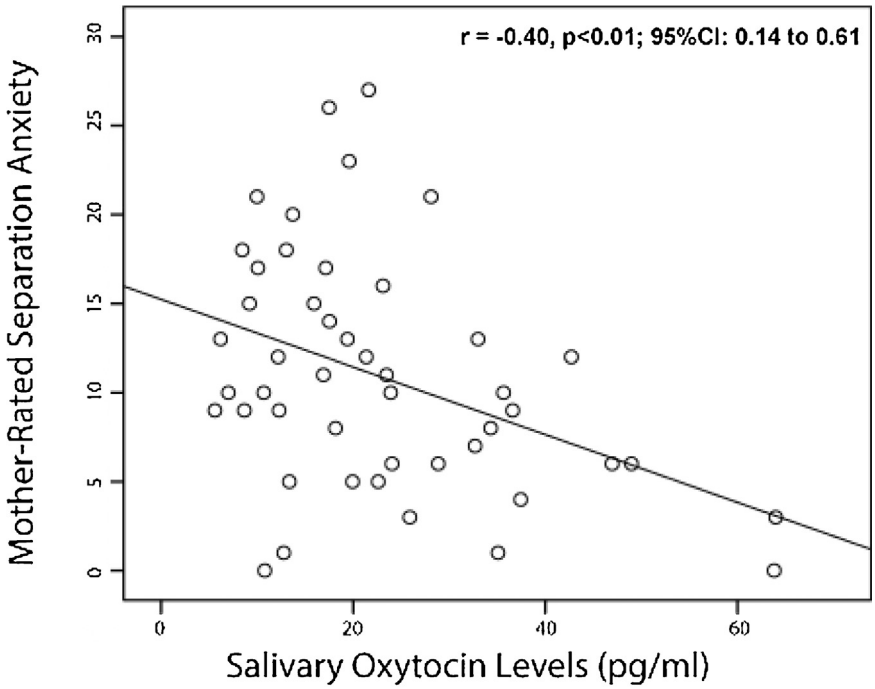


**Fig. 2.** Mother ratings of youth separation anxiety, and youth salivary oxytocin levels ($N = 50$).

mother-rated FASA scores were negative associated with youth age ($r_{48} = -0.30$, $p < 0.05$).

### 3.2.2. Youth-rated family accommodation

Youth salivary OT levelswere significantly negatively associated with youth's ratings of negative consequences such as becoming distressed or anxious when not accommodated ($r_{48} = -0.33$, $p < 0.05$; 95% CI: 0.06–0.56), but was not significantly associated with youth-ratings of family accommodation levels.

### 3.3. Hierarchical multiple regression

We conducted hierarchical linear multiple regression to examine the relative contributions of the three families of variables found to be correlated with child salivary OT levels: child demographic variables (age), child level variables (anxiety indices), and interpersonal or family-level variables (accommodation indices). Including child age in the multiple regression allowed us to examine the effect of the other variables above and beyond the relation between child salivary OT levels and child age. Youth salivary OT level was the dependent variable. Variables were entered in the equation in three blocks. Youth age was entered first as the predicting variable. Next the three anxiety measures that were most significantly related to child salivary OT levels were entered into the equation: child-rated separation anxiety subscale of MASC2, mother-rated separation anxiety subscale of MASC2, and one dummy variable coded to reflect meeting or not meeting criteria for SAD based on the clinician administered ADIS. Finally, in a third block we included the two family accommodation indices that correlated with child salivary OT levels: mother-rated participation subscale of FASA, and child-rated negative consequences of not being accommodated. Collinearity between all variables was acceptable (VIF < 1.5 and tolerance below 1.0 for all variables). The overall regression model was significant ($F = 5.74$, $p < 0.01$) and explained 36.5% of the variance in child salivary OT levels (adjusted $R^2 = 0.30$). Each step in the model significantly increased the explanatory power of the regression. The first equation, including only child age, yielded $R^2$ of 0.16 ($F = 8.49$, $p < 0.01$). Adding the separation anxiety measures, significantly increased the $R^2$ to 0.24 ($F_{Change} = 4.20$, $p < 0.05$). Adding the family accommodation scores, further significantly increased the $R^2$ to 0.36 ($F_{Change} = 3.90$, $p < 0.05$). Table 2 summarizes the final third-step regression model.

## 4. Discussion

To our knowledge, this is the first investigation of oxytocinergic functioning in youth with anxiety disorders. Convergent evidence from a multi-method/multi-source anxiety assessment supports the role of OT in two key areas of youth anxiety that involve close interpersonal behavior: separation anxiety and family accommodation.

Youth with separation anxiety disorder had lower salivary OT levels than youth not meeting criteria for separation anxiety disorder. Likewise, using a dimensional approach, elevated separation anxiety based on both youth and mother ratings, was associated with lower youth salivary OT levels. Anxious behavior displayed by youth during interactions with their mothers was also associated with lower youth salivary OT levels.

Another key interpersonal feature of youth anxiety that was associated with youth salivary OT levels was family accommodation, or the degree to which mothers were involved in helping the youth to avoid distress related to the anxiety symptoms. Mothers of youth with lower salivary OT levels reported higher levels of family accommodation, suggesting that lower OT levels in youth are associated with greater reliance on primary attachment figures for the regulation or avoidance of internal distress and anxiety. Youth self-ratings indicated that greater distress at not being accommodated was associated with lower youth salivary OT levels, further supporting the link between OT and reliance on parents for accommodation in anxious youth.

Evidence of a complex role for the oxytocinergic system in the regulation of distress and the modulation of close interpersonal behavior in humans as well as other mammals has been mounting for several years (Carter, 2003; Feldman, 2015; Feldman et al., 2007; MacDonald and Feifel, 2014). But the current report is the first to examine salivary OT levels in clinically diagnosed youth

**Table 2**
Unstandardized and standardized values from final step in hierarchical multiple regression model predicting salivary oxytocin in clinically anxious youth ($N = 50$) from youth age, separation anxiety, and family accommodation ($R = 0.365$, Adjusted $R^2 = 0.30$, $F = 5.74$, $p < 0.01$).

| Independent variable | B | SE | BETA |
|---|---|---|---|
| Youth age | 1.14 | 0.69 | 0.24 |
| Child rated separation anxiety (MASC2) | −0.39 | 0.40 | −0.15 |
| Mother-rated separation anxiety (MASC2) | 0.20 | 0.41 | 0.10 |
| Presence of separation anxiety disorder (ADIS C/P) | −3.62 | 4.80 | −0.12 |
| Mother-rated family accommodation (FASA participation subscale) | −0.84 | 0.44 | −0.30 |
| Child-rated consequences of not being accommodated (FASA) | −1.1 | 0.60 | −0.25 |

*Note*: MASC2 = Multidimensional Anxiety Scale for Children; ADIS C/P = Anxiety Disorders Interview Schedule for Children, Child and Parent Versions; FASA = Family Accommodation Scale Anxiety.

with anxiety disorders, and opens up exciting new directions in this line of research. Human anxiety symptoms are frequently conceptualized as having their roots in highly conserved mammalian 'defense systems' which overlap with systems for social signaling, attachment and bonding (Belzung and Philippot, 2007; Feldman et al., 2013; MacDonald and Feifel, 2014). Pediatric anxiety rests at this overlap, as fear and distress in young mammals activate the attachment system and are regulated interpersonally through the provision of protective and soothing behaviors by caregivers. Separation anxiety disorder exemplifies this, as separation from the primary attachment figure is the key trigger for the anxiety symptoms and the presence of the attachment figure is the main means of reducing or avoiding the anxiety. The specific associations between separation anxiety and salivary OT levels in the current data underscore the interplay between systems for anxious arousal and systems for social signaling and attachment.

Further research is crucially needed to advance understanding of the causal chains linking lower salivary OT levels to separation anxiety disorder. Factors affecting the attachment system, such as early rearing environment and parental psychopathology, may contribute to reduced or disrupted functioning of the oxytocinergic system and to greater anxiety about separation from attachment figures (Carter et al., 2001; De Wolff and van Ijzendoorn, 1997; van, 1995). Insecure maternal attachment has been found to predict childhood anxiety and insecure attachment in children, which can manifest as separation anxiety (Colonnesi et al., 2011; Manassis et al., 1994). Data linking early adversity to lower peripheral OT levels in adulthood may support this hypothesis (Opacka-Juffry and Mohiyeddini, 2012).

It is also possible that lower salivary OT levels signal more reliance on caregivers and more attachment-oriented responses to anxiety in general. Rather than separation being the trigger for the anxiety, the links between OT, separation anxiety, and family accommodation may reflect *how* anxiety is managed (i.e., through parental proximity and family accommodation) rather than *what* triggers it.

Parental variables may also be implicated in shaping offspring's oxytocinergic functioning and in contributing to, or maintaining, symptoms of childhood anxiety. Parental peripheral OT has been linked to parenting behavior, which in turn has been shown to influence the oxytocinergic system of infants, (Apter-Levy et al., 2013; Feldman et al., 2010b) and family accommodation has been found to mediate the link between anxiety in mothers and youth (Jones et al., 2015).

Further research is also needed to understand more fully the neurobiological determinants of the levels of OT measured in saliva. Although salivary OT level has been widely used as a potential biomarker in human studies for a range of social behaviors for nearly a decade (Carter et al., 2007), questions remain concerning the extent to which salivary OT is reflective of central or even plasma levels of OT. It is well known that OT can be released in a coordinated fashion, within the brain and from the posterior pituitary (Neumann and Landgraf, 2012). As a consequence, it is not unexpected that OT has broad and synchronized behavioral and physiological consequences. Conceptualizations suggesting coordination between central and peripheral OT (Ross and Young, 2009) are supported by several lines of research including associations between peripheral OT levels and allelic variability on the OXTR gene (Apter-Levy et al., 2013; Feldman et al., 2012), and increased salivary OT levels up to seven hours after intranasal OT administration (van Ijzendoorn et al., 2012; Weisman et al., 2012) which is thought to have central effects (Burri et al., 2008), though this remains contested. A recent study of intranasal administration in rats and mice indicated that it reached behaviorally relevant areas of the brain, including the amygdala, with a parallel change in plasma OT levels (Neumann et al., 2013). Significant associations between plasma and salivary OT levels (Feldman et al., 2010a, 2011; Hoffman et al., 2012) have also been reported but this has not been a universal finding (Javor et al., 2014). While methodological considerations may well account for these discrepant findings, the nature of the links between central and salivary OT release are not fully understood and require further investigation. We speculate, however, that the innervation of the salivary glands by the autonomic nervous system and the engagement of the autonomic nervous system in mediating stress response in animal models may play an important role (Grippo et al., 2012; Neumann and Landgraf, 2012; Quintana et al., 2013).

The link between oxytocinergic functioning, separation anxiety, and family accommodation suggests novel directions for the treatment of anxiety in youth. Recently, treatments have been developed that target the reduction of family accommodation as a means of treating anxiety in youth (Lebowitz, 2013; Lebowitz et al., 2014a; Thompson-Hollands et al., 2014). The current results support the biological modulation of family accommodation and suggest that peripheral OT measurement may help to identify cases where a focus on family accommodation may be particularly valuable. Lower salivary OT levels were associated with greater resistance on the part of the youth to parental non-accommodation, suggesting the need for more intensive parent training to cope with the ensuing difficulties. High family accommodation has been associated with poorer treatment outcomes in OCD, (Garcia et al., 2010) and clinical experience suggests this is the case in anxiety disorders as well. Research is needed to determine whether peripheral OT level can be a useful predictor or moderator of treatment outcomes. Another intriguing potential clinical implication is the possibility of intranasal OT administration as a treatment for separation anxiety in youth. Studies have preliminarily examined the potential efficacy of intranasal OT for anxiety disorders, with mixed results, but have not yet focused on youth or on separation anxiety disorder (Feifel, 2011; Guastella et al., 2009; MacDonald and Feifel, 2012). OT administration is also being explored as a possible treatment for other disorders characterized by abnormal interpersonal behavior, such as autism (Andari et al., 2010). Replication of the current results would suggest the possibility of exploring OT administration as an independent or adjunct treatment strategy for

youth with separation anxiety, particularly in cases of high family accommodation.

In addition to our incomplete understanding of the determinants of salivary OT release (see above), the current results must be interpreted in light of certain additional limitations. First, the current study was not powered to examine the impact of comorbid nonanxiety disorders on salivary OT levels. The presence of comorbid disorders was not associated with significant differences in salivary OT levels in the current sample, but it is not possible to rule out potential interactions between anxiety and other disorders in relation to salivary OT levels. Relatedly, a larger sample would allow a more comprehensive examination of the various anxiety disorders, using a multifactorial model rather than the *t*-tests based on the presence of individual diagnoses included in the current study. The current results did not show a relation between gender and OT levels, but previous research has suggested divergent roles for peripheral OT in anxiety in males compared to females and a larger sample would allow for a fuller examination of this question (Domes et al., 2010; Kubzansky et al., 2012; Weisman et al., 2013). Second, focusing on clinically anxious youth with well-characterized symptomatology is strength of this study but additional research is necessary to determine whether or not similar patterns of associations exist in the nonclinical populations. The absence of a control comparison group is therefore a meaningful and important limitation. Third, the current study focused on anxious children and their mothers, as the role of mothers has been more thoroughly explored in child anxiety and in family accommodation. However, paternal variables including the presence, anxiety, accommodation, and oxytocinergic functioning of fathers also need to be explored, particularly in light of some evidence for the role of fathers in shaping or preventing child anxiety (Bogels and Phares, 2008). Fourth, in light of the evidence for multi-generational and possibly epigenetic influences on the development of the oxytocinergic system (Apter-Levy et al., 2013; Feldman et al., 2013; Kappeler and Meaney, 2010; Rilling, 2009) research is needed on the interplay between maternal oxytocinergic functioning, maternal care, and child salivary OT levels and anxiety symptoms. Such research is currently underway in our laboratory. Longitudinal research would also be invaluable in ascertaining the causal chains linking lower peripheral OT levels to the development and accommodation of childhood anxiety symptoms, in particular separation anxiety.

## 5. Conclusions

Salivary OT levels are negatively associated with anxiety symptoms in clinically anxious youth and specifically associated with two interpersonal domains of youth anxiety: separation anxiety and family accommodation, or parental involvement in the youth's anxiety symptoms.

## Conflict of interest

Dr. Lebowitz receives royalties from John Wiley and Sons, and Vandenhoeck & Ruprecht and research support from the National Institutes of Health and the Brain and Behavior Research Foundation. Dr. Leckman receives royalties from John Wiley and Sons, McGraw Hill, and Oxford University Press and research funding from the National Institutes of Health. Dr. Feldman receives research funding from the Simms–Mann Foundation and the Harris Foundation and the German–Israeli Foundation, and the US–Israel Bi-National Science Foundation. Dr. Silverman receives funding from National Institutes of Health. Drs. McDonald and Zagoory-Sharon have no financial interests to disclose.

## Contributors

Dr. Lebowitz had the idea for the study, collected the biological specimens and behavioral data, analyzed the data, and together with other authors prepared the manuscript.

Dr. Leckman contributed to the study conceptualization and planning, and to biological specimen collection and analysis, and contributed to manuscript preparation.

Dr. Feldman helped with study planning and methodological considerations, provided training and oversight for behavioral data analysis and for immunoassay, and contributed to manuscript preparation.

Dr. Zagoory-Sharon handled specimen preparation, conducted the immunoassay and was responsible for oxytocin quantification, and contributed to manuscript preparation.

Dr. McDonald contributed to analysis of behavioral data and to manuscript preparation.

Dr. Silverman contributed to study conceptualization and planning, and provided oversight of clinical assessment and characterization, and contributed to data analysis and manuscript preparation.

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