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Salivary oxytocin mediates the association between emotional maltreatment and responses to emotional infant faces

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ABSTRACT

Childhood emotional maltreatment has been associated with a higher risk for maltreating one's own offspring. In the current study, we explored a possible role of oxytocin in mediating the association between childhood emotional maltreatment and participants' interpretation of infant facial expressions. Oxytocin levels were measured in 102 female participants using saliva samples. They rated the mood of thirteen infants with happy, sad and neutral facial expressions. Emotional maltreatment indirectly influenced responses to happy infant faces by modulating oxytocin levels: higher self-reported emotional maltreatment was related to higher levels of salivary oxytocin which were in turn related to a more positive evaluation of happy infant expressions, but not to the evaluation of sad infant expressions. Oxytocin receptor polymorphism *rs53576* did not moderate the relation between maltreatment experiences and salivary oxytocin levels. Early emotional maltreatment might indirectly affect emotional information processing by altering the oxytonergic system.

1. Introduction

Childhood emotional maltreatment has a worldwide prevalence of 27% [1], and it has enduring effects on neural, physiological and behavioral development [2–4]. Emotional maltreatment has been associated with increased vulnerability to mental health problems such as depression and anxiety, and antisocial behavior [5,6]. In parenting, it might also lead to negative appraisal of infant signals [7] and a higher risk for maltreating one's own offspring [8–11]. In the current study, we explored a possible role of oxytocin in mediating the association between childhood emotional maltreatment and participants' evaluation of infants' mood as derived from infants' facial emotional expressions.

Oxytocin is a neuro-peptide associated with trust, empathy and emotion recognition [12,13]. It is well known for its anxiolytic effects and its effects on prosocial behaviors such as in-group favoritism [14] and sensitive parenting [15–17]. Oxytocin levels can be affected by stressful early life experiences [18,19]. However, the direction of effects is unclear. One study demonstrated a negative relation between early life stress and oxytocin levels, with more stress leading to lower levels of oxytocin [18] whereas other studies showed a positive relation [19]. The diverging outcomes might be (partly) explained by technical differences between these studies, as the oxytocin levels were measured in different body fluids, e.g. in the cerebrospinal fluid in the study of Heim et al. [18] and in plasma in the study of Pierrehumbert et al. [19]. In the present study, we assessed oxytocin levels in saliva. Salivary oxytocin levels have been found to be correlated to plasma oxytocin levels (although modestly; for a review see [20]) and associated with parent and child's social engagement, and affect synchrony and positive communication sequences [21]. We examined the relation between early life emotional maltreatment experiences and salivary oxytocin levels. Moreover, we tested a possible moderating role of oxytocin receptor polymorphism (OXTR) *rs53576* in the relation between emotional maltreatment and oxytocin levels [22]. In previous studies OXTR *rs53576* has been suggested to be a moderator of the effects of intranasal oxytocin administration on the preferences for infant faces as compared to adult faces. Intranasal oxytocin increased the preference for infant faces, but this effect was present only for individuals with GG genotype [22].

Using intranasal administration, oxytocin has been mostly investigated for its role in facial emotion recognition (for meta analysis see [12]). Although most of these studies show increased recognition of happy faces [23], some also report increased recognition of other emotions such as anger and fear [24]. To our knowledge, no studies have examined whether individual differences in endogenous levels of

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oxytocin are associated with differences in emotion recognition. Moreover, none of the previous studies assessed the association of oxytocin with recognition of emotional *infant* faces as opposed to adult faces. From an evolutionary perspective, oxytonergic functioning is strongly implicated in parent–infant bonding. For example, oxytocin selectively increases the preference for infant faces as compared to adult faces [16,22]. In the present study we used images of sad and happy infants to test whether salivary oxytocin levels were related to the evaluation of infant mood as derived from infants' facial emotional expressions.

Emotional maltreatment has been associated with processing biases for some negative emotional stimuli such as anger and sadness, yielding heightened responsivity and reactivity [25–28]. Impaired emotion recognition might result in more problematic interpersonal relationships [29] and more insensitive behavior towards offspring. We therefore examined the involvement of the oxytonergic system in the underlying mechanism responsible for the processing bias of emotional information in individuals with emotional maltreatment experiences.

To summarize, we hypothesized that childhood experiences of emotional maltreatment would be associated with oxytocin levels. However, given the contradictory findings from previous studies, we were not able to predict whether more maltreatment experiences lead to higher or to lower oxytocin levels. Furthermore, we explored the potential role of OXTR *rs53576* in moderating the relation between emotional maltreatment and oxytocin levels. Moreover, in line with previous studies with intranasal administration, we hypothesized that for women with higher levels of oxytocin, infant emotional expressions would be more salient than for women with lower levels of oxytocin. Furthermore, we tested whether oxytocin mediated any association between childhood maltreatment experiences and mood ratings as derived from infants' facial expressions.

2. Methods

2.1. Participants and procedure

Three hundred and fifty three undergraduate students from the Leiden University departments of Education and Child studies and Psychology completed online questionnaires about their childhood experiences of abuse and neglect. Of these, 102 healthy female students (age $M = 19.86$ years, $SD = 1.42$) were randomly invited to participate in the present study. All were nulliparous, a majority (85%) of the participants reported being in the luteal phase of their menstrual cycle (third or fourth week following menstruation) and 74% of the participants reported using oral contraceptives. Exclusion criteria were use of steroidal or any other interfering medications such as analgesics and anti-inflammatory drugs. All participants were non-smokers and reported not having used any recreational drugs in the six months before the experiment. Participants reported not having any current or past neurological or psychological disorder(s). Two participants were excluded from the analysis due to technical errors in the computer session. Seven participants were not included in the final analysis because of missing values of salivary oxytocin levels. The study was approved by the Leiden University Medical Center ethics committee.

Participants were invited to the laboratory for a computer session. The sessions started at 0900, 1200 or 1500 h. Participants provided saliva samples that were used to determine oxytocin levels. Next, they rated the emotion of images of faces of thirteen infants with happy, sad and neutral facial expressions. Participants also rated several infant faces following this task, which is described elsewhere (Parsons et al., submitted for publication).

2.2. Task and measures

2.2.1. Stimuli

The stimuli consisted of grayscale pictures of thirteen infants, each of which was shown with neutral, happy and sad expressions. Infant images were obtained from a standardized database (for detailed description of the stimuli see [30]). Faces were all forward facing, with direct eye gaze, matched for size (300 × 300 pixels) and luminosity. Participants saw a facial image at the center of a 15.3 inch monitor with a visual analog scale immediately to the right. The participants were instructed to rate the mood of the presented picture from *very positive* to *very negative*. The scale ranged from 4 to −4.

Reliability analyses of the mood ratings of the neutral, happy and sad infant faces showed that the internal consistency for the happy and sad faces was high, Cronbach's α (happy) = .81; Cronbach's α (sad) = .84. However, the internal consistency for neutral faces' mood rating was low (Cronbach's $\alpha = .49$); responses to neutral facial expressions were therefore not analyzed. Two scales, one for the mood rating of the happy facial expression and one for the mood rating of the sad facial expression, were created by averaging the ratings for the thirteen infants. The scale for sad facial expression was reversed so that a higher value would represent a more negative rating.

2.2.2. Salivary oxytocin

The saliva samples were immediately stored at −20 °C until batch assay. The samples were assayed using the standard procedures described in detail elsewhere, using the commercially available Enzyme Immuno Assay (EIA) kit (ADI-900-153, Enzo Life Science, Plymouth Meeting, PA) [31–33]. An extraction step was performed to concentrate the sample, increase precision and reduce matrix interference. A strata-X 33 μm polymeric reversed phase SPE sorbent was equilibrated in a 96-well plate containing 60 mg sorbent per well, Phenomenex, Torrance CA, by adding 1 ml MeOH followed by 1 ml of water. Next, 0.8 ml of saliva was acidified with 0.4 ml of 1.5% trifluoroacetic acid (TFA) and centrifuged at 6000 ×*g* for 20 min at 4 °C. The supernatant was loaded onto the pre-treated strata-X plate. The wells were slowly washed with 1.5 ml of 0.1% TFA, and then the peptide was eluted with 1 ml of 80% acetonitrile. The eluant was collected in a polystyrene tube and evaporated to dryness under a N_2 stream. The residue was reconstituted in 250 μl of assay buffer. Oxytocin extraction efficiency was 94%, as determined by spiking with a known amount of hormone and extracting this known amount along with the samples. Oxytocin levels in extracted saliva were then quantified using the oxytocin EIA, in which the endogenous oxytocin hormone competes with exogenously added alkaline phosphatase linked oxytocin, for binding sites on oxytocin antibody. After overnight incubation at 4 °C, excess reagents were washed away and the bound oxytocin phosphatase was incubated with a substrate. After 1 h this enzyme reaction, which generates a yellow color, was stopped and the optical density (OD) was measured on a Sunrise plate reader (Tecan, Research Triangle Park, NC) at 405 nm. The intensity of the color is inversely proportional to the concentration of endogenous oxytocin. The hormone content (in pg/ml) was determined by plotting the OD of each sample against a standard curve. One individual had extremely high oxytocin levels (>3 standard deviations above the mean). The oxytocin level values for this individual were substituted with the next highest score (Winsorized; [34]).

2.2.3. Genotyping

Another sample of saliva was collected using specialized DNA collection kits (Oragene DNA OG-500, DNA genotech) and was used to determine oxytocin receptor (OXTR) polymorphism, *rs53576*. Samples were analyzed at *BaseClear* laboratories, Leiden, Netherlands. DNA was extracted from the samples using the Chemagic buccal swab kit on a Chemagen Module I workstation (Chemagen Biopolymer Technologie AG, Baesweiler, Germany). DNA concentrations were measured using the Quant-iT DNA Assay kit (Invitrogen, Breda, Netherlands). The average yield was 4 μg of genomic DNA per sample. DNA was amplified in a polymerase chain reaction (PCR) using forward primer (5′-GCCCACCA TGCTCTCCACATC-3′) and a reverse primer (5′-GCTGGACTCAGGAGGA ATAGGGAC-3′). PCR reactions contained between 10 and 100 ng

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genomic DNA template and 10 pmol of forward and reverse primers. PCR was carried out in the presence of 5% dimethyl sufoxide with 0.3 U of BioThermAB polymerase (GeneCraft, Munster, Germany) in a total volume of 30 μl using the following cycling conditions: an initial denaturation step of 3 min at 95 °C, followed by 40 cycles of 30 s at 95 °C, 30 s at 60 °C, 1 min at 72 °C and a final extension step of 3 min at 72 °C. To determine the A/G polymorphism, PCR fragments were sequenced using the forward primer and dye terminator chemistry (BigDye v3.1, Applied Biosystems).

As might be expected in this predominantly Caucasian sample (>90% Caucasian), the number of AA carriers was small (Bakermans-Kranenburg & Van IJzendoorn, in press), AA = 6, AG = 36, and GG = 51. The genotype distribution was in the Hardy–Weinberg equilibrium, χ^2 (1, n = 93) = 0.01, p = 0.92. AA and AG genotypes were combined in the analyses.

2.2.4. Childhood Trauma Questionnaire

Participants indicated their experiences of abuse and neglect until the age of 16 using the Childhood Trauma Questionnaire Short Form (CTQ-SF; [35]). Twenty-eight items covered experiences of physical abuse, emotional abuse, sexual abuse, physical neglect, or emotional neglect. Each item (e.g. "During my childhood I felt hated by family") was rated on a 5-point scale ranging from *never true* to *very often true*. An emotional maltreatment scale was created by averaging the items tapping into the 'emotional abuse' and 'emotional neglect' dimensions. The internal consistency of this scale was high (Cronbach's α = .91). The mean scale score was M = 1.49 (SD = 0.48, range = 1–3.60). The distribution of scores was positively skewed, with all but one cases having experienced none to moderate maltreatment (range 1–3.10) and only one case (score 3.60) having extreme emotional maltreatment experiences (based on the classification suggested by the developers of CTQ). Log transformation was performed to obtain a normal distribution. The scores on the items of physical abuse and neglect and sexual abuse had a low variance and skewed distribution. These scales were not used in the current study.

2.3. Statistical analyses

Bivariate associations between the variables were computed. Participants' use of contraceptives and the phase of menstrual cycle were recorded but as they were not associated with any of the independent or dependent variables (Table 1), they were not co-varied in the analyses. Two mediation analyses were performed using a macro package for SPSS, available on-line (http://www.afhayes.com/spss-sas-and-mplus-macros-and-code.html) developed by Preacher and Hayes [36]. The mood ratings of the happy expression and sad expression were the dependent variables. Log transformed emotional maltreatment was entered as the independent variable and salivary oxytocin level as the mediator. We also tested whether the relation between emotional maltreatment and oxytocin levels was moderated by OXTR polymorphism. Centered predictors (emotional maltreatment and OXTR *rs53576* genotype) were entered first in a multiple regression and the interaction term of the polymorphism with emotional maltreatment was added in the next step.

3. Results

3.1. Bivariate associations

Table 1 presents the bivariate correlations between the variables. The mood ratings of happy infant faces and sad infant faces were correlated (r = .53, p < .001). Participants who rated the mood of the happy faces as more positive rated the mood of sad faces as more negative. Childhood experience of emotional maltreatment was correlated with salivary oxytocin levels (r = .25, p = .02). Participants who experienced more emotional maltreatment had elevated levels of oxytocin. Oxytocin levels were associated with the mood ratings of happy infant faces (r = .33, p = .001). Participants with higher oxytocin levels rated the mood of the happy faces as more positive than participants with lower oxytocin levels. The association between oxytocin level and mood rating of the sad faces was not significant (r = .16, p = .14). OXTR polymorphism was not associated with the mood ratings (all p > .05).

3.2. Multivariate analysis

Results of the mediation analysis with the mood rating of the happy infants as the dependent variable showed that the indirect path from emotional maltreatment through oxytocin level to mood rating was significant (b = 0.33, SE = 0.15, CI = .08, .69). Emotional maltreatment was positively related to oxytocin level (b = 2.75, SE = 1.12, p = .02), and oxytocin levels were positively related to the mood ratings of happy infants (b = 0.12, SE = 0.03, p < .001). The direct path between emotional maltreatment and infant mood rating was not significant, (b = −0.09, SE = 0.39, p = .82). The strength of this path increased somewhat after controlling for oxytocin levels, but it did not reach significance (b = −0.12, SE = 0.38, p = .27). This shows that the effects of emotional maltreatment on infant mood rating were indirect and emotional maltreatment appears to exert its influence by modulating oxytocin levels (see Fig. 1 in which β values are presented). For the mood ratings of the infant faces with sad expressions, the indirect path from emotional maltreatment through oxytocin level was not significant, (b = 0.12, SE = 0.11, CI = −.02, .42). The direct path between emotional maltreatment and negative mood rating was also not significant, (b = 0.57, SE = 0.39, p = .15).

We performed a hierarchical multiple regression analysis to examine whether the relation between emotional maltreatment and oxytocin levels was moderated by the OXTR genotype. The main effect of the OXTR genotype (GG vs. AG/AA) on oxytocin levels was not significant (b = −0.02, SE = 0.14, p = .90). The interaction between emotional maltreatment and OXTR genotype was not significant either (b = −0.45, SE = 1.21, p = .71), showing that the relation between emotional maltreatment and oxytocin level was not moderated by OXTR *rs53576*.

4. Discussion

More emotional maltreatment experiences predicted higher salivary oxytocin levels. Moreover, as expected, higher salivary oxytocin levels compared to lower oxytocin levels were associated with more positive

Table 1
Descriptive statistics and bivariate correlations between the predictors and ratings of infant facial expressions.

	Range	Mean (SD)	1	2	3	4	5
1. Oxytocin receptor *rs53576*	GG/AA;AG	55% (GG)		0.00	0.05	−0.01	−0.01
2. Oxytocin levels (pg/ml)	0.90 to 7.00	2.65 (1.32)			0.25*	0.33***	0.16
3. Emotional maltreatment (Log)	0.00 to 0.56	0.16 (0.12)				−0.02	0.15
4. Mood rating (happy expression)	1.53 to 3.93	2.63 (.45)					.53***
5. Mood rating (sad expression)	1.30 to 3.70	2.48 (.46)					

Note. * p < .05; ** p < .01; *** p < .001.

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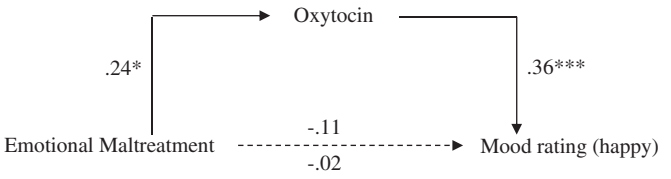

Fig. 1. Indirect effect of childhood emotional maltreatment on the mood rating of happy infant faces is mediated by oxytocin. The overall indirect effect is significant, $B = 0.33$, SE = .15, CI = .08, .69. Note. * $p < .05$, *** $p < .001$. β-values are presented in the figure.

ratings of infants' mood when happy infant faces were shown, indicating better recognition of happy infant faces. Our results suggest that having been emotionally maltreated may indirectly influence responses to emotional infant faces by modulating oxytocin levels.

Elevated oxytocin levels in participants with more emotional maltreatment experiences are in line with a study on sexually abused females (with mixed gender control subjects) showing higher plasma oxytocin levels in individuals with more maltreatment experiences [19]. A recent study with older children also showed higher urinary oxytocin levels in girls who experienced physical abuse as compared to physically abused boys and non-maltreated age-matched controls [37]. Our finding of an association between maltreatment and salivary oxytocin is however in contrast with a small pilot study ($N = 22$) showing decreased cerebrospinal oxytocin levels in females (of mixed ethnicity) with a history of maltreatment, in particular emotional abuse [18]. Our study differs from the two studies in several respects. The source of oxytocin levels varies across the studies (concentrations in cerebrospinal fluid, plasma or saliva), as did the type of abuse (sexual versus emotional maltreatment), whereas variations in gender and ethnic differences may also play a role. Moreover, our study included a non-clinical sample of female university students. It is not clear whether the previous studies used participants with clinical or non-clinical post traumatic symptoms of abuse.

Experiments with intranasally administered oxytocin have shown that recognition of various emotions at low intensities is enhanced after oxytocin administration [12,23,24]. In the present correlational study participants rated the mood of emotional infant faces. Higher levels of oxytocin appeared to be associated with more positive perceptions of infant mood when viewing happy infant expressions, which is generally consistent with experimental evidence of enhanced emotion recognition after intranasal administration of oxytocin. Of course, salivary oxytocin levels might not be direct reflections of oxytocin levels in brain regions relevant for empathic concern, an issue that also remains to be solved in experimental oxytocin studies on humans ([38], but see [39] for evidence in rodents).

Our results might provide some insight into the mechanisms by which oxytocin leads to more positive caretaking behaviors [16]. Oxytocin has been proposed to facilitate interpersonal trust by increasing sensitivity to happiness cues of adult faces [23]. Similarly, more positive appraisals of infant cues might represent an increased reward value of infant stimuli for the caretaker [40], thereby facilitating more sensitive parenting responses towards the infants.

Previous studies with adult faces have proposed various mechanisms explaining the effects of oxytocin on enhanced emotion recognition, such as modulation of eye gaze [24,41,42], decreased effortful processing of affective information [43], wider pupil dilatation [44], or decreased amygdala activation [45,46]. Oxytocin not only reduces amygdala activation but also enhances functional connectivity between the amygdala and the orbitofrontal cortex, the anterior cingulate, the hippocampus, the precuneus, the supramarginal gyri, and the middle temporal gyrus [40]. Increased functional connectivity between the amygdala and these brain regions involved in emotion regulation may reduce negative emotional arousal while enhancing the incentive salience of the infant laughter [40,47]. Similar enhanced neural connectivity might be present or elicited more easily in those individuals who have higher naturally produced oxytocin levels when happy infant faces are processed.

Emotional maltreatment has been associated with difficulty in discriminating emotional expressions [26]. In the present study, we found some evidence for an indirect effect of emotional maltreatment on the perception of emotional infant faces via elevated oxytocin levels: more emotional maltreatment was associated with higher levels of salivary oxytocin which were related to a more positive assessment of happy infant expression. Various animal and human studies have shown increased oxytocin levels in response to stressors [48,49]. Higher oxytocin levels have been found in females with more attachment anxiety [49,50]. The anxiolytic role of oxytocin [51,52] might explain why emotionally maltreated individuals 'need' more of it to cope with stressful events and situations, which may contribute to resilience in some individuals [53,54].

We did not find evidence for a role of OXTR *rs53576* in influencing salivary oxytocin levels, in this relatively small sample. The polymorphism did not moderate the relation between maltreatment experiences and salivary oxytocin levels either. To our knowledge, only one study examined the association between OXTR polymorphism *rs2254298* and plasma oxytocin levels, showing that the presence of the minor A allele was associated with higher oxytocin levels [55]. A recent meta-analysis however failed to find a significant association between the two most popular OXTR polymorphisms (*rs53576* and *rs2254298*) and various social and behavioral outcomes (Bakermans-Kranenburg & Van IJzendoorn, in press). The current study supports the general conclusion of the meta-analysis that the functional role of OXTR *rs53576* has not yet been established.

There were a number of limitations in this study. Firstly, our sample consisted of nulliparous female university students who did not report many severe past or current post-traumatic symptoms of emotional maltreatment. Generalizing our findings to experienced mothers, to males, or to individuals with clinical levels of post traumatic symptoms because of emotional maltreatment is not possible based on this sample. Oxytocin may follow an inverted U-shape relation (as shown between plasma oxytocin and trust, [56]) resulting in lower oxytocin levels with severe maltreatment experiences. Such a relation with maltreatment, if present, might show a different pattern of results compared to the findings presented here. Nevertheless clinical levels of post traumatic symptoms might not be needed to trigger depressive or neglectful parenting responses in individuals with child emotional maltreatment experiences, and the current results might thus be applicable to a more general, non-clinical population. Secondly, oxytocin levels were assessed in saliva, which might not reflect the actual *working* oxytocin levels in the brain. Studies using intranasal oxytocin administration however provide some evidence for the association between central oxytocin levels and salivary oxytocin levels [38,57], and for the association between intranasally elevated levels of oxytocin (also reflected in salivary levels; [33]) and altered resting state brain activity [47]. Moreover, differences in studies due to different assay methods (for e.g. extraction methods for reducing interference and radio- *versus* enzyme-immunoassay techniques) as well as the controversies regarding the differences and similarities between oxytocin levels measured in various body fluids such as plasma, cerebrospinal fluid and urine should be taken into account while interpreting these findings and should be addressed in future studies [20]. Finally, the moderating effect of social support on the relation between emotional maltreatment and oxytocin levels might be important and should be examined in future work. Social support has been shown to be associated with oxytocin levels as well as with sensitivity in infant caretaking [31,58,59], and is also an important factor in post-traumatic coping [54].

To summarize, our findings suggest that experiences of childhood emotional maltreatment may alter salivary oxytocin levels, which in turn are related to more positive perceptions of infant stimuli with positive emotion. Through this indirect effect, early emotional maltreatment might influence the processing of emotional information, although the

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causal relationship implied in this interpretation would need to be the subject of further investigation.

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Conflict of interest

None of the participating institutions and authors reported biomedical financial interests or potential conflicts of interest regarding this study.

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