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RESEARCH ARTICLE

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Oxytocin response to youth–mother interactions in clinically anxious youth is associated with separation anxiety and dyadic behavior

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Background: Anxiety disorders are common in youth and cause significant distress and impairment to the individual and family. Oxytocin (OT), a nine amino acid peptide, is implicated in anxiety regulation and modulation of close interpersonal and attachment behavior. Anxiety disorders have been linked to low levels of salivary OT in youth. Research has also linked oxytocinergic functioning to social support, warm contact, and bonding, and indicated that contact with attachment figures stimulates OT response. We examined OT response to a brief, positive youth–mother interaction in clinically anxious youth. We investigated whether quality of the youth–mother interaction as well as the presence of particular anxiety disorders, are associated with youth OT response.

Method: Salivary OT from 41 youth with primary DSM-5 anxiety disorders was assayed before and after a 7-min youth–mother interaction that was later systematically coded by two reliable coders. Youth and mothers also completed rating scales of youth anxiety symptoms.

Results: Affective touch, maternal sensitivity, maternal intrusiveness, youth engagement, and youth initiative all contributed significantly to predicting youth OT response. Repeated measures analyses showed that when affective touch was high youth had greater OT response. OT response was positively associated with the presence of separation anxiety disorder (SAD) and with child ratings of separation anxiety.

Conclusions: The findings highlight the importance of maternal and dyadic behavior patterns to oxytocinergic response in clinically anxious youth, shed light on the association between OT and SAD, and point to possible intervention strategies.

KEYWORDS

anxiety/anxiety disorders, child/adolescent, neurohypophyseal hormones, oxytocin, parenting/parent behavior

1 | INTRODUCTION

Anxiety disorders are common in children and adolescents (referred to hereon as youth), affecting up to one third of individuals by age 18 (Costello, Egger, Copeland, Erkanli, & Angold, 2011). Anxiety disorders are highly comorbid and show both homotypic and heterotypic continuity over the course of development, underscoring the importance of specific anxiety disorder diagnoses, as well highlighting the role of underlying factors that impact multiple anxiety disorders (Costello, Egger, & Angold, 2005; Ferdinand, Dieleman, Ormel, & Verhulst, 2007). In particular, there is evidence for the continuity of separation anxiety, social anxiety, and generalized anxiety in childhood (Ferdinand et al., 2006; Ferdinand et al., 2007).

Anxious youth rely heavily on family accommodation by parents to avoid or alleviate anxiety symptoms, epitomizing the overlap between systems for anxiety regulation and systems for social and affiliative behavior that is common across mammalian species (Benito et al., 2015; Chang et al., 2013; Lebowitz, Scharfstein, and Jones, 2015;

Lebowitz et al., 2015; Lewinsohn, Holm-Denoma, Small, Seeley, & Joiner, 2008). Immature and altricial mammals depend on parents for protection from threat and regulation of aversive internal arousal. Species-specific patterns of offspring signaling and parental response have evolved from this dependence, along with corresponding brain circuitry and neurochemistry (Feldman, Monakhov, Pratt, & Ebstein, 2016; MacDonald, & Feifel, 2014). At the behavioral level, youth with anxiety disorders rely on attachment figures to feel safe and secure, and parents respond by attempting to alleviate the child's anxiety and remove perceived threats. Separation anxiety disorder (SAD), in particular, exemplifies the interplay between anxiety and social processes in childhood. The central feature of SAD is fear or anxiety concerning separation from attachment figures (American Psychiatric Association, 2013), reflecting the child's perception of separation as a signal of threat and/or the child's dependence on attachment figures for the regulation of anxiety. The high levels of family accommodation reported by parents of children with SAD, including providing excessive reassurance and modifying their own behavior to remain in the child's proximity, reflect the parental attachment response but are also known to cause considerable distress to parents, and contribute to conflictual parent–child relationships (Lebowitz, Leckman, Silverman, & Feldman, 2016; Lebowitz et al., 2015).

Recent research points to a role for the oxytocin (OT) system as one factor maintaining the pattern of overlapping anxiety regulation and interpersonal behavior in clinically anxious youth (Feldman, 2016; Feldman et al., 2016; Lebowitz et al., 2016). OT is a nine amino acid peptide with a long evolutionary history originating from ancient peptides over 600 million years ago (Donaldson, & Young, 2008; Feldman et al., 2016). OT is implicated in anxiety regulation and in modulating close interpersonal and attachment behavior, underscoring its potential for informing the interpersonal aspects of youth anxiety disorders (de Oliveira et al., 2012; Hoge, Pollack, Kaufman, Zak, and Simon, 2008; Opacka-Juffry, and Mohiyeddini, 2012; Uvnas-Moberg, 1997; Weisman, Zagoory-Sharon, Schneiderman, Gordon, & Feldman, 2013).

A recent study reported on the first investigation of peripheral OT levels in youth with anxiety disorders (Lebowitz et al., 2016). Salivary OT levels were negatively correlated with severity of youth anxiety symptoms, with observations of youth anxious behavior, and with ratings of family accommodation. Separation anxiety was the domain of anxiety symptoms most strongly associated with youth salivary OT levels, and youth diagnosed with separation anxiety had the lowest OT levels.

One study has examined peripheral OT levels in clinically anxious adults, focusing specifically on social anxiety disorder (SoA), and compared them to healthy nonanxious adults (Hoge et al., 2008). Plasma OT levels did not differ significantly between the groups, but were associated with the severity of social anxiety symptoms in the clinical group. More recently, Eapen et al., 2014 examined plasma OT in postpartum women and reported significant negative correlations between OT levels and anxiety ratings.

The link between youth anxiety and low salivary OT levels is intriguing and underscores the need for more research to better understand its underlying causal pathways. One explanation for the emerging pattern of findings is that maintaining proximity to parents, especially in youth with SAD, stimulates a low functioning oxytocinergic system and aids in regulating anxiety. This hypothesis is consistent with several lines of research indicating that social stimulation and contact with attachment figures stimulates the OT system and elicits OT response.

Grewen, Girdler, Amico, and Light, (2005) examined serum OT levels in healthy couples in a study involving brief separation followed by a period of "warm contact" (talking about a time they felt close to each other, watching a romantic video clip, and hugging for 20 s). Peripheral OT levels before and after the period of warm contact were positively associated with the level of partner support reported by each participant. Morhenn, Park, Piper, and Zak, (2008), in a study involving 96 university students, reported that physical contact followed by an intentional act of trust led to elevated serum OT levels. A subsequent study in healthy adults found elevated OT response to a task involving intimate trust, but not to a nontrust-related task (Keri, & Kiss, 2011). OT levels following the trust task were also associated with a physiological index of anxiety regulation.

Feldman, Gordon, Schneiderman, Weisman, and Zagoory-Sharon, (2010) reported increases in salivary OT levels in mothers who provided high levels of affectionate touch during behavioral interactions with their infants, but not in mothers who provided low levels of affectionate touch. Strathearn, Iyengar, Fonagy, and Kim, (2012) reported elevated peripheral OT levels in first-time mothers in response to mother–infant interactions, and found that the OT response was associated with ratings of maternal emotional responsiveness.

Beyond the findings from peripheral markers of oxytocinergic functioning, findings from brain imaging studies and from OT administration studies corroborate the effects of social stimulation on oxytocinergic functioning. Strathearn, Fonagy, Amico, and Montague, (2009) used functional magnetic resonance imaging (fMRI) to examine central oxytocinergic activation in mothers, in response to viewing images of their babies. Mothers classified with secure attachment style had greater activation in OT-associated regions of the brain, compared to mothers with insecure attachment style. The brain activation also correlated positively with maternal peripheral OT response to contact with their babies. Heinrichs, Baumgartner, Kirschbaum, and Ehlert, (2003) reported that intranasal OT administration enhanced the anxiolytic effect of social support in adult men exposed to a stressful paradigm. In summary, converging evidence from multiple lines of research including both peripheral and central markers of oxytocinergic functioning, as well as OT administration, indicates that contact with attachment figures stimulates the OT system with a potential anxiolytic effect.

The current study builds on these data and on the emerging evidence for an association between anxiety in youth and low levels of peripheral OT. Participants in the current study were drawn from a larger sample for whom we previously published findings regarding baseline salivary OT levels and anxiety symptoms (Lebowitz et al., 2016). That study provided evidence for the relation between anxiety symptoms and OT levels in anxious youth, but left significant gaps in knowledge relating to OT response to interactions with attachment figures, the relations between OT response and anxiety symptoms, and the aspects of the interactions linked to OT response. The current study addresses these gaps and focuses on OT response to

child–mother interactions, and includes only participants who provided salivary samples before and after child–mother interactions.

The study asks whether salivary OT levels in clinically anxious youth increase after a positive youth–mother interaction, and whether maternal and youth dyadic behavior during the interaction contribute to predicting the OT response, defined as change in youth OT levels from before to after the interaction. Of particular interest are the degree of affectionate physical contact during the interaction, maternal behavior previously linked to youth anxiety including maternal sensitivity and intrusiveness (Bögels, & Brechman-Toussaint, 2006), and the degree of youth positive engagement in the interaction. Maternal sensitivity involves attunement to a child's behaviors and emotions, and positive and appropriate responses to the child's cues (Smith, & Pederson, 1988). Maternal sensitivity has been linked to lower child anxiety and better child anxiety regulation, and is associated with oxytocinergic functioning in mothers (Feldman et al., 2009, 2010, 2012). Maternal intrusiveness involves a pattern of overly controlling behavior and low autonomy granting, and has been linked to childhood anxiety disorders (Feldman, 2010; Lebowitz et al., 2016; van der Bruggen, Stams, & Bogels, 2008). The study also asks whether the presence of particular anxiety disorders, such as separation anxiety, is associated with youth OT response. We hypothesized that OT response would be greater in youth with SAD, and would be significantly predicted by each of the coded behavioral variables observed during the interaction.

2 | MATERIALS AND METHODS

2.1 | Participants and procedures

Participants were 41 clinically anxious youth aged 7–16 and their mothers, who presented consecutively to a large specialty anxiety disorders research clinic and met DSM-5 (American Psychiatric Association, 2013) criteria for a primary anxiety disorder. Primary diagnoses included generalized anxiety disorder (GAD, 30%), SoA (28%), SAD (22%), specific phobia (SP 15%), and panic disorder (PD, 5%). Including both primary and nonprimary diagnoses, 68% of youth had GAD, 65% had SoA, 32% had SAD, 22% had SP, and 13% had PD. Youth psychiatric medications included atypical antipsychotics ($N = 3$), antidepressants ($N = 6$), and stimulants ($N = 1$). The sample was predominantly White (83.3%) and non-Hispanic (94.5%) with a minority being African American (6%), Asian (2%), or of mixed ethnic background.

The study was approved by the Institutional Review Board and signed informed consent and assent were obtained from mothers and youth, respectively. Youth and mothers were separately administered a semistructured diagnostic interview and rating scales. Youth provided saliva samples before and after a 7-min youth–mother interaction.

2.2 | Measures

2.2.1 Anxiety disorders interview schedule—Children and parent (ADIS-C/P)

The ADIS C/P was administered separately to the youth and the mother (Silverman, Saavedra, & Pina, 2001). The ADIS C/P is a semi-structured interview with good to excellent reliability, and strong correspondence with anxiety questionnaire ratings (Silverman et al., 2001; Wood, Piacentini, Bergman, McCracken, & Barrios, 2002). The ADIS C/P was administered by graduate-level clinicians or licensed psychologists, trained to reliability in its use (ICC > 0.85) by one of the instrument's authors. Each assessment was discussed with a consensus team of expert clinicians to prevent rater drift. As in past research, in cases of discordance between parent and child reports, the clinician considered both informants' views to derive a final diagnosis (Silverman et al., 1999; Silverman, Kurtines, Jaccard, & Pina, 2009).

2.2.2 Multidimensional anxiety scale for children (MASC2)

Youth and mothers completed respective versions of the 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). MASC2 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 its factorial structure and ability to distinguish domains of anxiety (Baldwin, & Dadds, 2007; Grills-Taquechel, Ollendick, and Fisak, 2008; March et al., 1999). Internal consistency in the current sample was excellent for youth ($\alpha = .94$) and mothers ($\alpha = .91$).

2.2.3 Dyadic interaction

Youth and mothers participated in a 7-min dyadic interaction. All participants were given a uniform prompt asking them to "plan their best day ever together." Interactions were videotaped and coded for affective touch between mothers and youth, maternal sensitivity and Intrusiveness, as well as youth engagement and Initiative. Videos were coded using the *Coding Interactive Behavior* (*CIB*) system (Feldman, 1998). CIB is widely used, has been validated in multiple longitudinal studies of both normal and clinical populations, has good test–retest reliability, and construct and predictive validity, and several studies used the CIB in this age range in healthy and high risk populations (Feldman, Bamberger, & Kanat-Maymon, 2013). Videos were coded by two experienced and reliable coders trained by the developer of the CIB system. Inter-rater reliability was higher than 0.9. Maternal sensitivity was the average score of four specific codes: acknowledgment and validation, supportive presence, warmth, and emotional empathy (Cronbach's $\alpha = .95$). Youth engagement was the average of three specific behavioral codes: persistence, involvement, and cooperation (Chronbach's $\alpha = .97$). Affective touch was scored separately for mothers and youth ($r = 0.96$) and the average score across youth and mothers was used in analyses.

2.2.4 Sample preparation and immunoassay

Saliva was collected using salivettes (Sarstedt, Rommelsdorf, Germany), between 4 pm. and 5 pm., after a 2-hr fast. Samples were stored at −20°C until centrifuged twice, 2 days apart, at 4°C at 1,500 × *g* for 20 min. Liquid samples were kept at −80°C, lyophilized for 10 days, and stored at −20°C. On the assay day, samples were reconstituted in water and concentrated ×4 before immunoassay with an Enzyme

Linked Immunosorbent Assay (ELISA) kit from Enzo (NY, USA). Measurements were performed in duplicate and concentrations were calculated using MATLAB-7 according to relevant standard curves.

2.3 | Data analysis

OT response was defined as change in youth salivary OT levels from before to after the youth–mother interaction. Bivariate correlations were used to examine the associations between OT response and ratings of anxiety and the behavioral codes. Hierarchical linear regression, with change in youth salivary OT levels as the predicted variable, was used to examine the relative contribution of the behavioral codes to OT response. In the first step, baseline youth salivary OT level was entered as predictor to partial out variance related to baseline levels, and in a second step, the coded dyadic behaviors were entered as predictors.

Repeated measures ANOVA was used to examine interactions between TIME (before/after youth-mother interaction) and the behavioral codes on youth salivary OT levels. Dyadic variables were entered as between subject factors in the repeated measures analysis, with subjects split between high and low levels of each behavior variable, using a median split.

A series of one-way ANCOVA (analyses of covariance) were used to examine the impact of the presence of particular youth anxiety disorders on OT response. OT response was compared in youth with and without each of the anxiety disorders present in the sample (SAD, SoA, GAD, SP, PD), while controlling for baseline youth salivary OT levels.

3 | RESULTS

Baseline youth salivary OT levels ranged from 5.6 to 64 pg/ml (mean = 22.9 pg/ml; *SD* = 14.0). Youth salivary OT levels after youth–mother interaction ranged from 6.9 to 66.6 pg/ml (mean = 23.0 pg/ml; *SD* = 14.6). The wide range and considerable variance in distribution of peripheral OT levels are in line with previous studies of peripheral OT levels in both youth and adults, though direct comparison of OT concentrations across studies is impeded by changes to the commercially available ELISA kits (Feldman et al., 2010, 2012; Feldman, Gordon, and Zagoory-Sharon, 2011; Gordon et al., 2008; Weisman et al., 2013). Because no standard OT concentration values exist as yet for the currently available kit, a study limitation is that interpreting absolute values is not possible and we focus on change in OT levels as it relates to clinical and behavioral markers.

Youth age and sex, youth and mother ratings of youth anxiety, and coded dyadic behavior, as well as each variable's association with youth OT response are summarized in Table 1. Overall, anxiety ratings were consistent with those found in other clinical samples, and total youth and mother MASC2 ratings did not differ significantly from each other. Males and females did not differ significantly in salivary OT levels before or after youth–mother interactions, on parent ratings of youth anxiety, or on coded dyadic behavior. Youth total anxiety ratings were higher in females than in males ($t_{39} = 2.7$, $P < .05$). Youth age was not significantly correlated with youth salivary OT levels before or after youth–mother interactions or with any anxiety ratings apart from mother-rated separation anxiety ($r = -.46$, $P < 0.01$).

Youth salivary OT levels in the overall sample did not change significantly from baseline to after the youth–mother interaction ($F_{\text{repeated measures}} = 1.02$, $P = .32$), and OT levels before and after the interactions were moderately and significantly correlated in the overall sample ($r = .5$, $P < .01$). Change in youth OT levels following the dyadic interaction (OT response) correlated significantly with youth-rated total anxiety, as well as youth-rated separation and generalized anxiety, but not with mother-rated youth anxiety. Youth OT response also correlated significantly with affective touch during the interaction, see Table 1. Youth OT response did not correlate significantly with youth age. To further examine the impact of youth age, in light of the broad age range in the current sample, mean OT response was compared between younger and older youth using a median age split, with the median age of 11.5. Younger and older youth did not differ significantly in OT response ($t = 1.3$, $P = .2$).

Hierarchical linear regression revealed significant contribution of each of the coded dyadic behaviors to predicting OT response. Step 1 of the regression, predicting OT response from baseline youth salivary OT levels explained 25% of variance in OT response (adjusted $R^2 = .23$), and was significant, $F_{1,39} = 12.5$, $P < .01$. The second step, including the behavioral codes of affective touch, maternal sensitivity, and Intrusiveness and youth engagement and Initiative, explained 69% of variance in youth OT response (adjusted $R^2 = .63$), a significant change in explained variance, $F_{\text{CHANGE}} = 9.3$, $P < 0.001$. Each of the coded variables contributed significantly to the prediction: $P < 0.01$ for affective touch, maternal sensitivity, youth engagement, and youth initiative, and $P < .05$ for maternal Intrusiveness. Collinearity between the predictor variables was low with all tolerance levels below 1.0, and all variance inflation factor (VIF) scores below 5.5. See Table 2 for beta values and significance for each predictor in the model. Including youth age in the model did not improve prediction of youth OT response.

Repeated measures ANOVA comparing youth salivary OT levels before and after the youth–mother interaction revealed a significant TIME × affective touch interaction, $F_{1,39} = 5.95$, $P < 0.05$. Youth OT levels rose significantly for the high affective touch interactions, but not for the low affective touch interactions. Figure 1 illustrates the different patterns of OT response for the high and low affective touch groups. Interactions between TIME and the other coded behavior variables were not significant, nor was the interaction between TIME and youth age.

Repeated measures analysis examining the impact of particular anxiety disorders on OT response revealed a significant effect only for the presence of SAD, $F_{1,39} = 5.7$, $P < .05$. Salivary OT levels in youth with SAD rose significantly from a mean of 15.66 pg/ml before the youth–mother interaction to a mean of 21.32 pg/ml after the interaction. By contrast, for youth without SAD, salivary OT levels did not change significantly from a mean of 28.77 pg/ml before the interaction to a mean of 24.14 pg/ml after the interaction. Furthermore, youth with and without SAD differed significantly in salivary OT levels at baseline ($t = 3.0$, $P < .01$), but did not differ significantly after the youth–mother interaction. Figure 2 depicts the change in salivary OT from before to after youth–mother interaction in youth with and without SAD.

TABLE 1 Youth age and sex, youth and mother ratings of youth anxiety, and coded dyadic behavior in youth with clinical anxiety disorders, and their associations with youth oxytocin response ($N = 41$)

Variable	Frequency		Independent *t*-test for oxytocin response
Percentage of females	66%		1.9
	Mean	*SD*	Correlation with oxytocin response
Age: range 6–17 years	11.9	3.19	–.12
Youth-rated anxiety			
MASC2 total	69.9	30.8	.32*
MASC2 separation	10.9	5.8	.37*
MASC2 generalized anxiety	14.8	6.6	.32*
MASC2 social anxiety	14.1	7.9	.28
MASC2 obsessive–compulsive symptoms	12.4	8.3	.21
MASC2 physical symptoms	13.9	8.5	.33*
MASC2 harm avoidance	15.9	5.0	.16
Mother-rated youth anxiety			
MASC2 total	68.3	25.2	.16
MASC2 separation	11.8	7.1	.19
MASC2 generalized anxiety	16.8	5.5	.14
MASC2 social anxiety	16.8	5.9	.08
MASC2 obsessive–compulsive symptoms	7.4	7.6	.16
MASC2 physical symptoms	12.6	6.8	.12
MASC2 harm avoidance	16.7	4.5	–.02
Coded dyadic behavior			
Affective touch	1.4	.91	.36*
Maternal sensitivity	3.3	1.1	.08
Maternal intrusiveness	1.2	.49	.17
Youth positive engagement	3.9	1.2	.04
Youth initiation and creativity	3.5	1.2	.15

Note: MASC2, Multimodal Anxiety Scale for Children 2nd edition.
*$P < 0.05$.

TABLE 2 Hierarchical multiple linear regression predicting salivary oxytocin levels in clinically anxious youth after youth–mother interactions from baseline salivary oxytocin levels (Step 1), and coded dyadic behaviors during the interaction (Step 2)

Step	Predictor	β	*t*	*P*	*F* (model)	*P* (model)
1					12.5	.001
	Baseline youth oxytocin level	–.49	–3.5	.001		
2					12.2	.000
	Baseline youth oxytocin level	–.51	–5.0	.000		
	Affective touch	.42	3.6	.001		
	Maternal sensitivity	–.46	–3.4	.002		
	Maternal intrusiveness	–.28	–.26	.013		
	Youth engagement	1.1	4.8	.000		
	Youth initiative	–1.0	–4.8	.000		

To control for the lower baseline salivary OT levels in youth with SAD and possible regression to the mean, we conducted a one-way ANCOVA with Bonferroni correction. We tested whether youth with SAD differed significantly from youth without SAD in OT response to youth–mother interaction when controlling for baseline salivary OT levels. There was a significant effect of the presence of SAD on change in youth salivary OT levels after controlling for baseline OT levels, $F_{1,38} = 10.71$, $P < .01$.

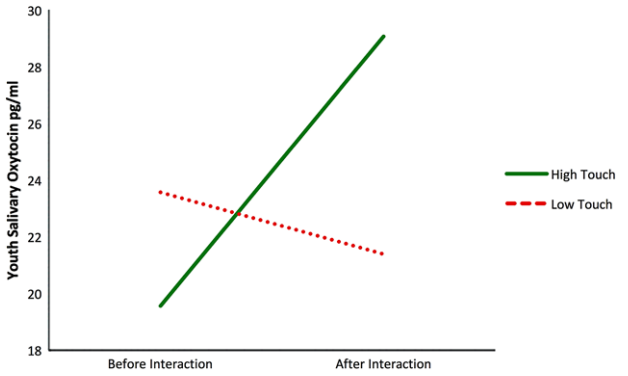

FIGURE 1 Salivary oxytocin levels in clinically anxious youth before and after youth–mother interactions with high and low affective touch. Time × touch interaction: $F_{1,39} = 5.95, P < 0.05$

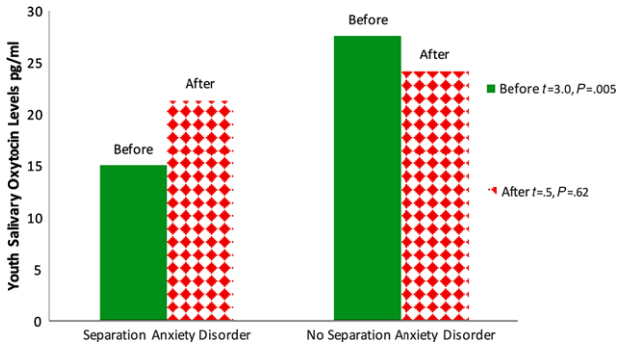

FIGURE 2 Salivary oxytocin in clinically anxious youth ($N = 41$) with and without separation anxiety disorder before and after youth–mother interaction ($N = 18$ and 23, respectively)

4 | DISCUSSION

The current study builds on recently reported findings from the first investigation of oxytocinergic functioning in youth with anxiety disorders (Lebowitz et al., 2016). The previous study found that salivary OT levels are negatively correlated with severity of youth anxiety symptoms, in particular separation anxiety. The current study expands these findings by demonstrating that OT response to a positive youth–mother interaction is higher among youth with SAD, compared to clinically anxious youth without SAD. OT response to youth–mother interactions in the current study was also significantly predicted by youth and mother behavior during the interaction.

These findings are in line with previous research showing that social stimulation, in particular by attachment figures, stimulates the oxytocinergic system with measurable impact on peripheral and central markers of oxytocinergic functioning (Feldman et al., 2010; Grewen et al., 2005; Keri, and Kiss, 2011; Morhenn et al., 2008; Strathearn et al., 2009, 2012). More frequent affectionate touch between youth and mothers during the interaction, as well as higher levels of positive engagement on the part of the youth, predicted greater OT response. Lower levels of maternal sensitivity and intrusiveness, and lower levels of youth initiative were also associated with greater OT response. Repeated measure analysis of youth OT levels indicated that touch significantly interacted with time to predict youth OT levels, with more frequent touch predicting greater OT response.

OT is implicated in attachment behaviors in both children and mothers, and the present study adds to the growing understanding of the role of oxytocinergic functioning for attachment behavior in the context of a child's anxiety. OT administration increases social behavior and cognition (Heinrichs, & Domes, 2008; Heinrichs, von Dawans, & Domes, 2009), and its effects are moderated by attachment style (Bartz et al., 2015, 2011). Plasma OT levels in parents predict attachment behaviors including gaze, touch, and sensitivity toward infants (Feldman et al., 2010, 2012; Feldman, Weller, Zagoory-Sharon, & Levine, 2007), and maternal behavior interacts with maternal OT to shape OT response and social behavior in children (Feldman, Gordon, Influs, Gutbir, & Ebstein, 2013). The present study adds to current knowledge by examining the impact of dyadic child–mother interactions on child oxytocinergic functioning in clinically anxious children who rely on parents and the interpersonal attachment system for aid in coping with anxiety symptoms.

The importance of affective touch for OT response is in line with previous research showing that somatosensory stimulation is linked to OT release and to soothing mechanisms (Uvnas-Moberg, Handlin, & Petersson, 2015). OT release due to sensory nerve activation during birth and breastfeeding is well known, but external stimulation (e.g., stroking) is also associated with OT release, reduced stress, and prosocial behavior in humans (Matthiesen, Ransjo-Arvidson, Nissen, & Uvnas-Moberg, 2001) and animals (Lund et al., 2002; Stock, & Uvnas-Moberg, 1988). Intranasal OT administration also increases brain response to social touch, and its perceived pleasantness (Scheele et al., 2014).

The seminal studies by Harlow (1960, 1959) on attachment in young primates exposed the importance of tactile stimulation for soothing anxiety. The current findings also underscore the importance of maternal touch, but indicate that (in humans) the quality of maternal and dyadic behavior also contributes meaningfully to predicting oxytocinergic regulation during youth–mother interactions. The current findings also extend earlier research demonstrating a link between oxytocinergic functioning and stress during triadic interactions between parents and their infant (Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010). Frequency of synchronous moments involving affectionate touch and coordinated gaze between all three individuals during such triadic interactions was associated with both maternal and paternal OT levels, and independently predicted lower maternal cortisol levels.

The key role of affective touch for OT response in anxious youth, and the elevated response in youth with SAD specifically, also shed light on the clinging behavior commonly observed in anxiety and most prominent in SAD. One clinical implication is that maintaining physical contact with parents is likely to be negatively reinforced in youth with SAD. Mothers of youth with SAD report engaging in high levels of family accommodation, in particular maintaining proximity to the youth (Lebowitz et al., 2013; Norman, Silverman, & Lebowitz, 2015). Family accommodation can cause significant distress to

mothers and the accommodating interactions are often fraught and tense (Lebowitz, Panza, & Bloch, 2016). It is not uncommon for youth to forcefully impose accommodation on parents through verbal or physical aggression and shows of distress (Lebowitz, Omer, & Leckman, 2011; McGuire et al., 2013). The current findings suggest that even such fraught interactions, if they include physical contact between mother and youth, may stimulate the youth's OT system and are likely to endure. Providing parents with tools to reduce family accommodation and to manage the allocation of attention and physical contact may be an important step in promoting more independent coping in anxious youth. Recent research has supported the potential of this approach (Lebowitz, Omer, Hermes, & Scahill, 2014).

The current findings are in line with the hypothesis that parental proximity is key to regulating a low-functioning oxytocinergic system in some clinically anxious youth. This possibility has potential implications for the etiology and treatment of anxiety in youth, especially SAD, and contributes to the understanding of neurobiological regulation in close interpersonal relationships. An intriguing clinical implication of the current results is the possibility for OT-based treatment of SAD in youth. Intranasal OT administration is reflected in human saliva (Weisman, Zagoory-Sharon, & Feldman, 2012) and has behavioral, emotional, and cognitive effects which are most frequently described as prosocial but are moderated by individual differences such as attachment style (Macdonald, 2012). OT administration has been examined in a small number of treatment trials for anxiety in adults. Guastella, Howard, Dadds, Mitchell, and Carson, (2009) examined whether OT administration would enhance a 5-week group exposure therapy for adults with SoA, and found that patients who received OT had more positive self-evaluations after treatment than patients who received a placebo. In another small randomized trial of adults with GAD, OT administration was associated with a significant reduction in self-ratings of anxiety in male participants (Feifel, 2011). These studies provide preliminary support for the potential use of intranasal OT in the treatment of anxiety and other disorders characterized by abnormal interpersonal behavior. No studies have yet investigated intranasal OT administration for SAD or other anxiety disorders in youth, and the current results highlight the potential of this possibility.

The current findings should be considered in light of certain limitations. The current sample was of only moderate size, was fairly homogenous in terms of race and ethnicity, and included a wide age range spanning development from prepuberty to adolescence. To address this, youth age was included in the various analyses and we compared OT response in younger and older youth. Youth age was not associated with OT levels before or after the interactions, younger and older youth did not differ in OT response, and youth age did not contribute to predicting OT response or interact with time in repeated measure analyses. More research is needed to determine whether current results are applicable to broader, and more diverse populations. Results should also be interpreted with caution given that youth with lower baseline OT levels were also those who showed the greatest OT response to the interaction, suggesting some possibility of regression to the mean. This risk was mitigated by controlling for baseline salivary OT levels and the results appear robust, but further replication studies are needed. The fact that youth OT levels changed significantly from before to after the interaction in youth with SAD but not in the overall sample is an important finding. However, along with the moderate but significant correlation between youth OT levels at the two time points, it also underscores the need for replication of these findings in additional studies. Another limitation is the absence of a control sample of nonanxious youth. Examining OT response in well characterized clinically anxious youth is a strength of the study, but the absence of a control sample is another limitation and additional research is needed to determine to what extent the current results are specific to youth with clinical anxiety. As noted earlier, because of differences in methodology including the specific ELISA kit used in different studies, it is not feasible to directly compare the current findings with reported OT levels from other studies, and no norms have yet been published for the currently commercially available kit used in this study. Our laboratory is currently collecting a control sample of nonanxious youth, which will allow for comparisons between anxious and nonanxious youth and will help to clarify to what extent the associations in the current findings reflect anxiety pathology or normal variations linked to pathological anxiety. For these reasons, the current study focused only on relations within the measured variables, and on comparisons between youth with and without specific anxiety disorders.

5 | CONCLUSIONS

The current findings shed novel and important light on the role of oxytocinergic functioning in youth with anxiety disorders, and contribute to the understanding of SAD in particular. The findings also underscore the importance of maternal and dyadic behavior patterns and point to possible novel intervention strategies aimed at modifying them.

CONFLICT OF INTEREST

The authors have no conflicts of interest or financial disclosures relating to this work.

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