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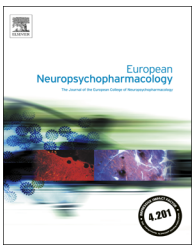

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Oxytocin administration alters HPA reactivity in the context of parent-infant interaction

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Abstract
The neuropeptide oxytocin (OT) and the steroid cortisol (CT) have each been implicated in complex social behavior, including parenting, and one mechanism by which OT is thought to exert its pro-social effects is by attenuating hypothalamic-pituitary-adrenal (HPA) response to stress. Yet, no study to date has tested whether OT functions to reduce CT production in the context of the parent-infant attachment. In the current study, we examined the effects of intranasal OT administered to the parent on parent's and infant's CT levels following parent-child interaction that included a social stressor. Utilizing a double-blind, placebo-controlled, within-subject design, 35 fathers and their 5-month-old infants were observed in a face-to-face-still-face paradigm twice, one week apart. Interactions were micro-coded for social synchrony, and salivary CT were repeatedly assessed from parent and child. Results showed that OT increased fathers' overall CT response to the stress paradigm. Furthermore, OT altered infants' physiological and behavioral response as a function of parent-infant synchrony. Among infants experiencing high parent-infant synchrony, OT elevated infant HPA reactivity and increased infant social gaze to the father while father maintained a still-face. On the other hand, among infants experiencing low social synchrony, parental OT reduced the infant's stress response and diminished social gaze toward the unavailable father. Results are consistent with the "social salience" hypothesis and highlight that OT effects on human social functioning are not uniform and depend on the individual's attachment history and social skills. Our findings call to further investigate the effects of OT administration within developmental contexts, particularly the parent-infant relationship.

1. Introduction

The contribution of the neuropeptide oxytocin (OT) to shaping social orientation and affiliation has been well-established through research in both humans and animal models (Heinrichs and Domes, 2008; Insel, 2010; McCall and Singer, 2012). The involvement of OT in the formation of parenting behavior and parent-infant engagement has been of particular interest (e.g., Feldman, 2012a). One mechanism by which authors suggest that OT exerts its pro-social effects is through the well-known anxiolytic and stress reducing properties of the oxytocinergic system (Macdonald and Macdonald, 2010; Bartz et al., 2011; Churchland and Winkielman, 2012). Animal studies

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point to the anxiolytic and anti-stress effects of OT (Neumann, 2008) and, following, human studies have shown that OT administration reduces HPA reactivity (Heinrichs et al., 2003; Meinlschmidt and Heim, 2007; Ditzen et al., 2009; Quirin et al., 2011; Linnen et al., 2012; Cardoso et al., 2013). Still, no study to date has tested whether OT administration functions to reduce physiological and behavioral markers of stress within the parenting context. Understanding the effects of exogenous OT on the stress reactivity within attachment relationships is of developmental and clinical significance and is the focus of the current investigation. Specifically, we examine how the intranasal administration of OT to the parent alters the parent's as well as the infant's cortisol (CT) reactivity following parent–infant interaction that includes a social stressor.

Research has shown that intranasal administration of OT reduces CT reactivity to a variety of stressors. For example, OT interacts with social support to decrease CT response to a social stressor among healthy male participants (Heinrichs et al., 2003). Similarly, OT administration reduces CT response of healthy adults as a function of their childhood rearing experience and CT reduction was found in those who experienced early parental separation and no response was observed among those growing in well-adapted families (Meinlschmidt and Heim, 2007). In addition, OT decreased CT levels in couples following marital conflict discussion (Ditzen et al., 2009), and altered CT reactivity in healthy adults as a function of their emotion regulation capacities (Quirin et al., 2011), with CT increase observed among individuals with low emotional regulation following OT administration but not after placebo application. No OT effect on CT reactivity was found in individuals with high emotion regulation capacities and the authors suggested that such individuals are able to self-regulate their neuroendocrine stress responses independently of the external effects of OT (Quirin et al., 2011).

Among individuals suffering from a variety of psychopathologies, the picture is more complex. In individuals diagnosed with borderline personality disorder (BPD; Simeon et al., 2011) OT was found to marginally reduce the CT response to stress, compared with placebo. OT was found to decrease CT response in individuals with fragile X syndrome in a dose-dependent manner, with 48 IU but not 24 IU OT showing effect on CT as compared to placebo (Hall et al., 2012). When tested among non-clinical human populations, OT reduced CT concentrations between male and female participants exposed to a social rejection paradigm (Linnen et al., 2012). Similarly, a single-dose of OT was found to attenuate salivary CT levels in male volunteers following physical exercise (Cardoso et al., 2013), but the response was observed only after 24 IU but not 48 IU of OT. Other studies showed no effects of OT administration on circulating CT (Burri et al., 2008; de Oliviera et al., 2012). These findings are consistent with those of Parker et al. (2005), who showed that OT-induced attenuation of pre-adrenal [ACTH] stress, but not of the CT response in squirrel monkeys. Overall, the aforementioned studies demonstrate that the effects of intranasal OT on the individual's CT response to stressful situations is not uniform and is affected by multiple individual and contextual factors, such as child rearing history, emotion regulation capacities, social support (Heinrichs et al., 2003), drug dosage (24 vs. 48 IU; Hall et al., 2012; Cardoso et al., 2013), and diagnostic status (Meinlschmidt and Heim, 2007; Quirin et al., 2011). These factors often interact to determine whether and to what extent OT administration would increase, decrease, or have no effect on the individual's stress response. The findings also highlight the need for a nuanced approach in assessing the effects of OT administration on reducing the stress or enhancing social functioning (Bartz et al., 2011).

In assessing the effects of OT on the formation of human attachment, the *bio-behavioral synchrony* model (Feldman, 2007; Feldman, 2012b, 2012c) provides a conceptual framework for addressing the mutual influences between the parent and child's physiological and behavioral response as they unfold during the social contact. For instance, during face-to-face interaction mothers and infants were found to synchronize their heart rhythms online within lags of less than 1 s and the degree of coordination increased during moments of vocal and affect synchrony and decreased during non-synchronous episodes (Feldman et al., 2011). Mothers' and fathers' salivary OT response to social interactions synchronized with the infant's OT response, indicating a cross-generation transfer similar to that shown in other mammals; however, the degree of interactive synchrony moderated the level of neuroendocrine synchrony between parent and child's OT levels (Feldman, et al., 2010b). Similarly, genetic and peripheral markers on mothers' and fathers' OT neuropathways interacted with the early parenting to shape the child's OT response and social reciprocity with their first best-friends (Feldman et al., 2013). Finally, OT administration to fathers increased father salivary OT, autonomic response, and parenting behavior, but, moreover, had a similar effect on increasing the infant's salivary OT, autonomic response, and interactive behavior indicative of greater social engagement (Weisman et al., 2012). These findings highlight the close fit between parent and child's physiological and behavioral response to face-to-face exchanges and demonstrate that OT manipulation to the parent can alter the infant's hormonal response and social behavior. The findings also lend support to the hypothesis that OT administration to the parent may impact the infant's CT response to a social stressor.

One experimental paradigm that enables the assessment of infant stress reactivity within early dyadic contexts is the face-to-face-still-face (FTFSF) procedure (Tronick et al., 1978). In this paradigm, the parent interacts freely with the infant for several minutes, then refrains from social communication and maintains a 'still-face', and finally resumes play. The FTFSF paradigm has been extensively studied, is suggested to simulate a situation of 'parental deprivation', and has repeatedly shown to reduce the infant's social behavior and increase negative emotionality (for review see Adamson and Frick, 2003). Moreover, a link between infant response to maternal still-face (SF) in the first months of life and attachment style at one year has been reported and greater maternal eliciting behavior and positive affect predicted secure versus insecure attachment (Mesman et al., 2009), albeit the infant's behavior during the SF is not a direct measure of attachment style. Studies have also shown that the FTFSF procedure increases CT production in 3–6 month old infants (Haley and Stansbury, 2003; Haley et al., 2006; Feldman et al., 2010c), indicating that the procedure causes sufficient stress to elicit physiological stress response in infants. Notably, however, in the few studies that examined the parent's stress response to the SF, no parallel CT response was detected in the parent (e.g., Feldman et al., 2010c). Importantly, studies have shown

that the infant's physiological and behavioral reactivity to maternal still-face was moderated by the degree of interactive synchrony during the free play part of the experiment (Moore and Calkins, 2004; Feldman et al., 2010c), suggesting that the infant's typical experiences within the parent-infant attachment modulate its response to the social stressor. Research involving the SF paradigm in clinical populations showed alterations in infant behavioral response. For instance, infants of depressed mothers exhibited little behavioral distress during maternal SF, possibly as these children do not experience the mother's synchronous engagement routinely and disruptions to her reciprocal behavior induce little behavioral change (Field et al., 2007). Yet, research has shown that infants of depressed mothers exhibit higher CT reactivity following interactions with their mothers as compared to controls (Feldman et al., 2009), indicating that interactions that contain minimal levels of synchrony induce higher physiological stress in the child.

In light of the above, the current study had two goals. First, we wished to examine whether intranasal administration of OT to the parent has an effect on the parent's and infant's CT response to a social stressor. Second, we tested whether the degree of parent-infant synchrony may moderate this effect. Prior research has suggested that the effects of OT administration are greater in individuals with lower social functioning (Bartz et al., 2010; Groppe et al., in press), and we therefore examined whether OT would reduce the stress response of infants who typically experience lower parent-infant synchrony. In contrast, the role of OT in enhancing social salience may increase the perception of the aberrant social context of the SF and increase the stress experienced by parent and child, particularly among infants expecting high parental responsiveness, leading to higher CT production during the OT condition.

2. Experimental procedures

2.1. Participants

Thirty-five healthy fathers (average age 29.7 years, SD=4.2, range 22-38) participated with their five-month-old infants (SD=1.25 months, range 4-8) in two lab visits, a week apart (total N=70). Fathers' exclusion criteria included smoking, chronic mental or physical illness, and medication intake. All fathers were educated middle-class and married to the infant's mother. Infants (18 girls) were healthy, and 68.5% were firstborns and exclusion criteria included premature birth, labor- or birth-related complications, multiple birth, or illness. The research was approved by the Institutional Review Board and conducted according to ethical standards, and all participants signed an informed consent.

2.2. Procedure

Fathers were instructed to abstain from alcohol or caffeine during the day of the experiment and to avoid food-intake 2 h prior to arrival. Upon arriving at the lab, infant was separated from father and cared by a trained research assistant. Following a short assessment of father's affect with the PANAS questionnaire (Watson et al., 1988), fathers were asked to self-administer 24 IU of either OT (Syntocinon Spray, Novartis, Switzerland; 3 puffs per nostril, each containing 4 IU) or PL. The PL was custom-designed by a commercial compounding pharmacy to match drug minus the active ingredient. Administration order was counterbalanced, and participants and experimenters were blind to drug condition. Forty minutes after administration PANAS was administered again, and infant joined father in the observation room. Infant was seated in an infant-seat mounted on a table. In accordance with the FTFSF paradigm, father interacted with infant freely for 3 minutes, then refrains from social engagement for 2 min, and resumes engagement for additional 3 min. Father-infant interaction began approximately 45 min after the substance administration. All experiments were held between 1300 h and 1700 h, with the two sessions starting at same time of day.

2.3. Salivary cortisol collection and analysis

Father and infant's saliva samples were collected at multiple timepoints: T1 (baseline)—before substance administration (father only); T2—40 min after administration prior to interaction; T3—20 min after interaction began, and T4—20 min thereafter. Saliva samples were collected by Sallivatte (Sarstedt, Rommelsdorft, Germany). Salivettes were immediately stored at −20°C to be centrifuged twice at 4 °C at 1500 × g for 15 min within one month. All samples were then stored at −20°C until assayed. CT levels were assayed using a commercial ELISA kit (Assay Design, MI, USA). Measurements were performed according to the kit's instructions. CT levels were calculated by using MatLab-7 according to the relevant standard curves. The inter-assay and intra-assay CVs for the low range (lower than 300 pg/ml) are 20.6% and 21.3%, respectively. The inter-assay and intra-assay CVs for the high range (higher than 300 pg/ml) are 9.8% and 14.3%, respectively.

2.4. Coding father-infant interaction

Interactions were videotaped using Flip Mino HD digital camcorder for off-line coding by trained observers blind to experimental condition. Father-infant interactions were micro-coded using a computerized system (Noldus, Wageningen, Netherlands) in .01 s frames. For the scope of the present study we chose to focus on specific indices of dyadic exchange that index the co-occurrence of social gaze between parent and infant during the free-play episode (hereinafter being referred to as Gaze Synchrony; GS), and infant's gaze towards parent during the SF (i.e., social gaze). The proportion - % of time from the free-play episode - was quantified for the GS and the social gaze variables. High and low GS groups were then created based on the median split (median=46.64%), yielding low and high GS groups of 18 and 17 dyads, respectively.

2.5. Parental stress

Parental stress was assessed using the Parenting Stress Index (PSI) short form (Abidin, 1995). The total stress score is designed to provide an indication of the overall level of parenting stress an individual is experiencing.

2.6. Statistical analysis

CT data were normalized using logarithmic (log10) transformation. Baseline CT concentrations were compared between high and low GS groups and treatment conditions using two-way analysis of variance (ANOVA) with treatment [OT, PL] as the within subjects factor, and Groups [High vs. Low GS] as the between subjects factor. Three-way repeated-measures ANOVA of Time [four\three levels], Treatment [OT, PL], and Group [High vs. Low GS] was used to compare CT concentrations over time between groups and conditions. To clarify further a significant three-way interaction effect, baseline-corrected indices of change (pre-application minus mean of post-application CT concentrations) were compared between

groups and treatment conditions using two-way ANOVA. For presentation purposes, placebo-corrected OT-induced change indices were computed and compared between groups using *t* tests. Finally, Pearson correlations between father and infant's mean baseline CT levels and parent–infant behaviors during the free-play episode of the FTFSF (PL condition) were assessed. Behaviors during the free-play episode were coded and reported within the framework of a previous publication (Weisman et al., 2012). All statistical tests were two-tailed and the level of significance was set at .05. Statistical analysis was adapted from Meindelschmidt and Heim (2007).

3. Results

3.1. Father CT response

No differences related to group (high vs. low synchrony) or treatment conditions were observed before administration. A three-way repeated measures ANOVA analysis yielded main effect for TIME, $F(3,99)=16.77$, $p=.000$, $\eta^2=.34$. Bonferroni post hoc comparisons revealed that CT levels at T4 (85 min following administration were significantly lower than CT levels at T1, T2, and T3, *p*'s =.00, .00, and .013, respectively, regardless of group or condition (Fig. 1a). A three-way repeated ANCOVA analysis, controlling for the parent general parenting-related stress, showed a significant effect for condition, $F(3,99)=4.63$, $p=.039$, $\eta^2=.12$. Fathers' overall CT production was higher during the OT as compared to the PL condition (Fig. 1b).

3.2. Infant CT response to father's OT administration

No differences were found in infant CT levels before administration. However, a three-way interaction effect of the group, condition, and time emerged, $F(2,66)=4.83$, $p=.011$, $\eta^2=.13$, indicating differences in CT profiles over time in the OT versus PL condition for infants experiencing high versus low synchrony (Fig. 2a). CT reactivity (baseline-corrected CT change) showed a significant two-way interaction of group by condition, $F(1,33)=7.91$, $p=.008$, $\eta^2=.19$. Among infants experiencing high synchrony, OT administration to parent resulted in CT increase. However,

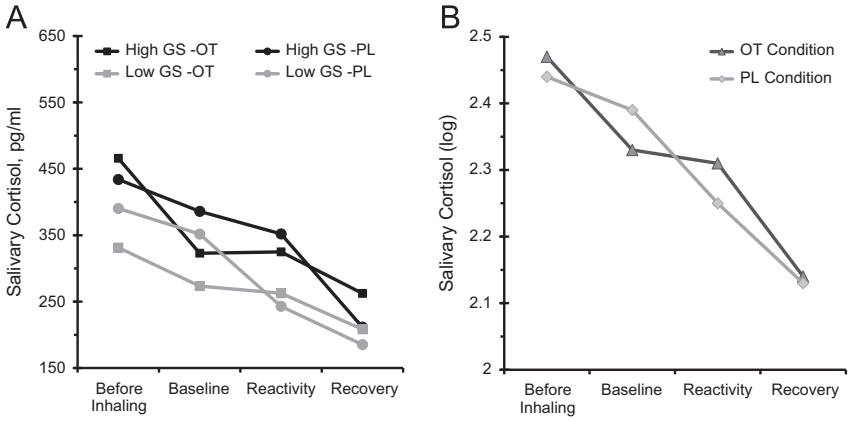

Fig. 1 (A) Fathers' salivary cortisol (CT) concentrations following intranasal administration of 24 IU oxytocin (OT) or placebo (PL), in dyads characterized by low vs. high gaze synchrony (GS). (B) Fathers' salivary CT change following OT vs. PL application. See text for statistics.

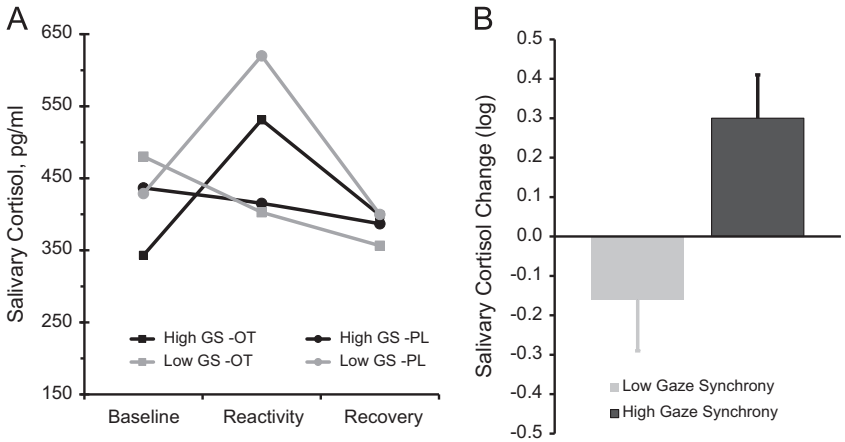

Fig. 2 (A) Infants' salivary cortisol (CT) concentrations following intranasal administration of 24 IU oxytocin (OT) or placebo (PL) to father, in dyads characterized by low vs. high gaze synchrony (GS). (B) Placebo-corrected index of salivary CT change after OT application. Standard bars depict standard error of mean (SEM).

OT administration decreased CT production among infants in the low synchrony group, $t(33)=2.69$, $p=.011$ (Fig. 2b).

3.3. Infant behavioral response during the SF episode

Interestingly, infant's placebo-corrected social gaze towards the father while father was maintaining a still-face position increased in the high-synchrony group but decreased in the low-synchrony group, $t(31)=-2.27$, $p=.03$, indicating greater expectation and puzzlement in parental termination of communication in the high-synchrony infants (Fig. 3). *Fathers' baseline CT level is associated with parent-infant social behaviors*: Fathers and infants' baseline CT did not differ between the OT and PL conditions, $p>.05$ and the two scores were averaged to create a baseline CT composite for fathers and infants separately. Associations between baseline CT and parent–infant behaviors during the free-play episode of the FTFSF (PL condition) were assessed. Significant correlations were found for paternal behaviors and parent–infant dyadic behaviors, but not for infants' behaviors per-se (see Table 1). Specifically, father's CT was negatively correlated with the mean durations of father's neutral affect; mean duration, frequency, proportion (i.e., total duration), and latency to father's proprioceptive touch; frequency of gaze synchrony between father and infant; and touch mys-synchrony – which index the co-occurrence of father touching the infant in a proprioceptive manner while infant is averting gaze from father.

Findings concerning the effect of OT administration on fathers' circulating (salivary) testosterone (T) levels, the relationship between salivary OT and T, and associations between basal level of father's T and specific indices of parent–infant dyadic social interaction are detailed in another publication (Weisman et al., under revision).

Finally, the assessment of change in fathers' self-reported affect, measured by the PANAS before and 40 min after administration, showed no change in either session.

4. Discussion

The current study is the first to test the effects of OT administration on HPA reactivity in the context of parent-infant dyadic interaction and to address its bio-behavioral influences on parent and child's hormonal and behavioral response. Consistent with the *bio-behavioral synchrony* model (Feldman, 2007, 2012a, 2012b), our findings indicate that OT manipulation to the parent altered both parent and infant's physiological and behavioral response to social stress. In accordance with perspectives suggesting that one mechanism by which OT exerts its effects is by increasing the salience of social cues (Bartz et al., 2011; Feldman, 2012a), we found that OT administration increased fathers' HPA response to a social stressor which normally does not induce CT response in parents, only in infants. Moreover, OT administration to the father altered the infant's CT response to the SF paradigm, pointing to a process of biological synchrony. This effect was moderated by the nature of the parent–infant attachment relationship. Among infants experiencing high parent–infant synchrony, OT increased infant HPA reactivity as well as his/her social gaze to the father during the SF episode of the paradigm. On the other hand, among infants experiencing low social synchrony, parental OT functioned to reduce the infant's stress response and diminish social gaze toward the unavailable father. Finally, correlations between father's baseline CT levels and parent–infant behaviors are reported. Overall, these findings are consistent with research indicating that the effects of OT are not uniform and depend on the individual's attachment history and social-collaborative abilities (Bartz et al., 2010; Groppe et al., in press).

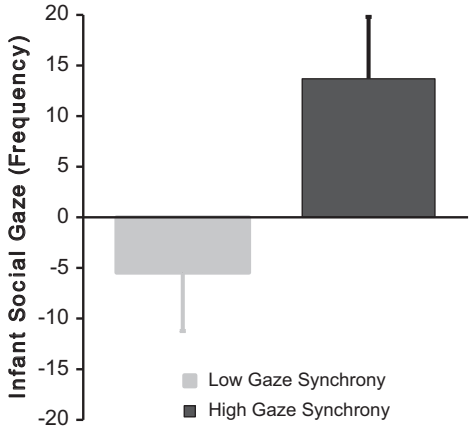

Fig. 3 Number of infants' social gaze towards the father while father was maintaining a still-face position. Standard bars depict standard error of mean (SEM).

Table 1 Pearson correlations between father's mean basal cortisol (CT) level and parent-infant behaviors during free-play (PL condition).

Father basal CT level	
Parental behaviors	
Neutral affect	
Mean duration	−.46**
Proprioceptive touch	
Mean duration	−.54***
Frequency	−.39*
Proportion	−.41*
Latency	−.48**
Parent-infant dyadic behaviors	
Gaze synchrony	
Frequency	−.39*
Proprioceptive touch mys-synchrony	
Mean duration	−.34†
Frequency	−.29†
Proportion	−.31†
(Latency)	−.29†

*$p<.05$.
**$p<.01$.
***$p\leq.001$.
†$p\leq.1$.

The current findings, however, are the first to show such effects based on the concrete assessment of attachment relationships *in real time*, rather than on retrospective accounts of adults' attachment to their parents.

What may be the mechanisms causing CT increase in fathers following OT administration? Previous research has shown that parental CT does not increase in response to maintaining a SF (Feldman et al., 2010a, 2010b, 2010c). Yet, extensive research has shown that between three and six months, infants react with much distress to parental SF, as expressed in high negative arousal, social withdrawal, increased self-soothing behavior, and re-engagement attempts (for review, see Mesman et al., 2009). Plausible explanation for the finding in fathers may be attributed to the effects of OT on increasing social salience in humans (e.g., Bartz et al., 2011; Groppe et al., in press; Weisman and Feldman, in press). The "social salience" hypothesis suggests that OT alters the perceptual salience and/or processing of social cues, regardless of valence. In support of this suggestion are findings indicating that intranasal OT increases gaze to the eye region (Guastella et al., 2008; Andari et al., 2010). An fMRI study showed that gaze to the eye region was linked with enhanced functional connectivity between the amygdala and the superior colliculi (Gamer et al., 2010), brain circuits involving social information processing. Similarly, a recent fMRI study found that OT administration enhanced activation in the ventral tegmental area (VTA) area, which is associated with social reward (Groppe et al., in press). Possibly, under OT fathers were more sensitive to their infants' distress during the SF episode, which led to increased overall father CT concentrations in the OT condition. This finding corresponds with the previous report describing higher baseline salivary CT and greater CT decline in mothers who experienced more sympathy in response to infant cries (Stallings et al., 2001).

Among infants, level of dyadic synchrony was found to moderate the effect of OT on the CT response to the social stressor. Numerous studies have shown that OT effects are especially notable among individuals with lower social skills or poorer attachment histories. On the other hand, among subjects who report more optimal parent-child relationship or better social abilities, the OT system is thought to be sufficiently adaptive and exogenous OT may encounter a ceiling effect and does not have such pro-social effects. For example, a single-dose of OT was found to increase empathic accuracy among individuals with lower social-cognitive proficiency, while no such effects were observed among more socially proficient individuals (Bartz et al., 2010). Groppe et al. (in press) reported that OT impacted response to socially relevant cues only among individuals rated low on sociability. These findings are consistent with the aforementioned research, which points to positive effects for OT only among individuals with low emotion regulation or early abuse. Possibly, the transition from the free-play to the still-face episode was experienced more strongly among the high-synchrony as compared to low-synchrony infants due to their daily experience, and, as seen, the effects of OT on reducing stress functioned only for those dyads whose attachment relationship was less optimal. Such findings are likely to be specific to synchrony and cannot be attributed to greater activity or more parenting behavior. Decreased synchrony is observed in both cases of maternal depression, where minimal parental activity is observed, and maternal anxiety, which co-occur with higher levels of activity, touch, and overt behavior (Feldman et al., 2009). Parent–infant synchrony has been associated with more optimal functioning of several physiological systems, including vagal tone (Feldman and Eidelman, 2007), greater infant salivary oxytocin (Feldman et al., 2010a), and neurodevelopmental maturity (Feldman et al., 2004). Thus, the findings may suggest that for infants experiencing bio-behavioral synchrony, the disruption of such expectations may lead to greater distress and activation of the stress response.

Results of the current study further emphasize the stress-reducing properties of OT treatment in human subjects, and are the first to explore this soothing effect in a developmental context during a concrete parent–infant social interaction. Moreover, present findings suggest that OT treatment to parent may shape the infant's endocrine stress response without direct manipulation to the offspring. This finding, although confined to the scope of the present study, may be fruitfully applied to test the effects of OT administration on a range of stress-related child conditions, although much further research is required to test the effects of acute or chronic OT administration during early developmental stages (Bales et al., in press; Rault et al., 2013). To date, only few published studies have utilized intranasal administration paradigms in children and adolescents (Guastella et al., 2010; Kosaka et al., 2012; Tachibana et al., 2013), with no study directly manipulating OT levels in infants. As the OT system plays a critical role in shaping the child's HPA axis via early caregiving experiences (Hostinar et al., 2013), a more comprehensive understanding on the involvement of OT in children's emerging physiological and behavioral stress responses is in need.

Future research is required to test the multi-level effects of OT administration on reducing stress and anxiety in infants, children, and adults. In particular, anxiety disorders related to social functioning, such as social phobia, or disorders associated with maladaptive social functioning, such as depression, autism, or schizophrenia, may be good candidates for the application of OT interventions (e.g., Meyer-Lindenberg et al., 2011). In order to gain a broader view of OT effects in shaping children's stress-related physiology and behavior within the parental context, future studies should examine OT effects in a dose-dependent manner (MacDonald et al., 2011; Goldman et al., 2011); test the effects of single versus multiple administration (MacDonald and Feifel, 2013); include both healthy and high-risk participant (e.g., depressed); and pay specific attention to the child's developmental stage and emerging social competencies.

Role of the funding sources

The study was supported by the German-Israeli Science Foundation. Sponsors had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Authors OW and RF designed the study. OW ran the experiment. OZS conducted hormonal analyses. OW and RF conducted statistical

analyses and wrote the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Drs. Weisman, Zagoory-Sharon, and Feldman have no conflict of interest to disclose.

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