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# Perception of infant cues :the role of childhood experiences and oxytocin

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# *Perception of infant cues*
# *The role of childhood experiences and oxytocin*

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# *Perception of infant cues*

# *The role of childhood experiences and oxytocin*

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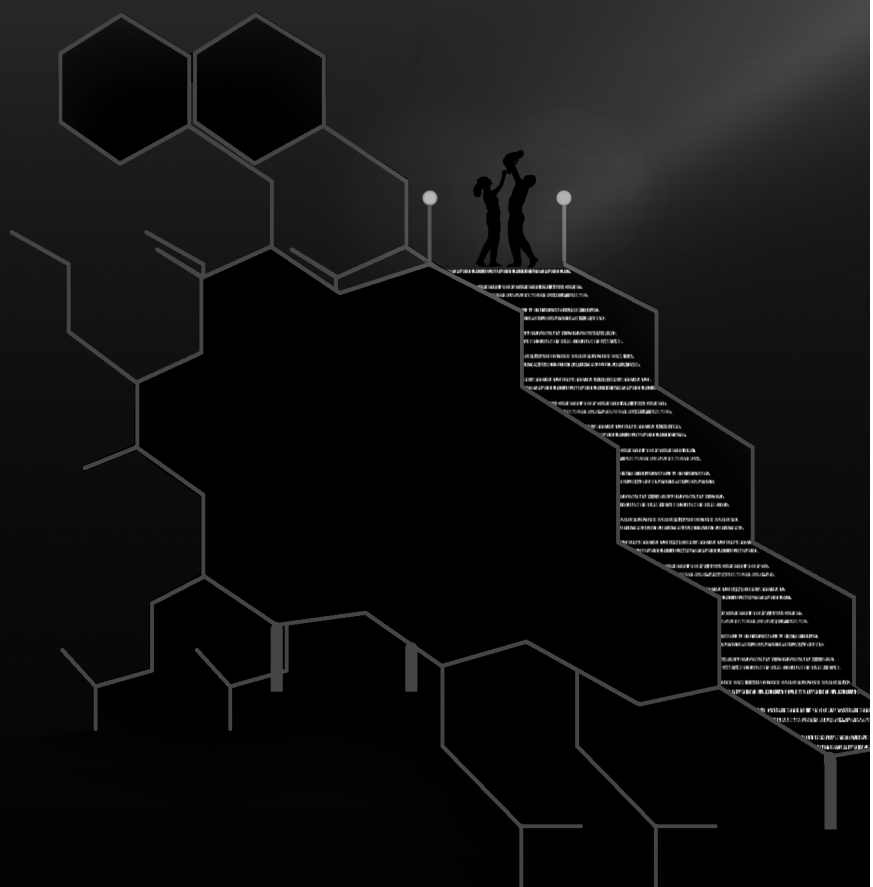
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# 1

# General Introduction



Parenting an infant is not easy. It is a process that requires correct perception of an infant's signals, followed by a timely and appropriate response to relieve the infant from discomfort or distress (Ainsworth *et al*, 1978). However, individuals differ in their perception of infant signals and in their ability to provide appropriate responses (Montoya *et al*, 2012). In the present thesis, we studied individual differences in the perception of infant signals due to adverse childhood experiences. Moreover, we tested whether experimental interventions, more specifically social reward training and administration of oxytocin, might change the perception of infant signals, to be perceived as more positive or less negative.

***Infant signals***

Preverbal infants use a combination of facial expressions and vocalizations to communicate their physical and affective states, such as their need for social engagement, feelings of hunger or anxiety (Vallotton, 2009). However, depending on their temperament, perinatal stress experiences and responses from the caregiver, infants differ in the intensity and frequency of these displayed emotions (Nugent *et al*, 1996; Schmid *et al*, 2011; Van der Wal *et al*, 2007). Both intensity and frequency of the displayed emotions have in their turn been shown to affect the responsiveness and quality of caregiving provided by parents (Dessureau *et al*, 1998; Zeskind, 1988). More positive behavior of an infant is rewarding for the parent and might therefore lead to more positive responses (Strathearn *et al*, 2009), whereas frequent infant crying may be stressful for the caregiver and might result in insensitive, harsh, or even maltreating responses (Reijneveld *et al*, 2004). Besides temperamental cues, infants' cuteness as perceived by the caregiver might also affect the perception and responses to infants' signals (Langlois *et al*, 1995). In the present studies, we used a standard set of infant stimuli to minimize the variations in perception caused by such natural variations in infant related attributes. This was done in order to study individual differences in caregivers' characteristics in a standardized way, shaping their perception of infant facial expressions and vocalizations.

***Individual characteristics***

Individual differences between caregivers, possibly brought upon by differences in genetic makeup and life experiences, may affect the perception of infant cues (Crouch *et al*, 2008; Out *et al*, 2010). Early life experiences, life stressors, hormone levels such as testosterone and oxytocin, social support, and socio-economic status have all been related to differences in perception of infant signals, thereby affecting the quality of caregiv-

ing responses (Crockenberg, 1988; Crowe and Zeskind, 1992; Donovan *et al*, 1978). For example, fathers with lower testosterone levels show higher empathy and responsiveness to infant crying than fathers with higher testosterone levels (Fleming *et al*, 2002; but also see Van Anders *et al*, 2012); and mothers who experience more social support are more positive towards their infants and provide more sensitive caregiving (Crockenberg, 1988; Lee *et al*, 2009a). In the present thesis, we examined the influence of early experiences of emotional maltreatment on the perception of infant cues. We tested how experiences of childhood emotional maltreatment and experienced maternal use of love withdrawal as a discipline strategy might affect individuals' perception of infant cues such as smiling and crying.

***Childhood emotional maltreatment and maternal love withdrawal***

Emotional abuse and neglect and excessive use of love withdrawal may be considered psychological maltreatment (Euser *et al*, 2010). Experiencing this in childhood has been shown to affect individual's psychological development and to influence social behavioral outcomes (Egeland *et al*, 2002; Shenk *et al*, 2013; Sroufe, 2005; Van Harmelen *et al*, 2010). For instance, experiences of childhood emotional maltreatment have been associated with processing biases during recognition of emotional states such as fear and anger (Cicchetti and Curtis, 2005; Curtis and Cicchetti, 2011; Masten *et al*, 2008), and experiencing love withdrawal from parents has been associated with heightened processing of emotional stimuli (Huffmeijer *et al*, 2011). Moreover, these adverse early life experiences also affect parenting and perceptions of self and others (Belsky and Vondra, 1989; Crawford and Wright, 2007). We studied the effects of childhood experiences with emotional maltreatment or with love-withdrawal on individuals' evaluation of infant emotional facial expressions and infant temperamental cues. Sensitive parenting is of great societal importance and intergenerational transmission of caregiving behaviors has been noted (Belsky *et al*, 2009; Van IJzendoorn, 1992). However, the underlying biological mechanisms that are responsible for the influence of early life experiences on the perception of infant cues are not well understood. We studied the involvement of the oxytonergic system in affecting infant cue perception to shed light on some of the neurobiological mechanisms.

***Oxytonergic system***

Oxytocin is a nona-peptide which apart from its peripheral actions in facilitating vaginal birth and milk ejection (Lee *et al*, 2009b) has been widely studied for its actions

on central nervous system controlled behaviors (Guastella and MacLeod, 2012; Heinrichs *et al*, 2009; MacDonald and MacDonald, 2010). It has been shown to affect behaviors such as mate recognition, sensitive parenting, memory of conspecifics, and other social behaviors such as trust and empathy (Baumgartner *et al*, 2008; Churchland and Winkielman, 2012; De Dreu, 2012; Feldman, 2012). In parenting, serum and salivary oxytocin levels are associated with parent and child social engagement, positive communication and affect synchrony (Feldman *et al*, 2011). We studied whether endogenous oxytocin levels as assessed in saliva were associated with the perceived mood from infant facial pictures. Next to the endogenous levels of oxytocin, single nucleotide polymorphisms on the oxytocin receptor gene are shown to moderate the relation between oxytocin and social behaviors (Feldman *et al*, 2012; Marsh *et al*, 2012), and to affect sensitive parenting (Bakermans-Kranenburg and Van IJzendoorn, 2008; Riem *et al*, 2011b), although a recent meta-analysis did not confirm any main effect of oxytocin receptor polymorphism on human behavior (Bakermans-Kranenburg and Van IJzendoorn, 2013). In the present thesis we assessed the potentially moderating influence of oxytocin receptor gene polymorphism *rs53576* on the relation between early life adverse experiences and salivary oxytocin levels.

In humans, intranasal administration has become a commonly used method for experimentally increasing the oxytocin level in order to study its causal effects (Baumgartner *et al*, 2008; Domes *et al*, 2007; Heinrichs *et al*, 2009; Kirsch *et al*, 2005). Brain activity and behavioral changes after nasal spray administration provide evidence for the efficacy of this method. Intranasal administration of oxytocin increases salivary levels for seven hours post nasal spray, giving an indication of time-line of its bioavailability (Van IJzendoorn *et al*, 2012). Moreover, using intranasal administration, oxytocin seems to enhance sensitive caregiving in fathers towards their toddlers (Naber *et al*, 2013; Naber *et al*, 2010). Oxytocin may also decrease aversion to infant stimuli such as infant crying (Riem *et al*, 2011a) and affect the neural connectivity in response to infant laughing (Riem *et al*, 2012). Oxytocin has been implicated in emotion processing such as early detection of positive or negative emotion in adult faces, and better reading of the mind in the eyes (Guastella *et al*, 2012; Guastella *et al*, 2008a; Marsh *et al*, 2010; Petrovic *et al*, 2008). It increases recognition of both positive emotions such as happy facial cues and negative emotions such as angry and fearful facial cues (Domes *et al*, 2012; Marsh *et al*, 2010). However, emotion recognition has so far been studied using adult facial cues. Even though oxytocin has been highly implicated in the initiation and quality of caregiving behaviors, recognition of infant emotion and temperament remained largely unexplored.

In the present thesis we studied the association of endogenous oxytocin levels with the perception of infant stimuli. Moreover, we conducted a double-blind, randomized experiment to see how increased levels of oxytocin affect the memory for infant temperamental cues.

***Baby Social Reward Task (BSRT)***

Infant temperament is associated with maternal sensitivity and (indirectly) with attachment security (Van IJzendoorn and Bakermans-Kranenburg, 2012). It refers to the basic characteristics of a trait and shows stability over time, as opposed to mood which reflects the current state of mind and is transient (Gray *et al*, 2001). In order to study the effect of perceived temperament on individuals' perception of infant cuteness and amount of expended effort towards the infant, we developed a novel learning task together with a team of researchers from Oxford University, UK (Chapter 3). The BSRT is a probabilistic task in which infant mood information is experimentally manipulated, making some infants more *happy* or more *sad* than other infants. During the task participants get information about the mood of various infants, which can range from *very happy - moderately happy - moderately sad - very sad*. We tested whether experimental manipulation of infant mood affected perception of infant cuteness and other dimensions such as *easy* and *difficult* temperament. We also tested whether intranasal administration of oxytocin modulated the recognition memory of these manipulated temperaments.

***Thesis outline***

In the present thesis we studied the individual differences associated with differences in perception of infant signals. Chapter 2 and 5 focus on the relation between experiences of childhood psychological maltreatment and perceived mood of infants with happy and sad facial expression or infant crying (using the infant simulator; described in chapter 5). As childhood maltreatment has been associated with altered levels of oxytocin (Heim *et al*, 2008; Pierrehumbert *et al*, 2010), and with enhanced recognition of various emotions (Van IJzendoorn and Bakermans-Kranenburg, 2012), we tested whether oxytocin mediated the relation between childhood emotional maltreatment and perceived positivity of infant mood from pictures of happy and sad infants (Chapter 2).

As perception affects the quality of caregiving (Out *et al*, 2012), in Chapter 3 we describe the novel BSRT to experimentally manipulate mood of infants and study the changes in perceived cuteness and perceived *easiness* of infants in terms of positive versus negative temperaments.

Oxytocin has been implicated in emotion recognition memory and sensitive parenting (Feldman *et al*, 2007; Guastella *et al*, 2008b). In Chapter 4 we report on a study testing whether intranasal oxytocin administration affected the memory for infant temperament and whether experiences of childhood emotional maltreatment moderated these effects. In the Discussion we elaborate on our findings in the broader context of a search for neurobiological mechanisms explaining variations in parenting.

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# 2

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



***Ritu Bhandari**, Marian J. Bakermans-Kranenburg, Rixt van der Veen, Christine E. Parsons, Katherine S. Young, Karen M. Grewen, Alan Stein, Morten L. Kringelbach, Marinus H. van IJzendoorn.*

*Manuscript submitted for publication.*

## 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. Increased levels of endogenous oxytocin may make happy infant stimuli more salient in individuals with childhood emotional maltreatment experiences, and lower the risk for maltreating their own offspring.

## Keywords

Oxytocin, Emotional maltreatment, Healthy females, Infant faces, Face processing, Emotion processing.

## Introduction

Childhood emotional maltreatment has a worldwide prevalence of 27% (Stoltenborgh *et al*, 2012), and it has enduring effects on neural, physiological and behavioral development (Spinhoven *et al*, 2010; Van Harmelen *et al*, 2010; Van Harmelen *et al*, 2012). Emotional maltreatment has been associated with increased vulnerability to mental health problems such as depression and anxiety, and antisocial behavior (Egeland *et al*, 2002; Gibb *et al*, 2007). In parenting, it might also lead to negative appraisal of infant signals (Crouch *et al*, 2008) and a higher risk for maltreating one's own offspring (Belsky and Vondra, 1989; Berlin *et al*, 2011; Dixon *et al*, 2005; Van IJzendoorn, 1992). 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 (MacDonald and MacDonald, 2010; Van IJzendoorn and Bakermans-Kranenburg, 2012a). It is well known for its anxiolytic effects and its effects on prosocial behaviors such as in-group favoritism (De Dreu *et al*, 2010), and sensitive parenting (Feldman, 2012; Feldman *et al*, 2007; Naber *et al*, 2013). Oxytocin levels can be affected by stressful early life experiences (Heim *et al*, 2008; Pierrehumbert *et al*, 2010). 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 (Heim *et al*, 2008) whereas other studies showed a positive relation (Pierrehumbert *et al*, 2010). 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*, (2008) and in plasma in the study of Pierrehumbert *et al*, (2010). In the present study, we assessed oxytocin levels in saliva. Salivary oxytocin levels have been found to be correlated to plasma oxytocin levels and associated with parent and child's social engagement, affect synchrony and positive communication sequences (Feldman *et al*, 2011). 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 (Marsh *et al*, 2012). 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 (Marsh *et al*, 2012).

Using intranasal administration, oxytocin has been mostly investigated for its role in facial emotion recognition (for meta analysis see Van IJzendoorn *et al*, 2012a). Although most of these studies show increased recognition of happy faces (Marsh *et al*, 2010), some also report increased recognition of other emotions such as anger and fear (Lischke *et al*, 2012). To our knowledge, no studies have examined whether individual differences in endogenous levels of 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 (Feldman *et al*, 2007; Marsh *et al*, 2012). 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 (Curtis and Cicchetti, 2011; Masten *et al*, 2008; Pollak *et al*, 2000; Pollak *et al*, 1997). Impaired emotion recognition might result in more problematic interpersonal relationships (Crawford and Wright, 2007) 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.

## Methods

### *Participants and procedure*

Three hundred and fifty three undergraduate students from the Leiden University Institute of Education and Child Studies and Department of 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*, in press).

### *Task and measures*

***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 Kringelbach *et al*, 2008). Faces were all forward facing, with direct eye gaze, matched for size (300x300 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 α = .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 more negative rating.

***Salivary oxytocin.*** The saliva samples were immediately stored at -20$^{0}$C until batch assay. The samples were assayed using standard procedures described in detail elsewhere, using the commercially available Enzyme Immuno Assay (EIA) kit (ADI-900-153, Enzo Life Science, Plymouth Meeting, PA) (Grewen *et al*, 2010; Holt-Lunstad *et al*, 2008; Van IJzendoorn *et al*, 2012b). Briefly, an extraction step was performed to concentrate the sample, increase precision and reduce matrix interference. 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$^{0}$C, excess reagents were washed away and the bound oxytocin phosphatase was incubated with a substrate. After 1h 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 was substituted with the next highest score (Winsorized; Tabachnick and Fidell, 2006).

***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, the 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, the 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'-GCCCACCATGCTCTCCACATC-3') and a reverse primer

(5'-GCTGGACTCAGGAGGAATAGGGAC-3'). PCR reactions contained between 10 and 100 ng genomic DNA template, 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: 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 and Van IJzendoorn, 2013), AA = 6, AG = 36, GG = 51. The genotype distribution was in Hardy–Weinberg equilibrium, $\chi^2(1, n = 93) = 0.01$, $p = 0.92$. AA and AG genotypes were combined in the analyses.

***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; Bernstein *et al*, 2003). 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 $\alpha$ =.91). As the distribution of scores was positively skewed, 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.

***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 covaried 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 (Preacher and Hayes, 2008). 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.

## Results

### *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).

### *Multivariate analysis*

Results of the mediation analysis with 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 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 modu-

*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 (0.45) | | | | | 0.53*** |
| 5. Mood rating (sad expression) | 1.30 to 3.70 | 2.48 (0.46) | | | | | |

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

lating oxytocin levels (see Figure 1 in which $\beta$ 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 OXTR genotype. The main effect of 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*.

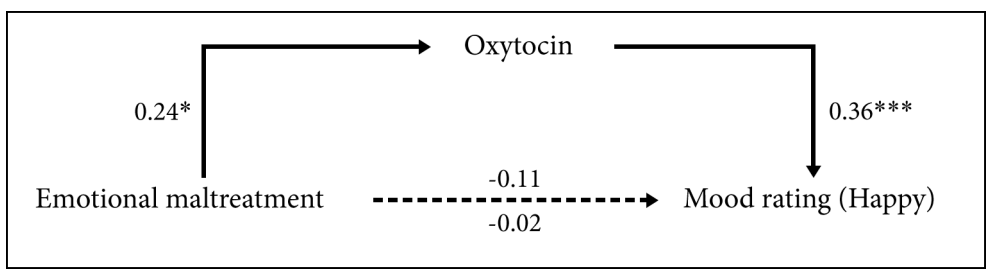



***Figure 1. Indirect effect of childhood emotional maltreatment on the mood rating of happy infant faces is mediated by oxytocin.*** *The overall indirect effect is significant, B = 0.33, SE = .15, CI = .08, .69. * p < .05, *** p < .001.* β*-values are presented in the figure.*

## 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 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 (Pierrehumbert *et al*, 2010). 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 (Heim *et al*, 2008). 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 (Lischke *et al*, 2012; Marsh *et al*, 2010; Van IJzendoorn *et al*, 2012a). 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 (Guastella and MacLeod, 2012; but see Neumann *et al*, 2013 for evidence in rodents).

Our results might provide some insight into the mechanisms by which oxytocin leads to more positive caretaking behaviors (Feldman *et al*, 2007). Oxytocin has been proposed to facilitate interpersonal trust by increasing sensitivity to happiness cues of adult faces (Marsh *et al*, 2010). Similarly, more positive appraisals of infant cues might represent an increased reward value of infant stimuli for the caretaker (Riem *et al*, 2012), 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 (Domes *et al*, 2012; Guastella *et al*, 2008; Lischke *et al*, 2012), decreased effortful processing of affective information (Ellenbogen *et al*, 2012), wider pupil dilatation (Prehn *et al*, 2013), or decreased amygdala activation (Domes *et al*, 2007; Petrovic *et al*, 2008). 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 (Riem *et al*, 2012). 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 (Riem *et al*, 2012, in press). 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 (Pollak *et al*, 1997). 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 (Taylor *et al*, 2010; Tops *et al*, 2007). Higher oxytocin levels have been found in females with more attachment anxiety (Taylor *et al*, 2010; Weisman *et al*, 2013). The anxiolytic role of oxytocin (Ditzen *et al*, 2009; Neumann and Landgraf, 2012) 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 (DuMont *et al*, 2007; Feder *et al*, 2009).

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 (Feldman *et al*, 2012). 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 *et al*, 2013). 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 any 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 symp-

toms because of emotional maltreatment is not possible based on this sample. 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 (Guastella *et al*, 2012; Weisman *et al*, 2012), and for the association between intranasally elevated levels of oxytocin (also reflected in salivary levels; Van IJzendoorn *et al*, 2012b) and altered resting state brain activity (Riem *et al*, in press). 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 (Grewen *et al*, 2005; Holt-Lunstad *et al*, 2008; Quittner *et al*, 1990), and is also an important factor in post-traumatic coping (Feder *et al*, 2009).

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 causal relationship implied in this interpretation would need to be the subject of further investigation. We speculate that an evolutionary adaptive, buffering mechanism may be involved: In individuals with experiences of emotional maltreatment, increased levels of oxytocin might mitigate or lower the risk of maltreating their own offspring and render the individuals more open to rewarding infant stimuli.

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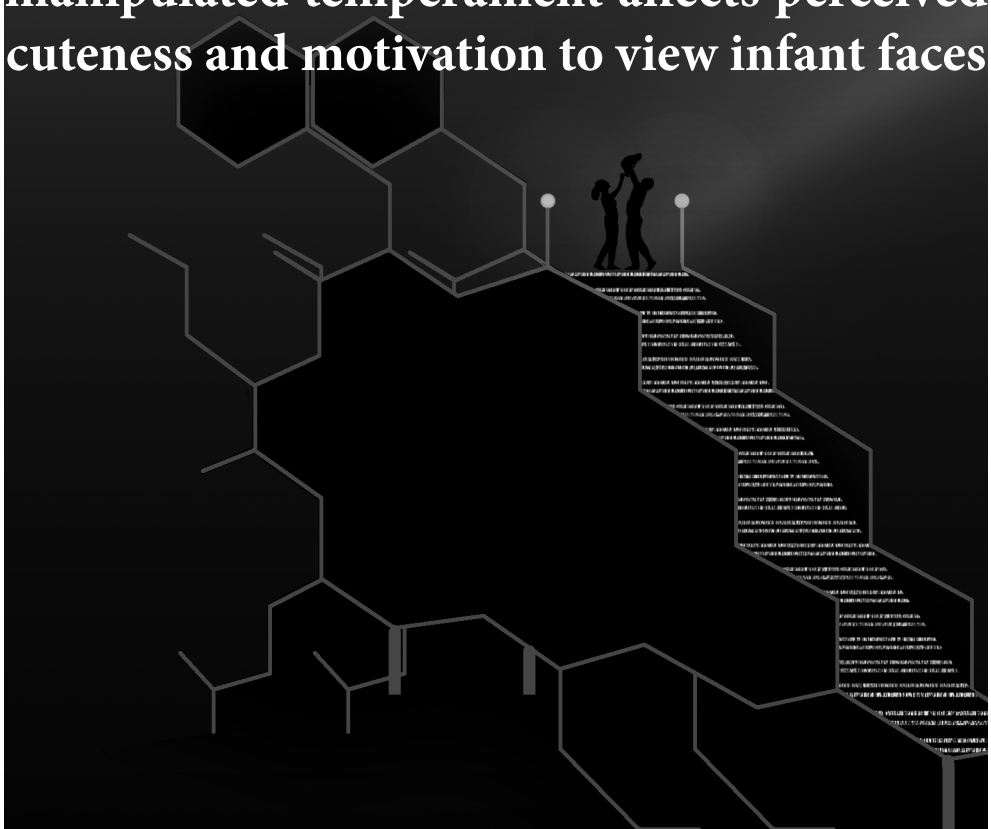
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3

# The Bonnie baby: Experimentally manipulated temperament affects perceived cuteness and motivation to view infant faces



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## Abstract

Attractive individuals are perceived as having various positive personality qualities. Positive personality qualities can in turn increase perceived attractiveness. However, the developmental origins of the link between attractiveness and personality are not understood. This is important because infant attractiveness ('cuteness') elicits caregiving from adults and infant personality ('temperament') shapes caregiving behaviour. While research suggests that adults have more positive attitudes towards cuter infants, it is not known whether positive infant temperament can increase the perception of infant cuteness. We investigated the impact of experimentally established infant temperament on adults' perception of cuteness and desire to view individual faces. At baseline, adults rated the cuteness and keypressed to view a set of unfamiliar infants with neutral facial expressions. Training required adults to learn about 'temperament', through repeated pairing of the neutral infant face with positive or negative facial expression and vocalisations. Adults then re-rated the original neutral infant faces. Post-training, there were significant changes from baseline: Infants who were mostly happy were perceived as cuter and adults expended greater effort to view them. Infants who were mostly sad were not perceived as cuter and adults expended less effort to view them. Our results suggest that temperament has clear consequences for how adults perceive 'bonnie' babies. Perception of infant cuteness is not based on physical facial features alone, and is modifiable through experience.

## Keywords

Infant Social Reward Task, Temperament, Cuteness ratings, Wanting, Reward processing.

## Introduction

We instinctively make judgements about others based on physical appearance. An attractive face can lead viewers to make positive inferences about personality, a bias termed the "what is beautiful is good" stereotype. In almost every context, attractive people fare better than unattractive people (Eagly *et al*, 1991; Langlois *et al*, 2000), be it in mating success, job applications or election results. Although studied to a far lesser extent, attractiveness in children also appears to be a determinant of treatment by unfamiliar adults. Adults tend to rate the misbehaviour of attractive children less harshly compared to that of less attractive children (Berkowitz and Frodi, 1979; Dion, 1972) and provide more positive academic evaluations (Parks and Kennedy, 2007; Ritts *et al*, 1992). For infants, research is more limited, but one correlational study has demonstrated that mothers of more attractive offspring have more positive attitudes and affectionate behaviours towards their infants compared with mothers of less attractive offspring (Langlois *et al*, 1995).



Infant attractiveness also correlates with judgements of infant health, pleasantness and adoption preferences (Karraker and Stern, 1990; Maier Jr *et al*, 1984; Ritter *et al*, 1991; Stephan and Langlois, 1984; Volk and Quinsey, 2002). Perhaps the most convincing evidence for the importance of infant facial features in eliciting care comes from instances of facial anomaly, signalling compromised health. Cleft lip in infants has been associated with disruption of parental care (Field and Vega-Lahr, 1984; Murray *et al*, 2008), particularly in the case of severe disfigurement (Murray *et al*, 2008). Adults who are not parents have also been shown to react negatively to both specific and global changes to the infant face, such as in cleft lip, fetal alcohol syndrome and prematurity (Frodi *et al*, 1978; Parsons *et al*, 2011b; Waller *et al*, 2004).

The strength of preference for attractive over less attractive faces is also exemplified by experimental evidence showing that adults will expend greater effort to view more attractive faces compared to less attractive faces (Aharon *et al*, 2001; Hahn *et al*, 2012; Parsons *et al*, 2011a). Neuroimaging studies have demonstrated a biological basis for this preferential response to attractive faces, be they young or old. Brain regions that typically respond to reward, such as money or pleasant sensory stimuli, also respond more to attractive compared to unattractive adult faces (e.g., Aharon *et al*, 2001; O'Doherty *et al*, 2003). One reward region, the orbitofrontal cortex, has been shown to respond rapidly to typical infant faces (Kringelbach *et al*, 2008) but not to infant faces with a structural abnormality (Parsons *et al*, 2013a). Activity in another key reward region, the nucleus

accumbens, can also be modulated by subtle graded manipulation of the cuteness of infant faces (Glocker *et al*, 2009). The predominant interpretation of these findings is that differential activation of these brain regions occurs because attractive faces are rewarding (e.g., Said *et al*, 2011).

Our bias in favour of attractive individuals is inherently unfair but appears to be deep-rooted, and has an effect even early in life. Therefore, it is important to understand its implications and given its apparent ubiquity, how to alter perceptions of attractiveness for the better. By tradition, we tend to explain facial attractiveness in terms of physical features. For an infant, these features include big eyes, round cheeks, a large forehead and a small nose (Lorenz, 1943). For adults, these are gender-dependent, but symmetry and how close the face is to the population average are considered important markers of attractiveness. 'Beautiful faces', those that come closest to the prototypical attractive structure, are strongly preferred. For faces of any age, ratings of attractiveness, or the infant-appropriate 'cuteness', are remarkably consistent across viewers (for review, see Langlois *et al*, 2000) and positively correlate with favourable judgements.

While the link between attractiveness and positive personality attributions appears robust, what about in the other direction? Does personality have an impact on the perception of beauty? There is some evidence that adults' perceptions of the attractiveness of other adults can be altered by personality information and familiarity. For instance, perception of physical attractiveness, based on evaluations of known individuals in high school yearbooks, can be influenced both by familiarity and personality traits (Kniffin and Wilson, 2004). Providing positive personality information can also decrease the threshold for what is considered attractive, while negative personality information can increase the threshold (Swami *et al*, 2010). However, the relationship between personality, or 'temperament', and perceived cuteness has not been investigated in infants. This is of interest because temperament can dictate how infants respond to the environment (for review, see Van IJzendoorn and Bakermans-Kranenburg, 2012) and infant cuteness is hypothesized to elicit nurturing responses in adults (Glocker *et al*, 2009; Lorenz, 1971; Tinbergen, 1951).

Temperament is thought to render some infants more or less susceptible to environmental influences, be they positive or negative (Belsky *et al*, 2007; Ellis *et al*, 2011). While the definitions, interpretations and measures of temperament are manifold, there is a consensus that temperamental characteristics should be present early in life, show moderate stability, and have neurobiological correlates (e.g., Rothbart and Bates, 2006;

Zentner and Bates, 2008). It is also generally accepted that the advantages or disadvantages of temperamental characteristics vary depending on context (e.g., deVries, 1984). That is, there is no 'ideal' temperament independent of environmental factors (Van IJzendoorn *et al*, 2012).

One aspect of infant temperament, 'emotionality', has been shown to impact upon the quality of parental care and child outcome, in the presence of other risk factors. Negative emotionality has been associated with less supportive parenting in low socioeconomic status (SES) families in a recent meta-analysis (but not in high SES families, Paulussen-Hoogeboom *et al*, 2007). Persistent infant crying, lasting more than several months, has also been associated with greater hyperactivity and academic difficulties into childhood (Wolke *et al*, 2002). Findings have been more variable in studies where infant temperament is measured using observation rather than parental report (Paulussen-Hoogeboom *et al*, 2007). This measurement issue is challenging; parent and observer measures of infant temperament do not always correspond (e.g., Seifer *et al*, 1994) and caregivers' negative emotion can influence rating of infant temperament (Youngstrom *et al*, 1999). It has therefore been argued that temperament should be measured in observational settings because the concept of temperament refers to behavioural style and not to parental perceptions (e.g., Kagan, 2007; Kagan, 2009).

In this study, we designed a novel paradigm to create a sense of the emotional 'temperament' of a number of previously unfamiliar infants. As in real life, temperament was graded, such that some infants were happy most of the time, some were sad most of the time, and others fell somewhere in the middle. We examined the impact of this experimentally manipulated temperament on perception of infant cuteness and also willingness to work to view the infant. These two measures were chosen because adults have been shown to be sensitive to subtle computer-manipulations of infant cuteness, as well as real-world differences in infant facial configuration (Parsons *et al*, 2011a; Sprengelmeyer *et al*, 2009). In addition, adults will work more to see infants with a 'cuter' face structure compared with less 'cute' faces.

We hypothesized that 'positive' infant temperament would be associated with increased ratings of infant cuteness and desire to view, whereas 'negative' infant temperament would be associated with decreased attractiveness and desire to view.

## Methods

### *Participants*

Participants were 47 healthy women aged between 17 and 27 ($M$ = 19.81 years, $SD$ = 1.59), none of whom had children. All participants were undergraduate students from the Institute of Education and Child Studies, University of Leiden. Thirty-five of the participants reported having some experience caring for infants (baby-sitting). All participants reported no current or past neurological/psychological disorders, were non-smokers and reported no recreational drug use for at least 6 months. The majority of participants (83%) reported being in the luteal menstrual phase at the time of the study. The study was approved by the ethics committee at the Leiden University Medical Centre.

### *Procedure*

The experiment consisted of three stages: baseline measures of participants' responses to the infant faces, the experimental manipulation of infant temperament, and post-manipulation measures of participants' responses to the infant faces (see Figure 1). In the first stage, participants were asked to rate a series of images of infant faces for 'cuteness'. Next, they rated the same images for two characteristics of infant temperament: how 'difficult' or 'easy' they were perceived to be. They then completed a key press task (referred to elsewhere as a 'wanting' task, e.g., Parsons et al., 2011). In this task, participants were told to indicate the length of time that they would like to see the images appear on screen by key pressing 'up' (retain) or 'down' (remove, Parsons *et al*, 2011a). The actual time the picture remained onscreen for did not vary.

In the second stage of the experiment (approximately one hour later), participants performed a novel probabilistic infant social reward task, based on a widely-used learning paradigm using three stimulus pairings (Frank *et al*, 2004; Kringelbach and Rolls, 2003) which has also been used with adult faces (Kringelbach *et al*, 2003). This task is described in detail below. Over the course of this task, participants learned about the 'temperament' of different infants. Participants were required to select one infant image from a concurrently presented pair and were provided with feedback in the form of a change of facial expression and an equivalent vocalisation (either 'happy' or 'sad').

Finally, in the third stage, participants were asked to rate the cuteness and temperament of each infant again and complete the 'wanting' task again. Identical instructions were provided for the baseline and post-manipulation measures. All tasks were

programmed and performed using Presentation software (Version 14.4 Neurobehavioral Systems, Inc., www.neurobs.com).

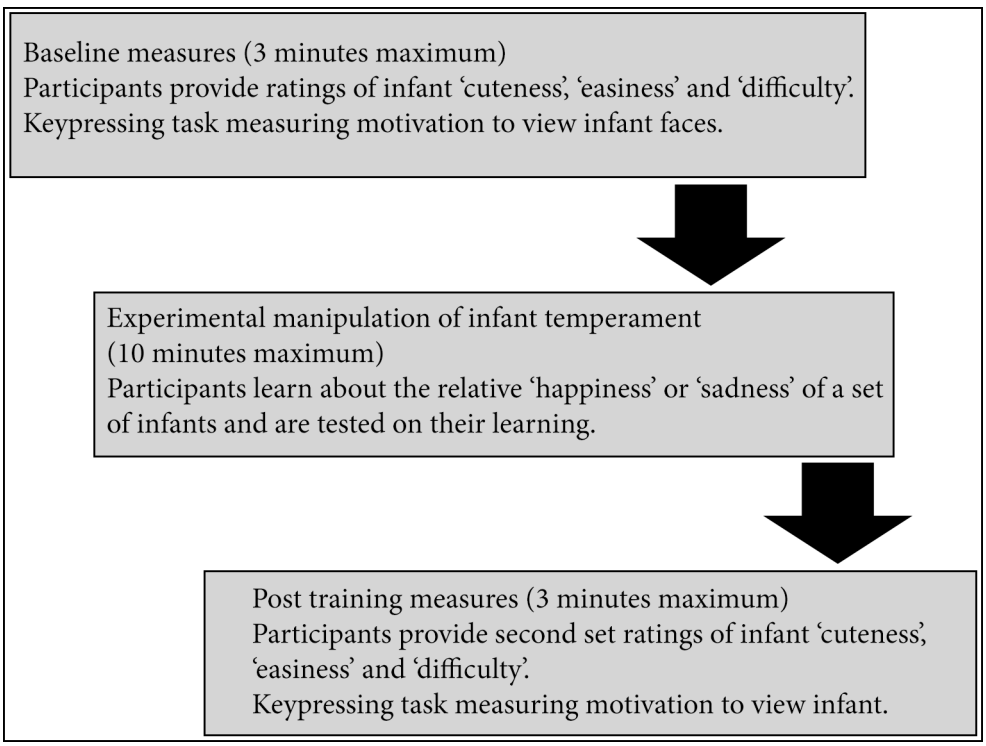



***Figure 1. The three stages of the experimental procedure and their timings.***

***Stimuli***

All infant face images and vocalisation recordings were taken from two standardised databases previously described (for faces, see Kringelbach *et al*, 2008; for vocalisations, see Parsons *et al*, 2013b; Young *et al*, 2012). In brief, visual and audio recordings in these databases were collected from infants filmed in their own homes during a play and feeding session with a caregiver. All stimuli were then matched on a number of important parameters (faces matched for size, eye gaze etc., vocalisations matched for root mean square intensity, length etc.). An independent sample of adults rated these stimuli on measures of valence and how they made the rater feel ('please rate your mood after listening to this sound'). Categorisation of stimuli as 'happy', 'sad' or 'neutral' was based on these ratings.

Visual stimuli were 'happy' (smiling), neutral and 'sad' (crying) faces of six different infants. All of the 'neutral' infant faces had approximately similar valence ratings (scale from –4, very negative affect, to +4, very positive affect; $M$ = –0.3, $SD$ =0.6). For each infant, the most positive ($M$ = 2.7, $SD$ = 0.4) and most negative expressions ($M$ = –1.8, $SD$ = 0.5) available were used for the "feedback" during training. Infants were all full-term, healthy, Caucasian and aged between 6 and 8 months at the time of recording. Parental permission was provided for the use of these images for research purposes, which was also approved by the Oxford Research Ethics Committee.

In order to reduce any confounding effects of stimulus gender, we had an independent sample of adult females ($n$ = 40) rate faces from a larger set of thirteen (Kringelbach *et al*, 2008) as 'male', 'female', or 'cannot tell'. These ratings were then used to select six faces such that there were two faces clearly perceived as female, two as male, and two with ambiguous ratings. In the 'infant social reward task' (described later), we also used these gender ratings to form same-gender pairings (i.e., both faces in a pair perceived as male). All faces were forward facing, with comparable direction of eye gaze and were matched for size (300x300 pixels) and luminosity. Images were presented in greyscale on a 15.3 inch computer monitor.

Six recordings of 'happy' (laughing) and 'sad' (crying) vocalisations were selected. These vocalisations were selected based on ratings from an independent sample of adults to ensure that they unambiguously conveyed these emotions (Young *et al*, 2012). Vocal stimuli were free from background noise, matched for peak and average root-mean-square intensity, clipped to 1500ms and had 150ms linear rise and fall times (Adobe Audition CS5.5 v4.0). Vocalisations were presented at 50 dB SPL above threshold for each participant using in-ear earphones (Sennheiser CX300II). For the feedback (visual & auditory), positive and negative vocalisations were paired at random with positive and negative face expressions respectively.

***Baseline measures: Ratings of cuteness and temperament***

All participants in the current study rated the neutral facial expressions of each of the six infants on a 'cuteness' scale. These faces were all unfamiliar to participants. Face images were presented in the centre of the screen with a vertical visual analogue scale (VAS) immediately to the right. Participants were asked to 'indicate how cute you find each baby' from 'cute' to 'not cute' on the VAS. The ratings bar started at the midpoint on the scale (halfway between 'cute' and 'not cute') and participants adjusted the height

of this bar using the 'up' and 'down' arrows on a standard keyboard. Scale scores on the VAS ranged from a maximum of 4 (cute) to a minimum of -4 (not cute), with intervals of .0025. This allowed us to obtain sensitive ratings. Each stimulus was presented for 5 seconds and each participant rated each face once. The order of images presented was randomised between participants. This provided a measure of 'subjective liking' of each image, similar to procedures described in other studies (Hahn *et al*, 2012; Parsons *et al*, 2011a; Parsons *et al*, 2011b).

Similar to the cuteness ratings, participants also provided ratings of how 'difficult' or 'easy' each infant was perceived to be. The aim of this was to assess the extent to which participants viewed the infant faces as having different 'temperaments'. That is, these ratings provided a test of the efficacy of the infant social reward task in creating a sense of easy (happy, positive reactivity) and difficult (sad, negative reactivity) infants. This measure of perceived temperament is similar in some respects to reports of infant temperament that might be obtained from a parental questionnaire. Such measures of perceived temperament are important regardless of whether, objectively evaluated, they are correct or not, because they can guide caregiving (e.g., Mäntymaa *et al*, 2006).



Face images were presented in the centre of the screen and participants used a VAS to rate how 'difficult' they found each baby (from 'difficult' to 'not difficult') and how 'easy' they found each baby (from 'easy' to 'not easy'). In total, it took participants approximately 2 minutes to complete all of these ratings.

Average cuteness ratings were normally distributed, as confirmed by Kolmogorov-Smirnoff tests (before training cuteness rating, $D(47) = 0.093$, $p = 0.20$). Temperament ratings were also normally distributed as confirmed by Kolmogorov-Smirnoff tests ('difficulty' rating: $D(47) = 0.117$, $p = 0.12$, 'easiness' rating: $D(47) = 0.064$, $p = 0.20$).

***Baseline measure: Wanting task***

In the wanting task, participants were asked to keypress to indicate how long they would like to view each image for (similar to procedure described in Parsons *et al*, 2011a). The onscreen appearance was similar to that for the ratings task, with a face image in the centre of the screen and a vertical VAS to the right. The VAS provided a real-time indication of how much keypressing a participant had done (similar to an egg-timer). The actual viewing duration of each image did not vary from trial to trial. However, the amount of keypressing provides a measure of the incentive salience or amount of 'wanting' to view each image, similar to other paradigms (Aharon *et al*, 2001; Parsons *et*

*al*, 2011a). Each stimulus was presented onscreen for 6 seconds and all participants were presented with each face once, lasting a total of 36 seconds. Data from the 'wanting' task were frequency of 'up' and 'down' keypresses, ranging from a minimum of 0 to a maximum of approximately 30.

Due to computer errors, there were two participants with missing data for this task only. After removal of one participant (whose data fell out with the mean plus 3 standard deviations), data were normally distributed, as confirmed by Kolmogorov-Smirnoff tests (before training, $D(44) = 0.128$, $p = 0.07$). Analyses were conducted including and excluding this outlier and the pattern of results was the same. Results reported here include this outlier.

***Infant social reward task***

The infant social reward task consisted of a probabilistic learning task, in which participants learned about the 'temperament' of six infants. It was split into two phases: the 'training', where participants learned about each infant, and the 'testing', where the extent of each participant's learning was measured.

***Training.*** The participants' task was to establish which infant from a choice of two was the 'happy' and which was the 'sad' infant through trial and error. Participants selected one of the images and were provided with feedback in the form of a positive or negative facial expression and vocalisation. Through repeated trials, participants could then compare how often each baby laughed or cried and work out which baby was the happier or sadder of the pair.

Participants were presented with pairs of neutral infant faces and were instructed that, "in each pair of faces, there is one happy and one sad baby. Like in real life, the happy baby will not always be happy and the sad baby will not always be sad. In each set, your task is to find the happier baby, the one who smiles most often, and continue to always select this baby even if this baby may sometimes appear sad". For each trial, stimuli were presented in a pair and a total of three pairs were used. The pair combinations were fixed in this phase.

The three pairs varied in the probability of each infant being 'happy' or 'sad'. In the 'easiest' pair, the baby laughed on 80% of trials and cried on the remaining 20% of trials. The sad baby in this pair only laughed in 20% of trials and cried in the other 80% of trials, if selected. In the second pair, the happy baby laughed 70% of the time and the

sad baby laughed 30% of the time. In the final, and hardest to learn pair, the happy baby laughed 60% of the time while the sad baby laughed 40% of the time. Participants only received feedback about the baby that they selected (it was inferred that the baby *not* selected would show the opposite emotion on each trial). In this way, the aim was to establish a sense of graded temperament across the group of infants.

Participants completed two training rounds each consisting of 60 trials. In each training round, every pair of babies was presented 20 times. In one round, participants were asked to select the 'happy' baby in each pair and in the other round to select the 'sad' baby. The order of training rounds (selecting the 'happy' or selecting 'sad' baby) was counterbalanced. By asking participants to deliberately choose the happy or sad babies, we aimed to prevent greater exposure to one individual face in each pair.



At the start of each trial, neutral faces were presented, one on the top half of the centre of a computer screen and the other in the bottom half (see Figure 2a). Participants then selected one image using either the 'up' key (for the top image) or the 'down' key (for the bottom image). Participants were then presented with feedback: the selected image changed to either a happy face accompanied by a laugh, or a sad face accompanied by a cry. The unselected image remained neutral during feedback (see Figure 2b).

In each trial, neutral faces were presented on screen until participants made a response. After participants made a response, visual feedback was presented immediately for 1.5sec accompanied by a 1.5sec vocalisation. There was a 500ms gap between the end of the feedback and the beginning of the next trial during which a red fixation cross was presented in the centre of the screen.

The order of trials during this phase was fully randomised between sessions and participants. The identity of the image from each pair that appeared at the top of the screen was also randomised between trials. Further, the actual identities of which baby face was the 80% happy, 70% happy and so on were randomised between participants. This was to exclude the possibility of differences in perceived temperament being related to the appearance of the babies. Depending on the rate of participants' responses, this phase typically lasted between 3 and 5 minutes. In general, participants found learning the contingencies in this task difficult, as evidenced by accuracy rates in the first round of training. For the 80-20% pair, mean accuracy scores were 78% ($SD$ = 21), for the 70-30% pair, 76% ($SD$ = 26) and for the 60-40% pair, 67% ($SD$ = 27). By the second round of training, accuracy rates were higher, but participants were still scoring below 80% on the

most difficult pair (60-40% comparison, *M* = 75%, *SD* = 32). For the other two pairings, mean accuracy rates were at 88% (*SD* = 23) for the 80-20% pair and at 86% (SD = 20.33) for the 70-30% pair.

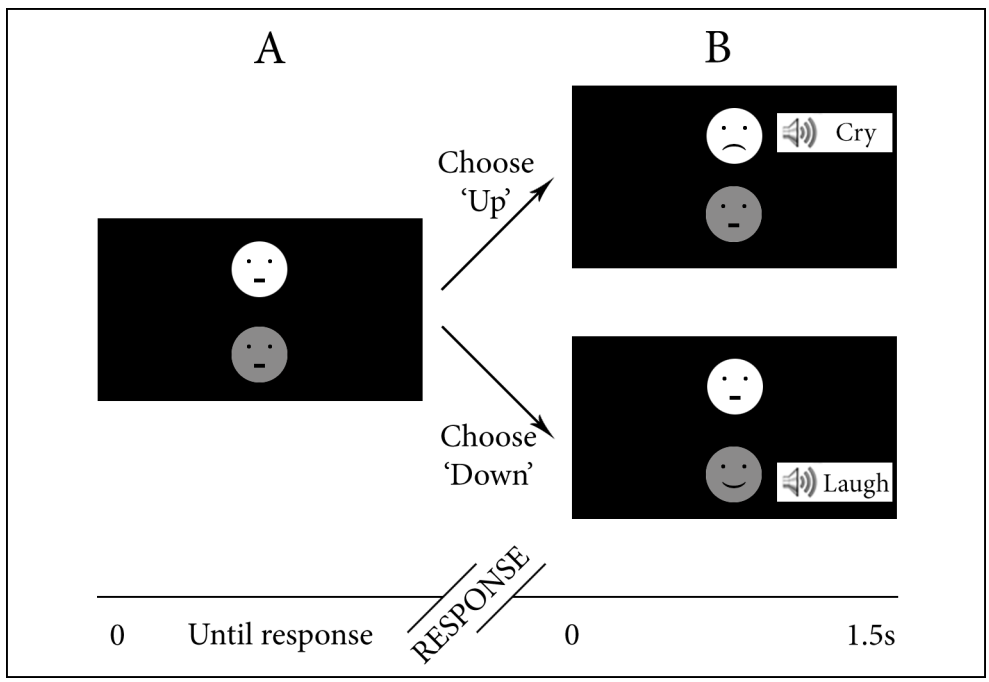



***Figure 2. Example of a single trial in the infant social reward task.*** *A) Participants are presented with neutral infant faces. B) After choosing one of the images, participants are presented with audio-visual feedback. (Original infant faces are replaced by cartoon images, as required by the ethical committee.)*

***Testing.*** In the 'testing' phase of the task, participants were presented with randomly paired infant images (e.g., 80% with 60% happy baby) and were asked to select the happier of the two babies. This task measured how well each individual learned the previous contingencies and therefore the temperament of the babies.

The set-up of the testing phase was identical to the training phase with a few exceptions. First, no feedback was provided after each trial. Once a participant made a response, there was a 500ms gap before the next trial was presented, during which a red fixation cross was presented in the centre of the screen. Second, faces were no longer presented just with their specific partner; each face was presented a total of four times with each of the other five faces. This resulted in a total of 60 trials. Finally, participants

were instructed to: "Please choose the face of the baby that 'feels' the most happy based on what you have learned during the previous task". If you are not sure which one to pick, just go with your gut feeling. If a participant failed to make a response within 4.5 sec, the word 'missed' appeared onscreen for 500ms and the task moved on to the next trial. This phase lasted for a maximum of 5 minutes but typically around 3 minutes.

Correct responses were counted if participants chose the 'happier' of the two faces (e.g., the 70% happy infant face over the 60% happy infant face). Participants' scores ranged from 40% to 91% ($M$ = 71%, $SD$ = 14%).

***Post infant social reward task measures: Cuteness, temperament, and the wanting task***

In the final stage of the experiment, participants completed the cuteness ratings, temperament ratings and wanting task again. Kolmogorov-Smirnoff tests showed that all rating data were normally distributed (cuteness rating: $D(47) = 0.099$, $p = 0.20$; 'difficult' rating: $D(47) = 0.071$, $p = 0.20$; 'easy' rating: $D(47) = 0.109$, $p = 0.20$). With the outlier (mentioned previously) removed, the wanting task data were also normally distributed ($D(44) = 0.093$, $p = 0.20$).



## Results

***Impact of cuteness on temperament***

We compared the initial cuteness ratings with temperament ratings to investigate the association between physical face structure and perceived 'personality' characteristics. These ratings were obtained prior to learning about the manipulated temperament of individual infants, so were based solely on facial configuration. A linear regression was used to compare cuteness ratings with perceived temperament. A measure of perceived 'temperament' was obtained by taking an aggregate score of the separate 'easy' and 'difficult' characteristic ratings (which were significantly correlated: $r = -0.76$, $p < .001$). The sign of 'difficult' ratings was reversed and temperament was taken as the mean of the easy rating and the inverted difficult rating. There was a significant relationship between ratings of cuteness and perceived temperament ($R^2 = 0.03$, $p = 0.003$), indicating a small association between facial features and perceived temperament.

***Impact of manipulated temperament on cuteness***

To compare the effects of manipulated 'happy' or 'sad' temperament on ratings of infant cuteness, a 2x2 repeated-measures ANOVA was used. Time (before and after training) and valence (happy and sad) were the factors. There was a significant main effect of time ($F(1,46) = 16.83$, $p < .001$, $r = 0.52$), with faces rated as cuter after the training task ($M = 1.59$, $SD = 0.81$), compared with before ($M = 1.10$, $SD = 0.72$). There was no significant main effect of infant valence ($F(1,46) = 1.28$, $p = 0.26$, $r = 0.16$). There was a significant interaction between time and valence ($F(1,46) = 10.52$, $p = 0.002$, $r = 0.43$). Ratings for infants with happy temperament increased more (from $M = 1.03$, $SD = 1.02$ before training, to $M = 1.90$, $SD = 1.09$ after) than the ratings for infants with sad temperament (rated $M = 1.17$, $SD = 1.19$ before training and $M = 1.28$, $SD = 1.25$ after). For the 'sad' infants, the change in perceived cuteness was small and the variance in ratings was large. Therefore, the main effect of time appears to be a result of the change in ratings of the 'happy' infants. Indeed, paired t-tests comparing ratings before and after training (Figure 3) showed that only the ratings for the happy infants increased significantly (for the 80% happy infant, $t(46) = -2.90$, $p = 0.006$, $r = 0.393$; for the 70% happy infant, $t(46) = -3.03$, $p = 0.004$, $r = 0.408$, and for the 60% happy infant $t(46) = -3.14$, $p = 0.003$, $r = 0.42$). All other comparisons were non-significant.

***Impact of manipulated temperament on desire to view faces***

Again, a 2x2 repeated measures ANOVA with time and valence as factors was used. There was a significant main effect of valence ($F(1,44) = 4.95$, $p = 0.031$, $r = 0.32$) and a significant interaction between time and valence ($F(1,44) = 21.51$, $p < .001$, $r = 0.57$). There was no significant main effect of time ($F(1,44) = 0.03$, $p = 0.87$, $r = 0.03$). On average, there were a greater number of keypresses for happy infants ($M = 5.02$, $SD = 7.11$) compared with sad infants ($M = 2.49$, $SD = 6.41$). This effect was largely driven by the difference in keypressing after training. The amount of keypressing for happy infants increased after training ($M = 3.29$, $SD = 6.56$ before training to $M = 6.72$, $SD = 9.48$ after training), while the amount of keypressing for sad infants decreased ($M = 3.96$, $SD = 6.97$ before training, to $M = 0.79$, $SD = 7.34$ after).

Paired t-tests comparing key pressing before and after training for individual faces (Figure 4) showed significant increases for the 80% and 70% happy infants ($t(44) = -2.54$, $p = 0.015$, $r = 0.36$, and $t(44) = -2.15$, $p = 0.037$, $r = 0.31$ respectively). There were also significant decreases in the number of keypresses for the 30% and 20% happy infants

($t(44) = 2.79$, $p = 0.008$, $r = 0.39$, and $t(44) = 2.82$, $p = 0.007$, $r = 0.39$ respectively).

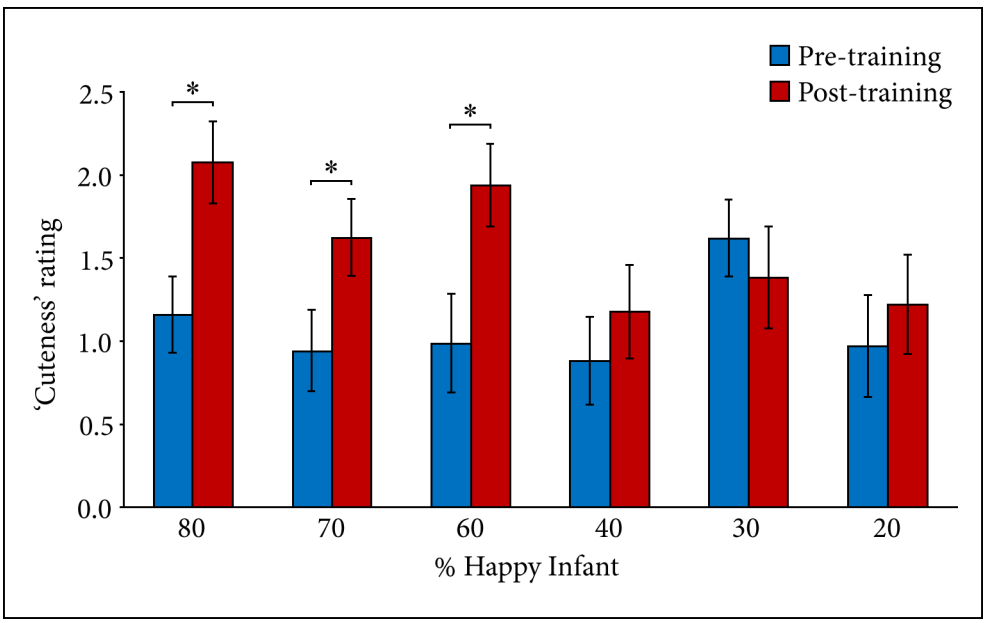



***Figure 3. Cuteness ratings before and after training.*** *'Happy' infants (80, 70, 60%) were rated as significantly cuter after training. Error bars indicate mean +/- standard error.*
** $p < 0.05$*

***Effects of manipulated temperament on 'easiness/difficulty' ratings***

Again, a 2x2 repeated measures ANOVA with time and valence as factors was used. There was a significant main effect of valence ($F(1, 46) = 20.96$, $p < .001$, $r = 0.56$) with the temperament ratings for the happy infants being significantly higher (or 'easier' $M = 0.79$, $SD = 0.83$) than for sad infants ($M = -0.05$, $SD = 0.66$). There was no significant main effect of time ($F(1, 46) = 0.03$, $p = 0.86$, $r = 0.03$), but a significant interaction between time and valence ($F(1, 46) = 38.29$, $p = .001$, $r = 0.67$). The interaction effect showed that this effect of valence was driven by the difference in ratings after training. Temperament ratings for the happy infants increased after training (before training, $M = 0.44$, $SD = 0.87$; after training, $M = 1.14$, $SD = 1.10$) and ratings for sad infants decreased (more difficult) after training (before training, $M = 0.32$, $SD = 0.72$; after training, $M = -0.42$, $SD = 0.99$).

Paired t-tests demonstrated a significant increase in temperament ratings for the 80% happy infant ($t(46) = -2.75$, $p = 0.008$, $r = 0.38$) and the 70% happy infant ($t(46) =$

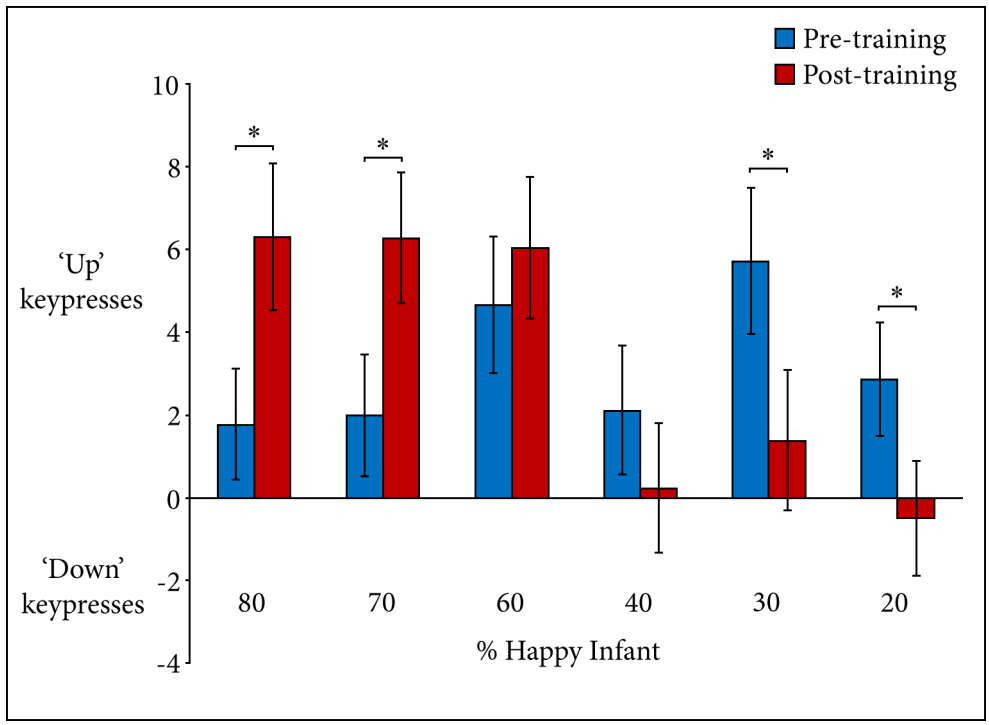



***Figure 4. Keypressing task.*** *Participants keypressed significantly more after training compared with before for the two happiest infants. Keypressing decreased significantly after training compared with before for the two least happy infants. * $p < 0.05$*

-3.28, $p = 0.002$, $r = 0.44$) (Figure 5); and a significant decrease in temperament ratings of the 30% happy infant ($t(46) = 4.97$, $p < .001$, $r = 0.59$) and the 20% happy infant ($t(46) = 3.48$, $p = 0.001$, $r = 0.46$).

Linear regression analyses were performed to investigate the impact of temperament on perception of cuteness and desire to view the infant faces. Change scores were calculated for the two measures by subtracting the pre-training ratings from the post-training ratings, and taking absolute values. This allowed us to obtain a measure of change in an individual's response after training, irrespective of whether the change was positive or negative across individual faces.

There was a significant positive relationship between change in temperament ratings and change in cuteness ratings ($R^2 = 0.26$, $p < 0.001$). In addition, there was a significant positive relationship between change in temperament ratings and change in number of keypresses ($R^2 = 0.11$, $p = 0.02$). There was also a significant positive relation-

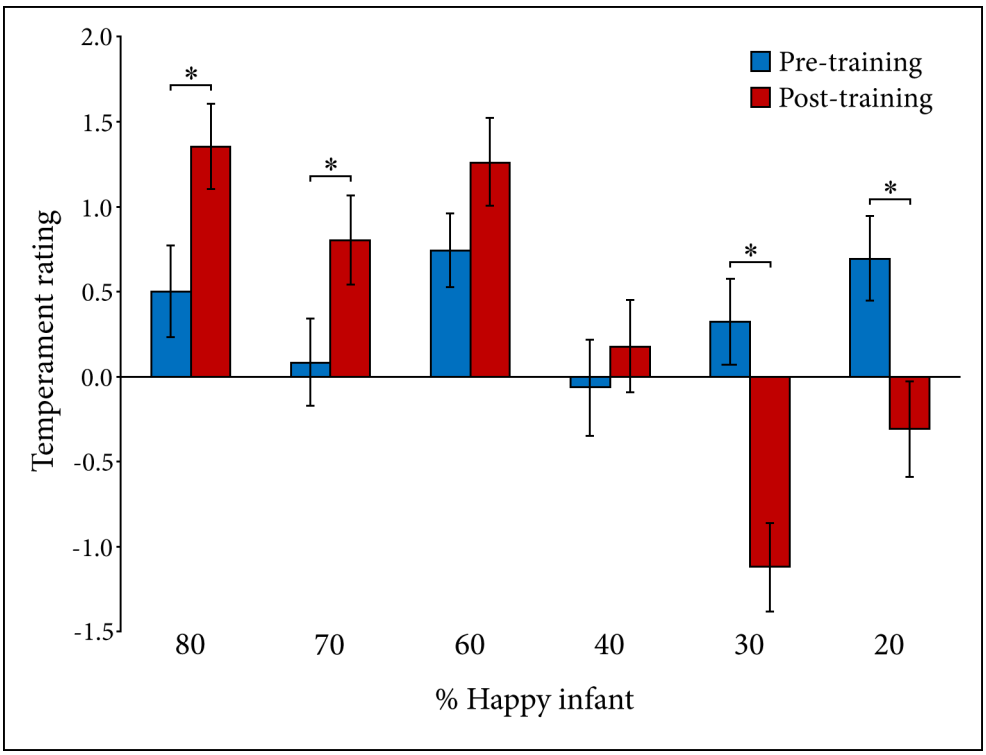



***Figure 5. Temperament ratings.*** *Following training, the two happiest infants were rated as having significantly more positive temperament. The two saddest infants were rated as having significantly more negative temperament. * $p < 0.05$*

ship between change in cuteness and change in number of keypresses ($R^2 = 0.20$, $p = 0.002$). As ratings of temperament increased, participants rated faces as cuter and demonstrated increased desire to view them.

It was hypothesised that the relationship between change in temperament ratings and change in number of keypresses was mediated by change in cuteness ratings. To investigate this, two models of the relationship between temperament ratings and number of keypresses were tested. In the first model, change in temperament ratings had a direct effect on change in number of keypresses ($R^2 = 0.11$, $p = 0.02$). In the second model, two variables were entered simultaneously: change in temperament and change in cuteness rating. In this model, the relationship between change in temperament ratings and change in number of keypresses was mediated by changes in cuteness ratings ($R^2 = 0.21$, $p < 0.01$). Adding the mediating variable of 'change in cuteness rating' significantly improved the model fit ($\Delta R^2 = 0.10$, $p = 0.03$). The relationship between temperament and

number of keypresses decreased substantially when controlling for cuteness (model two, relationship between temperament and number of keypresses: $R^2 = 0.02$, $p = 0.35$). The results of a Sobel test indicated that the association between temperament and keypresses was significantly mediated by cuteness ($z = 2.50$, $p = 0.01$). This suggests that participants want to look at images of 'happier' infants for longer because they find them cuter.

## Discussion

Our results demonstrate that infant 'temperament' can have a significant impact on adults' perception of cuteness and desire to view infant faces. We found that after only 6-8 minutes of learning about a set of previously unfamiliar infants, adults shifted their responses to each face, dependent on its experimentally established temperament. Infants who laughed more often than not were perceived as cuter and adults expended greater effort to view them after training. Infants who cried more often than not were not perceived as cuter and adults did not expend greater effort to view them after training.

Our learning task also had an effect on the extent to which adults perceived the infants as 'easy' or 'difficult', key descriptors of temperament. Infants who laughed more often were perceived as easier after training, whereas infants who cried more often were perceived as more difficult. These ratings indicate that participants were extrapolating what they had learned about the infant's mood (happy or sad) to ease of care. This link between infant mood and ease of care makes intuitive sense and is consistent with general conceptualisations of temperament (e.g., Van IJzendoorn *et al*, 2012).

It is well-established that physically attractive adults are perceived as having various positive personality qualities (e.g., Eagly *et al*, 1991; Feingold, 1992; Langlois *et al*, 2000). Here, we demonstrate the reverse relationship: personality, or its infant equivalent, 'temperament', can have an impact on both the perception of and motivation to view infants. To our knowledge, this is the first demonstration that infant temperament can alter cuteness perception. This provides a new way of thinking about the mechanisms through which infant temperament can impact on caregiving.

Previous studies of the perception of infant cuteness have examined factors related to the viewer, such as the adult's hormonal status, age and gender. Our results demonstrate that non-physical infant factors can also have an impact on cuteness perception. The findings reported here come from a within-subjects design, with a relatively homog-

enous sample of young females, at roughly the same stage of their hormonal cycle. Taken with previous findings, these results suggest that both viewer and infant non-physical characteristics can alter perceptions of infant cuteness.

***Strengths***

A major issue in understanding the impact of infant temperament on early parenting responses is related to its measurement. A strength of our study is the use of a novel, experimental method to establish a sense of infant temperament. This method allows us to circumnavigate some of the issues inherent in the measurement of infant temperament, such as mood of the reporter. In addition, this method allows us to make inferences about the directionality of the relationship between infant temperament and perception of infant appearance. This is important because it may be that 'cuter' infants are perceived as having a more positive temperament, but not vice versa. Our results provide evidence of bidirectional influence. Cuter infants are perceived as having a more positive temperament and changes in temperament for the better result in the infant being perceived as being cuter.

The effect of infant cuteness on perception of temperament was small, and we did not manipulate cuteness. Nonetheless, our findings are in line with other work demonstrating an impact of cuteness on perception of temperament (e.g., Langlois *et al*, 1995). The current paradigm would allow additional exploration of this relationship, for instance by deliberately using faces varying in cuteness.

***Limitations***

Our sample consisted of a relatively young sample of women, none of whom had children. We chose to test women only because previous studies of gender differences in processing of infant faces have reported mixed results (e.g., Hahn *et al*, 2012; Parsons *et al*, 2011a; Sprengelmeyer *et al*, 2009) and the clearest effects have emerged from women. Related to this, there have been some studies suggesting a greater response to infant stimuli in mothers compared to non-mothers (e.g., Giardino *et al*, 2008; Nishitani *et al*, 2011; Stallings *et al*, 2001). Therefore, an important follow up to this study would be to test a sample of mothers and indeed fathers, or adults with experience of caregiving in a professional context. It would also be of interest to examine whether our effects would extend to children's faces, given research suggesting adults' preference for younger compared with older children's faces (Luo *et al*, 2011). Finally, the infant faces used here were Caucasian and replication of our effects with infant faces of other ethnicities is clearly warranted.

Our manipulation of infant 'temperament' was necessarily simplified. We chose to focus on the intuitive, broad descriptors, 'happy' and 'sad' in training participants to learn about the infants. Infant temperament is of course more complex than a happy or sad division, and can be defined in terms of infant activity level, fear, distress to limitations, soothability and so on (Rothbart, 1986). Our 'happy/sad' training, which led to changes in perceived infant 'easy/difficulty', maps closely onto the temperament dimensions of 'emotionality', and 'irritability' or 'difficultness' (Bates *et al*, 1979; Deater-Deckard and Wang, 2012) rather than other important dimensions such as 'behavioural inhibition' (Kagan, 2012). Nevertheless, training adults to recognise infants as 'happy' or 'sad' is an intuitive starting point for understanding the relationship between temperament and adults' responses to infant faces. It would appear that temperament has clear consequences for how adults perceive 'bonnie' babies. Perception of cuteness is not based on physical features alone, and is modifiable through training.

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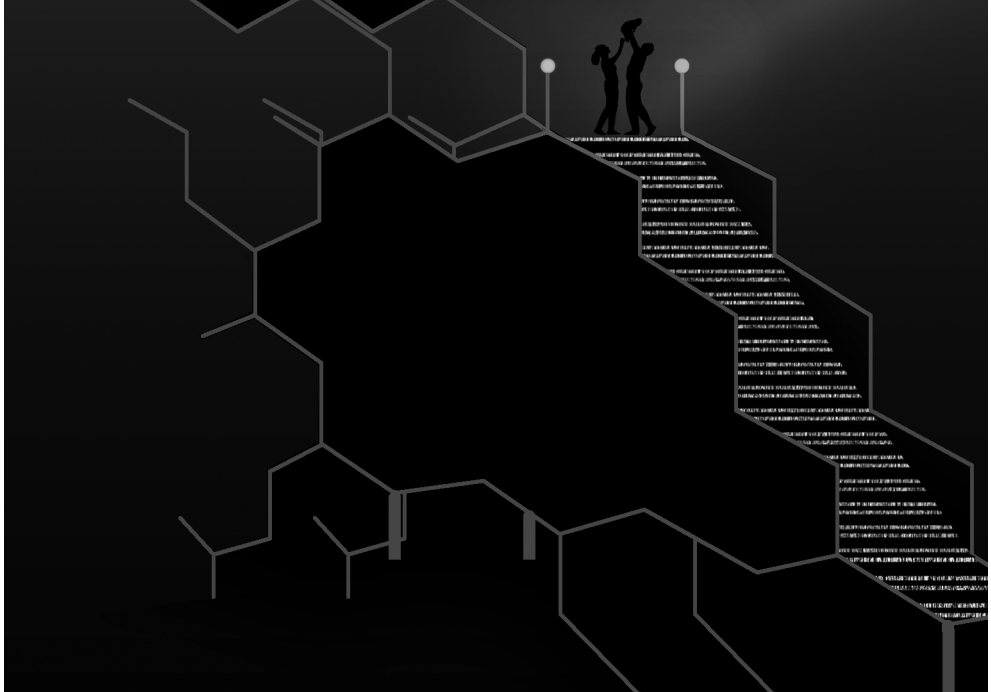
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4

# Effects of intranasal oxytocin administration on memory for infant cues: Moderation by childhood emotional maltreatment



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## Abstract

Oxytocin has been implicated in parent-infant attachment and social recognition. With respect to emotion recognition memory, both memory enhancing and memory impairing effects have been observed, suggesting an influence of individual factors on oxytocin effects. Despite its crucial role in parent-infant attachment, the effects of oxytocin on memory for infant cues have not been studied so far. In the present study, we assessed the effects of oxytocin on memory for infant temperamental cues, and we assessed whether these effects are moderated by childhood emotional maltreatment. Hundred and two healthy nulliparous females participated in a randomized, double-blind, between subjects experimental study with intranasal oxytocin or placebo administration. Experiences with emotional maltreatment before age 16 were self-reported using the Childhood Trauma Questionnaire. Participants' memory for positive and negative infant cues was tested using the Baby Social Reward Task, a probabilistic learning task with experimentally manipulated temperament of infant faces. Participants who reported more childhood emotional maltreatment made more recognition mistakes in distinguishing happy infants from sad ones after intranasal oxytocin administration. They were less accurate for infant pairs that were derived from the pairs in the learning task, but not for the pairs they were trained on. More specifically, they made more mistakes on the 'high conflict' pairs, with pairings that were more similar and thus more difficult to distinguish. We found evidence for amnesic effects of oxytocin in a decision making task, for infant stimuli in individuals with more experiences of emotional maltreatment. Our findings also suggest that the effects of oxytocin may depend on the uncertainty of the information being processed.

## Keywords

Oxytocin, Intranasal administration, Emotional maltreatment, Memory, Decision-making, Baby Social Reward Task

## Introduction

Oxytocin is considered a sociability hormone; it has been shown to elevate trust in and empathy for conspecifics (De Dreu *et al*, 2010; Kosfeld *et al*, 2005; For a meta-analysis see Van IJzendoorn and Bakermans-Kranenburg, 2012a). Oxytocin has also been widely implicated in parent-infant attachment. High postpartum levels of oxytocin have been associated with parents' synchronized and sensitive behavior towards their infants (Feldman *et al*, 2011; Feldman *et al*, 2007). Intranasal administration of oxytocin has been shown to increase sensitive caretaking behavior in parents (Naber *et al*, 2013) and to reduce aversion in response to infant crying as indicated by decreased amygdala activity (Riem *et al*, 2011).

Next to these prosocial and parent-infant bonding effects, oxytocin has also been implicated in social memory processes (for reviews see Guastella and MacLeod, 2012; Heinrichs *et al*, 2009; Striepens *et al*, 2011). The reported effects of oxytocin in memory are however not unequivocal. Whereas some studies have shown enhanced memory after intranasal oxytocin administration (Guastella *et al*, 2008; Rimmele *et al*, 2009; Savaskan *et al*, 2008), other studies have shown impaired memory (Heinrichs *et al*, 2004; Herzmann *et al*, 2012). The evidence for effects of intranasal oxytocin on emotion recognition has also been mixed. Oxytocin administration either increased recall of happy but not angry or neutral faces (Guastella *et al*, 2008), or improved recognition for angry and neutral, but not for happy faces (Savaskan *et al*, 2008). One study showed valence independent effects of oxytocin on facial memory, but no effect for non-social stimuli (Rimmele *et al*, 2009). More recently, amnesic effects of oxytocin for both social and non-social visual objects have been reported (Herzmann *et al*, 2012). Amnesic effects of oxytocin have also been shown for reproduction related words as compared to neutral words (Heinrichs *et al*, 2004).

Most of the research on oxytocin effects on memory processes has been conducted using adult facial stimuli. Infant cues may be processed differently compared to adults' (Kringelbach *et al*, 2008). Infant faces are preferred over adult faces and oxytocin has been shown to further increase this preference for infant faces (Marsh *et al*, 2012). Moreover, infant cues are related to higher activation in reward pathways that interact with the oxytonergic system (Glocker *et al*, 2009; Riem *et al*, 2011; Strathearn *et al*, 2009). Altogether these findings indicate that oxytocin administration may have different effects on memory processes when infant stimuli are used. In the present study we used intranasal oxytocin administration to examine effects on memory for infant temperamental

cues. In order to increase the ecological validity of the paradigm, we used a combination of facial and auditory cues, with a laughing sound accompanying smiling facial expressions and a crying sound accompanying sad facial expressions.

Recent research suggests an important role for individual factors moderating the effects of oxytocin on behavioral and neurobiological responses (for a review see Macdonald, 2013). Apart from gender differences (Fischer-Shofty *et al*, 2012) and genetic factors (e.g. oxytocin receptor gene; Marsh *et al*, 2012), attachment style has been suggested as a potential moderator of oxytocin effects. After intranasal administration of oxytocin less anxiously attached individuals remembered their mother as more caring and more close whereas more anxiously attached individuals remembered their mother as less caring and less close (Bartz *et al*, 2010). Moreover, childhood experiences with harsh discipline or emotional maltreatment may modulate the influence of oxytocin on behavior. Parental use of love withdrawal has been shown to moderate the effect of oxytocin on generosity, pro-social behaviors and behavioral responses to infant crying (Bakermans-Kranenburg *et al*, 2012; Riem *et al*, 2013; Van IJzendoorn *et al*, 2011). In the present study we assessed whether experiences of emotional maltreatment during childhood moderated the effects of oxytocin on memory for infant cues.

Emotional maltreatment is increasingly identified as negatively impacting on long-term psychological functioning, with effects comparable to or even stronger than other forms of maltreatment. The prevalence of emotional maltreatment is high. In the Netherlands, 26 per 1000 individuals were reported being emotionally abused or neglected (Euser *et al*, internal report). Emotional maltreatment has been associated with behavior problems such as internalizing and externalizing problems, social impairment, low self-esteem, and psychiatric illnesses (Stange *et al*, 2013; Valentino *et al*, 2009; Van Harmelen *et al*, 2010a). With respect to cognitive development, children with experiences of emotional maltreatment showed heightened false recognition memory (Cicchetti *et al*, 2010). Childhood emotional abuse has also been associated with lower oxytocin levels measured in cerebrospinal fluid (Heim *et al*, 2008). Moreover, childhood emotional maltreatment is associated with differential neural processing of emotions, for example, greater amygdala activity in response to emotional faces (Van Harmelen *et al*, 2012). Childhood emotional maltreatment may thus interact with the effects of oxytocin, as oxytocin is also associated with altered amygdala activity in response to emotional infant stimuli (Riem *et al*, 2011).

In the current study we assessed the effects of intranasal oxytocin administration

on memory for infant temperamental cues, and we examined potential moderation of these effects by experiences of emotional maltreatment during childhood. After oxytocin or placebo administration, participants performed a probabilistic social learning task, referred to as the "Baby Social Reward Task" (BSRT; Parsons *et al*, in press), in which participants learned about 'sad' and 'happy' infants, and were later tested to see if they could correctly differentiate happy infants from sad ones. We hypothesized that intranasal oxytocin would affect the performance of the participants and that this effect would be moderated by experiences of emotional maltreatment. Because earlier reports are equivocal in terms of the direction of the oxytocin effects, (memory enhancing versus amnesic) and about the role of valence (happy versus angry and neutral facial expressions) we did not further specify the direction of our hypotheses.

## Methods

### *Participants*

Three hundred and fifty three undergraduate students from the Institute of Eduaction and Child Studies, Leiden University completed questionnaires about their early life traumatic experiences. Of these, 102 females (age $M$ = 19.86 years, $SD$ = 1.42) were randomly selected to participate in the present study. All were nulliparous, 85% reported being in the luteal phase of their menstrual cycle and 74% of the participants used oral contraceptives. Exclusion criteria included pregnancy, breastfeeding and 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). Three participants were excluded from the analysis due to technical errors in the computer session. Fifty-three participants (age $M$ = 19.75, $SD$ = 1.08) received oxytocin and 46 participants (age $M$ = 19.94, $SD$ = 1.74) received placebo, intranasally. In the oxytocin group, 43 participants received 16 IU dose and ten received a higher volume dose of 24 IU. These different doses of oxytocin have been shown to make no difference in salivary oxytocin levels (Van IJzendoorn *et al*, 2012b). Seven participants ($n$ = 4 in the oxytocin condition; $n$ = 3 in placebo condition) were not included in the final analysis because of missing values of basal salivary oxytocin levels. The study was approved by the Leiden University Medical Center ethics committee.

***Procedure***

Participants were invited to the laboratory for an experimental session lasting for about 2 hours. Sessions started at 0900h, 1200h or 1500h. Participants first rated six neutral infant faces on physiognomic (e.g. cuteness) and temperamental characteristics (e.g. irritable, responsive) (Parsons *et al*, in press). They provided saliva samples for the assessment of basal oxytocin levels. Participants rated their mood using the Positive Affect Negative Affect Scale (PANAS; Crawford and Henry, 2004). Next, they received either oxytocin or placebo (saline) nasal spray in a randomized double blind design. Forty-five minutes after nasal spray administration participants again rated the infant faces and PANAS. Supplementary information (S1 and S2) provides further details on infant characteristics and participants' mood assessments. Approximately 55 - 60 minutes after the nasal spray they performed the BSRT (Parsons *et al*, in press) with experimentally manipulated temperament (happy or sad) of six different infants. A detailed description of the BSRT is provided below. All ratings and tasks were programmed and presented using Presentation software (Version 14.4 Neurobehavioral Systems, Inc., www.neurobs.com).

***Infant stimuli***

The visual stimuli consisted of the faces of six infants, each of which was shown with neutral, smiling and crying expressions. The infant images were obtained from a standardized database described in detail elsewhere (Kringelbach *et al*, 2008). Faces were all forward facing, with direct eye gaze, matched for size (300x300 pixels) and luminosity. Images were presented in grayscale on a 15.3 inch computer monitor. Auditory stimuli comprised twelve infant vocalizations of 1500 ms duration; six of infant crying and six of infant laughing (for a detailed description see Young *et al*, 2012). Vocalizations were presented at 50 dB SPL above each participant's measured threshold, using in-ear earphones (Sennheiser CX300II).

***Childhood emotional maltreatment***

Participants indicated their experiences of abuse and neglect until the age of 16 by rating the Childhood Trauma Questionnaire Short Form (CTQ-SF; Bernstein *et al*, 2003). Twenty-eight items were presented to assess experiences of physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. Each item (e.g. "During my childhood I felt hated by family") was rated on a 5-point rating scale ranging from *never true* to *very often true*. In our sample of college students, the prevalence of physical and sexual abuse and neglect was rather low. Emotional abuse and neglect had a wider

range and a better distribution for this sample. An 'Emotional Maltreatment' scale was created by averaging the items tapping into the 'emotional abuse' ($M$ = 1.36, $SD$ = 0.52) and 'emotional neglect' ($M$ = 1.61, $SD$ = 0.56) dimensions. Similar scales have been used in previous studies to assess the developmental and behavioural outcomes of emotional maltreatment (Van Harmelen *et al*, 2012; Van Harmelen *et al*, 2010b). Emotional maltreatment has been defined by American Professional Society on the Abuse of Children (APSAC; Binggeli *et al*, 2001) as acts of commission (emotional abuse, such as degrading, terrorizing, belittling, blaming, exploiting) and/or omission (emotional neglect such as isolation, rejection, denying emotional responsiveness), which conveys to the child that he/she is worthless, unloved, and unwanted, and are harmful to the child's emotional developmental needs. The scores on this scale ranged from 1 to 3.60. The internal consistency of this scale was high (Cronbach's $\alpha$ = .91). Scale scores were dichotomized into lower and higher levels of emotional maltreatment experiences using a median split (Bakermans-Kranenburg *et al*, 2012; Riem *et al*, 2013).

***Baby Social Reward Task***

Approximately 55 - 60 minutes after the nasal spray the participants performed the Baby Social Reward Task. The baby social reward task aims to manipulate the perceived temperament of a set of infant faces. The task is comprised of two parts, a training phase where the participants learn about the temperament of a series of infants by selecting an infant and receiving feedback and a testing phase measuring what they have learnt (Figure 1).

***Training.*** The training phase is a probabilistic learning paradigm where three fixed pairs of infant faces are presented to the participant in a random order. At the start of each trial, a pair of neutral faces are presented, one on the top half of the computer screen and the other on the bottom half. Participants then select one of the faces and receive feedback providing information about that infants' temperament. Feedback is in the form of a change in facial expression accompanied by an appropriate vocalization. Each pair of infants consists of a relatively 'happy' and a relatively 'sad' infant and participants come to learn which infant is which, by trial and error. The three pairs of infants vary in the probability of each infant being happy or sad. In the easiest pair, the happy infant smiles and laughs in 80% of the trials and frowns and cries in the remaining 20% of the trials. The sad infant in this pair laughs in only 20% of the trials and cries in the other 80% of trials. In the second pair, the happy infant laughs in 70% of the trials and the sad infant laughs in 30% of the trials. In the final and hardest to learn pair, the happy infant

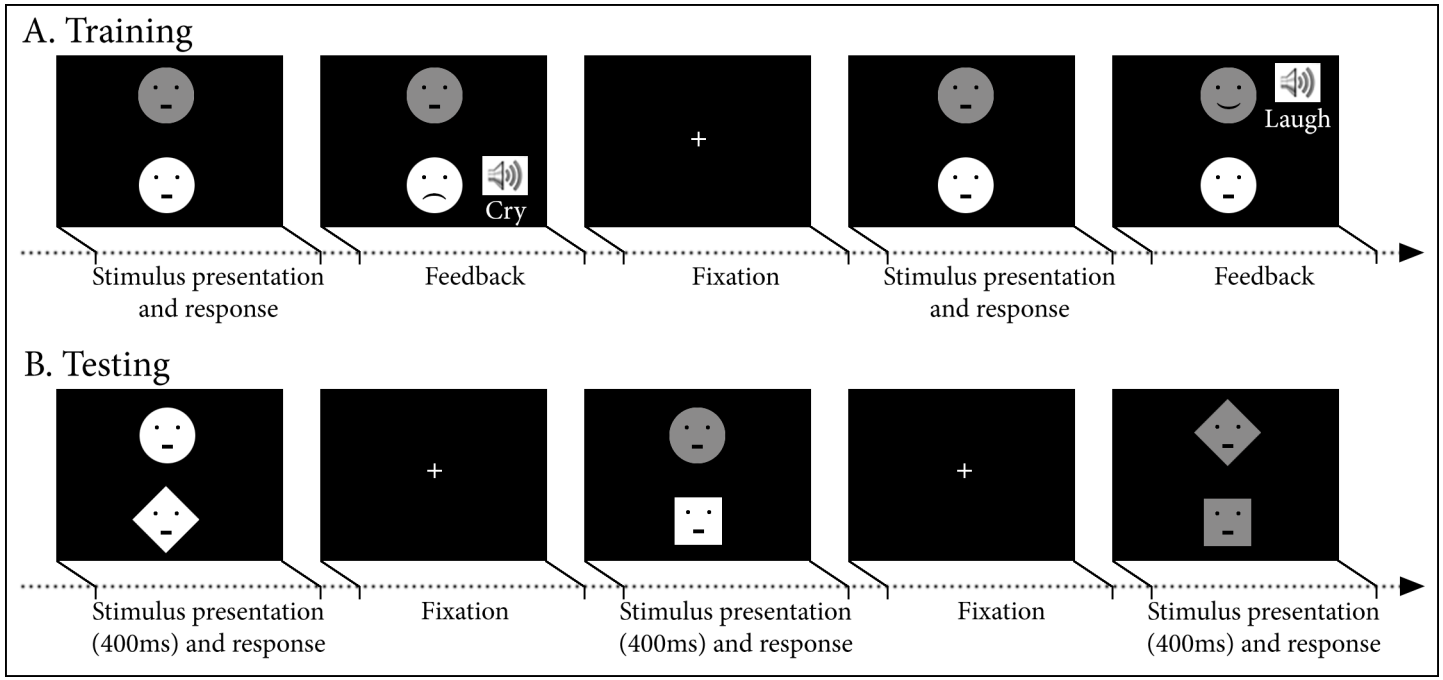



***Figure 1. The Baby Social Reward Task.*** *(A) In the training round, participants watch a pair of neutral infant faces and are asked to select the upper or lower face by pressing the UP or DOWN keyboard key. Feedback follows their selection: The selected image is replaced with either the smiling face image of the same infant accompanied by a laughing sound, or its frowning face image accompanied by a crying sound. (B) In the testing round, participants watch a pair of neutral infant faces and are asked to select the happier infant (based on what they learnt during the training round) by pressing the UP or DOWN keyboard key. Each trial is shown for a maximum of 4000ms and is counted as 'missed' if the participant does not respond within this time frame. After selecting an infant participants see a fixation cross for 500 ms before the next trial begins. (Original infant faces are replaced by cartoon images, as required by the ethical committee.)*

laughs in 60% of the trials while the sad infant laughs in 40% of the trials. Training was divided into 2 rounds, with 60 trials in each round (20 trials per infant pair). In one round, participants were asked to select the happy infant of each pair and in the other round they were asked to select the sad infant. This setting ensured a roughly equal exposure to the two infants of each pair. The order of training rounds (selecting the happy infant or selecting the sad infant) was counterbalanced among participants.

At the start of each trial, the participants had no idea about the happy and sad infant of each pair. The participant selected an infant by pressing the 'up' keyboard key for the infant presented on the top half of the computer screen and 'down' keyboard key for the infant presented on the bottom half of the computer screen. Visual and auditory feedback followed their selection: The selected image was replaced with either the smiling face image of the same infant accompanied by a laugh, or its frowning face image accompanied by a cry. The unselected image remained neutral during feedback. The total duration of the feedback was 1500 ms after which participants saw a fixation cross for 500 ms before the next trial started. Through repeated trials, participants could then estimate how often each infant laughed or cried and work out which infant was the happier or sadder of the pair.

The order of trials during this phase was randomized between sessions and participants. The identity of the image from each pair that appeared at the top of the screen was also randomized between trials. Further, the actual identities of which infant face was the 80% happy, 70% happy and so on were randomized between participants. This was to exclude the possibility of differences in perceived temperament or cuteness affecting the learning process. The training was self-paced and it took around 5-6 minutes for the participants to complete both training rounds.

A correct response was coded as '1' and an incorrect response was coded as '0'. Cumulative percentage scores were created for each trial by adding the correct responses and dividing the sum by the number of trials (e.g. response: $x_1$, $(x_1+x_2)/2$, $(x_1+x_2 \ldots x_n)/n$). The participants were instructed to find the happy or sad infant by trial and error. Therefore, all the participants had some incorrect responses in the beginning. As the cumulative percentage score at a later trial takes into account all correct and incorrect responses in the previous trials, the mean average across conditions show a final learning value between 70-80% (Figure 2) even though most of the participants were performing close to 100% in the final trials.

***Testing.*** Immediately following the training phase, in the testing phase participants were presented with random pairs (all possible combinations) of infants (e.g., 80 % happy paired with 70% happy; 30% happy paired with 40% happy) and were asked to identify the happier infant of the pair. There were 15 possible pairs, and each pair was presented four times, resulting in a total of 60 trials. The pairs were presented in a random order. Similar to the training phase, the participants saw two neutral faces, one on the top and other on the bottom of the computer screen. However, unlike the training phase, participants were instructed to make the selection as quickly as possible (for assessing reaction time). Each trial was shown for a maximum of 4000ms and was counted as 'missed' if the participant had not responded within this time frame. In the testing phase the participants did not receive feedback following their selection (in form of change in facial expression and accompanying sound); after selecting an infant participants saw a fixation cross for 500 ms before the next trial started.

Correct responses were counted if participants chose the happier of the two infants (e.g., the 70% happy infant over the 60% happy infant). The total number of correct responses was counted for all the trials and an average overall score was computed (the scores could range from 0 to 1). To further localize the effects, trials were divided into trained or explicit pairs (the three pairs that had been presented during the training phase) and derived or implicit pairs (the other pairs).

The derived pairs were further classified based on two principles; (a) Low conflict (pairs consisting of a happy and a sad infant, e.g., 70% happy infant paired with 40% happy infant) *versus* High conflict (pairs consisting of two happy or two sad infants, e.g., 30% happy infant paired with 20% happy infant). (b) Based on the presence of a particular infant in the pair (e.g. all trials containing 80% happy infant) (results for this pairing are presented as supplementary information S4). The average reaction time to select an infant was also recorded for all pairings.

***Statistical analyses***

A series of analyses of co-variances (ANCOVAs) were performed to analyze the effects of oxytocin administration and moderation of the effect by childhood emotional maltreatment on accuracy of performance and ratings of infant characteristics. Post-hoc analyses were performed to localize significant differences between the four groups; placebo with lower levels of emotional maltreatment, placebo with higher levels of emotional maltreatment, oxytocin with lower levels of emotional maltreatment, and oxytocin

with higher levels of emotional maltreatment. For a detailed description of the analyses and covariate(s) selection see supplementary information S3.

## Results

### *Training*

Three infant pairs (80% and 20% happy, 70% and 30% happy, 60% and 40% happy) were presented in random order the training phase; each pair was presented 40 times. Figure 2 represents the cumulative percentage of correct scores for the oxytocin and placebo groups for the three infant pairs, for the higher and lower emotional maltreatment groups separately.

In order to analyze the differences in learning between the oxytocin and placebo groups, difference scores were computed by subtracting the cumulative percentage score of each trial from the cumulative percentage score of the following trial (for e.g. trial3 - trial2, trial4 – trial3). For differences occurring in the acquisition phase of the learning, the first quarter of each pair's trials (excluding the first trial) were analyzed in a repeated measure ANOVA with trials as the within-subject factor and nasal spray and emotional maltreatment as between-subjects factors. Contraceptive use, basal salivary oxytocin level, and difference scores for negative affect and cuteness were used as covariates (see supplementary information S3). Similar analyses were performed for the last quarter of the trials in order to test for differences between the four groups in the final learning phase.

None of the main or interaction effects were significant. The four groups did not differ in the acquisition phase, or in the final phase of learning. Participants in the four groups learned to discriminate the happy and sad babies equally well.

### *Testing*

***Correct responses.*** Total accuracy was calculated for the 15 pairs of infants presented during the testing phase. A univariate analysis was conducted with nasal spray and emotional maltreatment conditions as fixed factors. Contraceptive use, basal salivary oxytocin levels, difference scores for negative affect and cuteness were used as covariates (see supplementary information S3). The total number of correct responses in the final stage of the training phase (final 10 trials for each infant pair) was also used as a covariate in order to control for individual differences in learning.

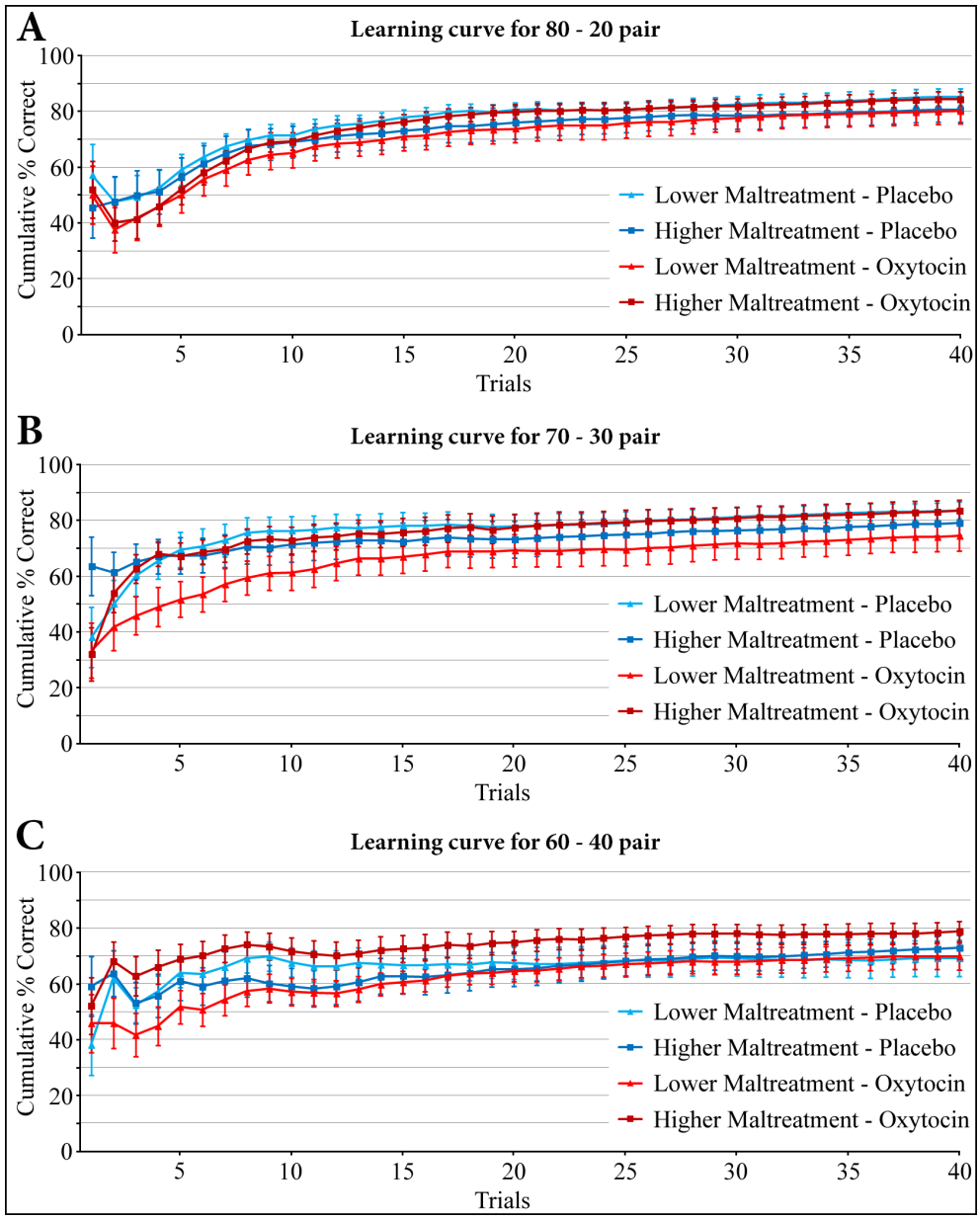



***Figure 2. Learning curves for the training phase.*** *Raw cumulative percentage correct scores for the lower and higher maltreated groups, with oxytocin or placebo treatment. (A) 80 - 20 Pair (B) 70 - 30 pair (C) 60 - 40 pair.*

We found a significant interaction effect of nasal spray by emotional maltreatment, $F$ (1, 83) = 4.55; $p$ = .036, $\eta^2$ = .052. Post-hoc analyses showed that participants in the oxytocin group with higher emotional maltreatment scores differed significantly from participants in the placebo group with higher maltreatment scores ($p$ = .004) and from participants in oxytocin group with lower maltreatment scores ($p$ = .024). Participants in the oxytocin group with higher maltreatment scores had fewer correct responses ($M$ = 0.63, $SE$ = 0.03) than participants in the placebo group with higher maltreatment scores ($M$ = 0.74, $SE$ = 0.03) and participants in the oxytocin group with lower maltreatment scores ($M$ = 0.71, $SE$ = 0.03) The means of the placebo group with lower maltreatment ($M$ = 0.71, $SE$ = 0.03) did not differ significantly from any of the other three groups (Figure 3).

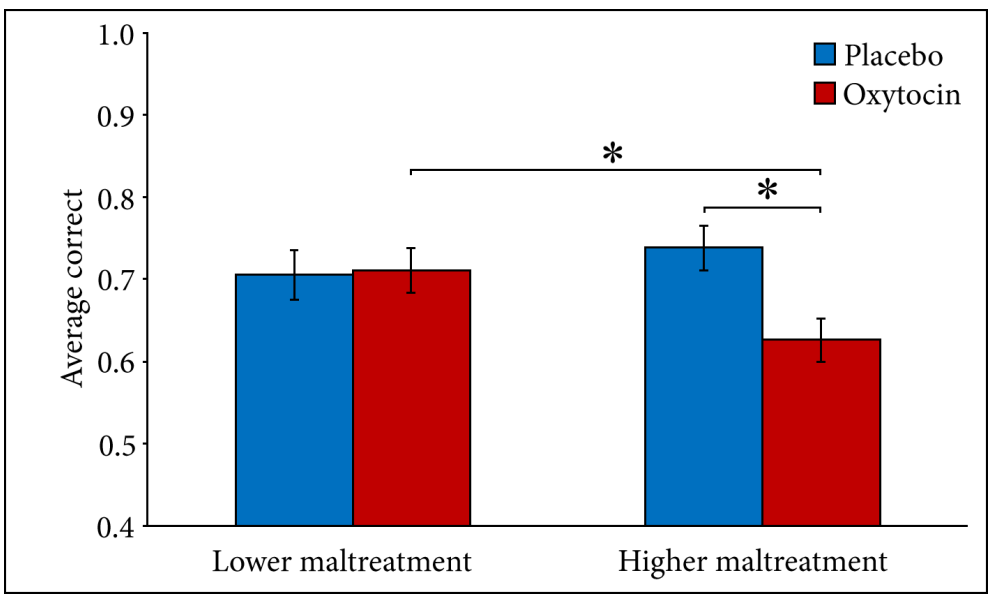



***Figure 3. Overall average correct responses in the testing phase.*** *Participants with higher emotional maltreatment scores and oxytocin administration were significantly less accurate than higher emotional maltreatment scores with placebo administration and lower emotional maltreatment scores with oxytocin administration. The scores on average correct could range from 0 to 1. Data are plotted as mean ± SEM. * p < .05*

Next, pairs on which the participants were trained (80% – 20% happy, 70% – 30% happy, 60% – 40% happy) and pairs on which the participants had to derive associations themselves (all other pairs e.g. 70% – 40% happy pair, 30% – 20% happy pair, etc.) were examined. Mean scores on trained and derived trials were tested using a MANCOVA

with nasal spray and emotional maltreatment as fixed factors. The set of five covariates used in the accuracy analysis were also used in this analysis. Participants in the four groups did not differ on the trained pairs. There was a significant interaction between nasal spray and emotional maltreatment for the derived pairs, $F(1, 83) = 6.23$, $p = .015$, $\eta^2 = .070$. Post-hoc analyses showed that participants in the oxytocin group with higher maltreatment scores differed significantly from participants in the placebo group with higher maltreatment scores ($p = .002$) and from participants in the oxytocin group with lower maltreatment scores ($p = .012$). Participants in the oxytocin group with higher maltreatment scores had fewer correct responses ($M = 0.60$, $SE = 0.03$) than the participants in the placebo group with higher maltreatment ($M = 0.72$, $SE = 0.03$) and from participants in the oxytocin group with lower maltreatment scores ($M = 0.69$, $SD = 0.03$) (Figure 4). The means of the placebo group with lower maltreatment ($M = 0.68$, $SE = 0.03$) did not differ significantly from any of the other three groups.

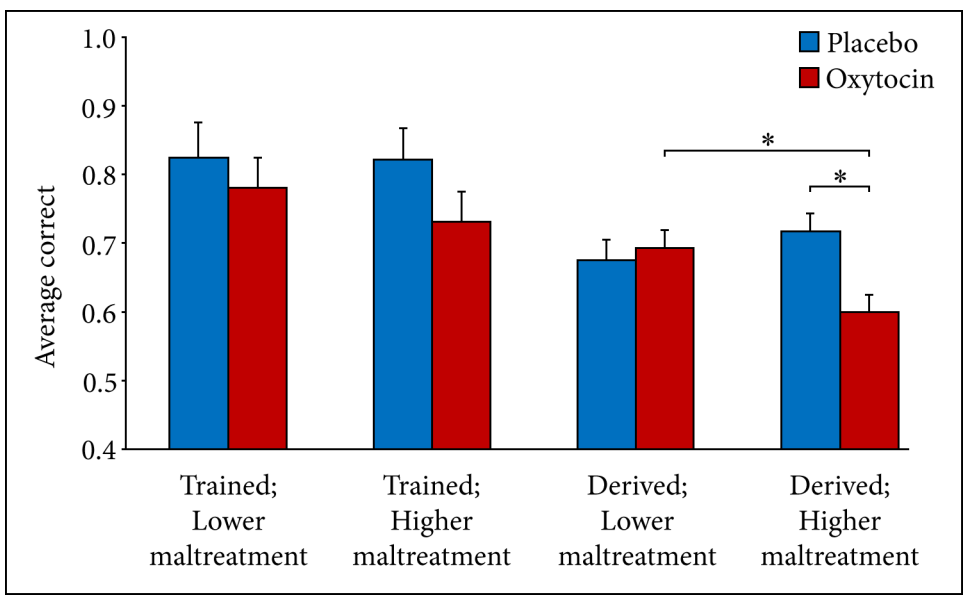



***Figure 4. Average correct responses in the testing phase on trained and derived trials.*** *Participants with higher emotional maltreatment scores with oxytocin administration were significantly less accurate than higher emotional maltreatment scores with placebo administration and lower emotional maltreatment scores with oxytocin administration on the derived trials. The scores could range from 0 to 1. Data are plotted as mean ± SEM. * $p < .05$*

The derived pairs were further classified into low conflict (pairs with a happy

and a sad infant, e.g. 70% – 20% happy pair) and high conflict (pairs with two happy or two sad infants, e.g. 30% – 20% happy pair, 80% – 70% happy pair). Means of low conflict and high conflict trials were tested using a MANCOVA with nasal spray and emotional maltreatment as fixed factors. The five covariates used in the previous analyses were also used in this analysis. There was a significant interaction between nasal spray and emotional maltreatment conditions for the high conflict pairs, $F$ (1, 83) = 4.60, $p$ = .035, $\eta^2$ = .053. Post-hoc analyses showed that participants in the oxytocin group with higher maltreatment scores differed significantly from participants in the placebo group with higher maltreatment scores ($p$ = .011) and from participants in the oxytocin group with lower maltreatment scores ($p$ = .046) for the high conflict trials (Figure 5). Participants in the oxytocin group with higher maltreatment scores had fewer correct responses ($M$ = 0.49, $SD$ = 0.03) than participants in the placebo group with higher maltreatment scores ($M$ = 0.62, $SD$ = 0.04) and participants in the oxytocin group with lower maltreatment scores ($M$ = 0.59, $SD$ = 0.04). The means of the placebo group with lower maltreatment ($M$ = 0.56, $SE$ = 0.04) did not differ significantly from any of the other three groups.

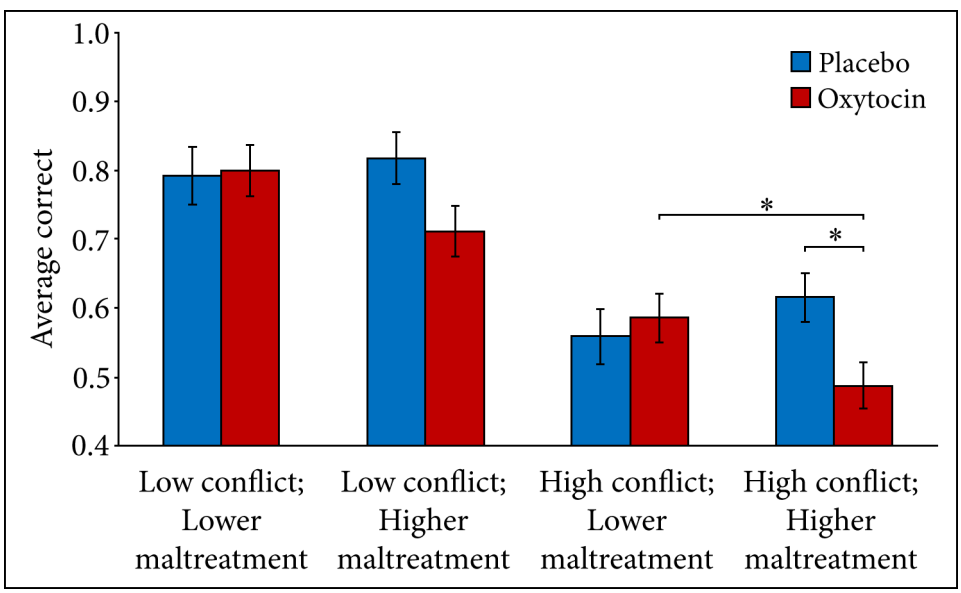



***Figure 5. Correct responses in the testing phase on derived trials divided on difficulty levels - low conflict and high conflict trials.*** *Participants with higher emotional maltreatment scores and oxytocin administration made significantly more incorrect choices as compared to either higher emotional maltreatment scores with placebo administration and lower emotional maltreatment scores with oxytocin administration on high conflict trials. The scores could range from 0 to 1. Data are plotted as mean ± SEM. * p < .05*

Further classification of high conflict trials into trials containing two happy infants, and trials containing two sad infants did not show any effect of the nasal spray or emotional maltreatment condition.

***Reaction times.*** All analyses were repeated with reaction times as the dependent variable. There were no effects of nasal spray or emotional maltreatment on reaction times. Participants in the oxytocin and placebo groups with lower and higher maltreatment scores did not differ in the speed of selecting the happier infant.

## Discussion

Participants who reported more childhood emotional maltreatment made more recognition mistakes in distinguishing happy infants from sad ones after intranasal oxytocin administration. This 'amnesic' effect was present only for the derived (or implicit) pairs and not for the trained pairs. More specifically, they made more mistakes on the 'high conflict' pairs, with pairings that were more similar and thus more difficult to distinguish.

The amnesic effect of oxytocin in individuals who had experienced higher levels of emotional maltreatment found here is consistent with studies reporting decreased familiarity with adult faces (Herzmann *et al*, 2012) or decreased recall of reproduction related words (Heinrichs *et al*, 2004) after intranasal oxytocin administration. Moreover, similar to an earlier study (Heinrichs *et al*, 2004), we found that the amnesic effect of oxytocin was present for the implicit trials, where the participants had to derive the information about the presented pair, whereas the training itself did not reveal differences between the oxytocin and placebo condition. Our findings also suggest that the effects of oxytocin may differ depending on the uncertainty of the information being processed. More difficult pairs, with more similar temperamental characteristics (e.g., an infant being happy in 40% of the trials coupled with an infant being happy in 30% of the trials) yielded more errors after oxytocin administration in individuals who had experienced more emotional maltreatment.

Our results contrast with the studies showing memory enhancing effects of oxytocin (Guastella *et al*, 2008; Savaskan *et al*, 2008). Various sampling and methodological differences might be responsible for these differential effects of oxytocin. For example, the effects of oxytocin may be moderated by individual factors such as genetic background,

attachment style or early life experiences (Bakermans-Kranenburg *et al*, 2012; Bartz *et al*, 2010; Marsh *et al*, 2012). In the present study, we showed the importance of participants' experiences of emotional maltreatment in moderating the effects of oxytocin. Participants with more emotional maltreatment experiences made more incorrect choices in differentiating between happy and sad infants after oxytocin administration. It should be noted that this outcome might depend on the distribution of maltreatment in the current sample. In clinical samples the amnesic effect of oxytocin might be even stronger.

Another issue is the difference in timing of oxytocin administration. In the present study, oxytocin was administered before the learning phase. The testing phase followed immediately after learning and therefore oxytocin levels were elevated throughout the session. In most of the earlier studies, the administration of oxytocin took place before or after the acquisition phase (Guastella *et al*, 2008; Savaskan *et al*, 2008), but the retrieval or testing phase in these studies was 24 hours after the administration of either oxytocin or placebo (Guastella *et al*, 2008; Rimmele *et al*, 2009). Intranasal oxytocin elevates salivary oxytocin levels substantially for at least seven hours after nasal spray administration (Van IJzendoorn *et al*, 2012b) but data about its effectiveness after 24 hours is lacking. Moreover, none of these study designs could assess the differences caused by oxytocin in the acquisition phase. In the present study, participants in the oxytocin and placebo condition with lower or higher experiences of emotional maltreatment did not differ in their learning to discriminate the happy and sad infants. Our results are in line with animal literature showing that oxytocin does not impact on learning but only on specific stages of memory processing (Kovács and Telegdy, 1982).

The type of stimuli also varies between studies. Whereas most of the earlier studies used adult faces or language memory, our study used infant faces coupled with infant crying and laughter sounds (tapping into attachment related memory processes). As infant cues differ from adult cues in how they are processed in the adult brain (Kringelbach *et al*, 2008), and as oxytocin selectively increases the preference for infants compared to adults (Marsh *et al*, 2012), it is possible that oxytocin administration acts differently in memory for infant stimuli. Moreover, childhood experiences might affect the salience and psychobiological relevance of emotional stimuli (Van Harmelen *et al*, 2012), thereby influencing infant emotion related memory processes as well.

Intranasal administration is the best available tool for testing the effects of oxytocin in humans experimentally. However, this method does not allow brain area specific delivery of the administered drug. Brain area specific oxytocin effects on memory

processes have been documented in animal literature. For example, while microinjection of oxytocin in limbic brain regions, dentate gyrus, or dorsal raphe nucleus attenuate memory consolidation; memory consolidation seems facilitated upon a microinjection into the dorsal septal nucleus (Kovács *et al*, 1979). Similarly varying processes occurring in different parts of the human brain after oxytocin administration might explain the inconsistencies among studies assessing effects of oxytocin on memory. In humans, the amygdala is implicated in partially mediating the effects of oxytocin (Kirsch *et al*, 2005; Riem *et al*, 2011). Differences in the bioavailability of oxytocin in the amygdala after intranasal administration may result in differential effects.

The mechanism behind the interaction between oxytocin and adverse childhood experiences affecting memory is not clear. One possibility is that these experiences impact upon amygdala activation. While emotional stimuli elicit increased amygdala activity in individuals who experienced emotional maltreatment (Van Harmelen *et al*, 2012), oxytocin decreases amygdala activity (Kirsch *et al*, 2005; Riem *et al*, 2011). Decreased amygdala activity may lower the salience of emotional cues with reduced memory of the cues as a result. Another possibility is that intranasal administration of oxytocin decreases cortisol responses to stressful tasks (Ditzen *et al*, 2009; Linnen *et al*, 2012), whereas experiences of emotional maltreatment are related to increased stress reactivity and higher cortisol levels (Carpenter *et al*, 2009). The interaction of oxytocin and maltreatment might alter cortisol reactivity to emotional stimuli, leading to impaired rather than facilitated memory processes (Smeets *et al*, 2008).

Oxytocin has long been acclaimed as a sociability hormone, increasing parental sensitivity (Naber *et al*, 2013) and interpersonal trust (De Dreu *et al*, 2010; Kosfeld *et al*, 2005). In decision making paradigms, participants make more prosocial choices towards in-group members after oxytocin administration (De Dreu *et al*, 2012). In the current study, participants with more experiences of maltreatment, who might be more at risk of abusing their own offspring (Sroufe, 2005), had more difficulty in identifying the happier infants after sniffing oxytocin. We might speculate that there is an adaptive evolutionary significance as in these participants oxytocin decreased aversion towards the sad infants and thus hampered distinguishing a happy infant from a sad infant. This lack of preference for the happier infants in the maltreated group might be seen as a protective mechanism enhancing their motivation to give the sad infants 'another chance'.

## Supplementary information (S1)

### *Participants' self-rated mood*

The PANAS was used to assess participants' mood at baseline (T1) and post nasal spray administration (T2). The PANAS consists of 20 items, ten items for positive affect and ten for negative affect. Each item was rated on a 5-point rating scale ranging from *not at all* to *a lot*. Two scales, 'positive affect' ($\alpha$ (T1) = .80, $\alpha$ ( T2) = .81) and 'negative affect' ($\alpha$ (T1) = .79, $\alpha$ (T2) = .57) were constructed by averaging the items.

Two 2x2x2 repeated measures mixed-design ANCOVAs were conducted to test the effect of nasal spray and time on participants' mood (separately for positive affect and negative affect). Time (baseline T1 and post nasal spray T2) was the within-subject factor and nasal spray and emotional maltreatment were the between-subjects factors. Contraceptive use and basal salivary oxytocin levels were the covariates.

There was a significant time effect on participants' rated positive affect, $F$ (1, 86) = 4.53, $p$ = .036, $\eta^2$ = .050, indicating that positive mood of the participants in all groups slightly declined over time. No other main or interaction effects were significant. For negative affect, we found a significant interaction between time and nasal spray, $F$ (1, 86) = 5.67; $p$ = .019, $\eta^2$ = .062, with a steeper decrease in negative affect in the oxytocin group compared to the placebo group (Figure S1). There were no main effects or interaction effects of emotional maltreatment group.

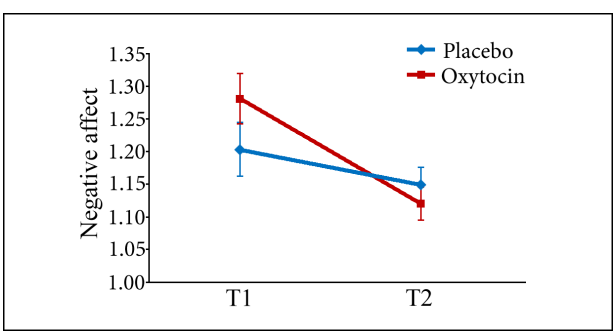



***Figure S1. Effect of oxytocin on the negative affect of the participants before (T1) and after nasal spray (T2).*** *Participants in oxytocin group have a steeper decrease in negative affect ratings compared to placebo group. Data are plotted as mean ± SEM. * p < .05*

## Supplementary information (S2)

***Effect of oxytocin on perceived cuteness and temperament***

Parental permission was obtained for the use of infant facial stimuli for research purposes, and was also approved by the Oxford Research Ethics Committee. At the beginning of the session (baseline; T1) and 45 minutes post nasal spray (T2), the participants rated the six infant faces with neutral facial expression on physiognomic and temperamental dimensions described by nine adjectives (attractive, cute, difficult, easy, irritable, responsive, secure, smart and spoilt). Face images were presented at the center of the screen with a vertical visual analogue scale (VAS) immediately to the right. The adjectives appeared at the ends of the VAS (for e.g. 'cute' at the top and 'not cute' at the bottom end of VAS). The rating bar started at the midpoint on the scale and participants could adjust the height of this bar using the 'up' and 'down' arrow keys on a standard keyboard. Scale scores on the VAS ranged from a maximum of 4 to a minimum of -4, with intervals of .0025. All nine adjectives for each infant were rated subsequently and the orders of both the adjectives and infant faces were randomized among participants.

Factor analysis was performed, with varimax rotation, on the nine characteristic ratings for the six infants separately. 'Attractive' and 'cute' ratings loaded on the same factor for all of the infants. 'Difficult', 'easy' (reversed) and 'irritable' ratings loaded on a factor for four out of six infants. Therefore, a 'cuteness' scale was created by averaging the 'attractive' and 'cute' ratings for each infant, for baseline ratings (T1) and for post nasal spray ratings (T2). Similarly, a 'perceived temperament' scale was created by averaging the 'difficult', 'easy' (reversed) and 'irritable' ratings for each infant.

Two repeated measures mixed-design ANCOVAs were performed to investigate the effects of nasal spray and emotional maltreatment on ratings of infant cuteness and perceived temperament. Within-subjects factors were time (baseline T1 and post nasal spray T2) and infant (6 infant faces). Nasal spray (oxytocin or placebo) and emotional maltreatment (higher or lower) were entered as between-subjects factors. Contraceptive use and basal salivary oxytocin levels were entered as covariates.

For the cuteness scale, there was a main effect of infant, $F$ (4.26, 366.19) = 3.57, $p$ = .006, $\eta^2$ = .040. Some infants were rated as significantly cuter than others. There was also a main effect of time, $F$ (1, 86) = 4.57, $p$ = .035, $\eta^2$ = .050, which was qualified by the significant time by nasal spray interaction, $F$ (1, 86) = 6.71, $p$ = .011, $\eta^2$ = .072. All infants

increased in mean cuteness ratings from T1 to T2, but there was a steeper increase in the ratings for the placebo group as compared to the oxytocin group (Figure S2). All other main and interactions effects were non-significant. There were no significant main or interaction effects for experienced emotional maltreatment.

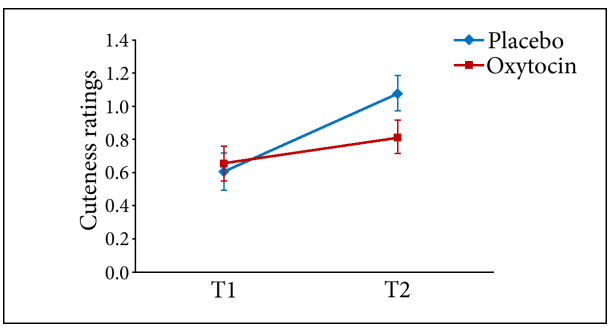



***Figure S2. Effects of oxytocin administration on cuteness scale of six infant faces before (T1) and after nasal spray (T2).*** *Compared to placebo, the increase in cuteness ratings with time is lower in the oxytocin group. Data are plotted as mean ± SEM. * $p < .05$*

For the temperament scale, there was a significant main effect of infant, $F$ (3.89, 334.45) = 2.99, $p$ = .020, $\eta^2$ = .034. Some infants were rated as having a more difficult temperament than others. No other main or interaction effects were significant (all $p >$ .050). Participants in the oxytocin group did not differ from those in the placebo group in their perception of infant temperament. Experience of emotional maltreatment did not moderate participants' perception of infant temperament.

## Supplementary information (S3)

### *Statistical analyses*

Analyses were performed using the IBM SPSS statistics 19 package. A series of analyses of co-variances (ANCOVAs) were performed to analyze the effects of oxytocin administration and moderation by self-reported experiences of childhood emotional maltreatment on accuracy of performance and ratings of infant characteristics. Nasal spray condition and the dichotomized emotional maltreatment scale were used as the predictor and moderator, respectively.

***Covariates.*** Basal oxytocin levels were co-varied to control for individual differences in the oxytonergic system. Moreover, physiological oxytocin levels have been shown to be affected by stressful life experiences such as emotional abuse and neglect

(Heim *et al*, 2008; Pierrehumbert *et al*, 2010). We therefore covaried basal oxytocin levels to control for any observed or unobserved individual differences in the oxytonergic system. One individual had extremely high basal oxytocin levels (> 3 standard deviations above the mean). The oxytocin level values for this individual were substituted with the next highest score (winsorized; Tabachnick and Fidell, 2006). Use of oral contraceptives was included as a covariate because there were significantly more participants using contraceptives in the oxytocin group than in the placebo group. This might result in a confounding effect of the use of contraceptives (and the resulting endocrinal and hormonal changes) on the memory related processes being tested here. Participants' self-reported negative affect also differed across oxytocin and placebo groups. Participants in the oxytocin group had a steeper decrease in negative affect ratings from T1 to T2 as compared to placebo group (supplementary information S2). Difference scores for negative affect were therefore calculated by subtracting T1 ratings from T2 ratings and these difference scores were used as covariates in the learning and testing analyses. Participant's mood might affect their performance at a task, as a more negative mood might lead to more negative perceptions of infant cues and therefore affect the memory in unknown ways. Given the differences in participant's mood after oxytocin or placebo administration, individual participant mood was co-varied to control for any indirect effects of oxytocin on memory which are mediated by changes in mood. There was a significant time by nasal spray interaction effect for the infant cuteness ratings. All infants increased in mean cuteness ratings from T1 to T2, but there was a steeper increase in the ratings for the placebo group as compared to the oxytocin group (supplementary information S3). Difference scores for cuteness were therefore calculated by subtracting the average ratings of the six infants at T1 from the average ratings of the six infants at T2, and these difference scores were used as a covariate in the learning and testing analyses. As participants' perception of the cuteness of an infant might also change the salience of the stimuli and thereby affect the familiarity of the face, we controlled for the change in attractiveness ratings of the faces, which were differentially affected by the nasal spray. Lastly, final level of learning was co-varied in the testing analyses in order to control for individual differences in performance during the training phase. This would result in differentiating the variability explained by the learning and would give clearer estimate of the effects of oxytocin and emotional maltreatment on memory for infant cues.

Greenhouse-Geisser corrections were performed wherever necessary. Post-hoc analyses were performed to localize significant differences between the four groups; placebo – lower levels of emotional maltreatment, placebo – higher levels of emotional mal-

treatment, oxytocin - lower levels of emotional maltreatment and oxytocin - higher levels of emotional maltreatment.

***Expectation effect.*** At the end of the session, participants were asked which nasal spray they thought was administered to them ('oxytocin', 'placebo' or 'don't know'). As performance might be influenced by participants' perception about the spray that was administered to them, we asked participants to guess the nasal spray that they received. Seventy percent of the participants reported not knowing which nasal spray they received. The remaining 30% of the participants were no more accurate than chance level in guessing their group correctly: 53% guessed incorrectly and 47% guessed correctly. We concluded that perception of the nasal spray did not affect the performance of participants.

## Supplementary information (S4)

### *Infant specific sub-pairs*

The derived pairs were classified into six infant specific sub-pairs, depending on the infant involved in it (for e.g. all the trials with 80 % happy infant), in order to see if the effect of nasal spray was specific to some of the infants depending on their manipulated temperament. A MANCOVA was conducted with the infant specific pairs (six pairs) as dependent variables and nasal spray and emotional maltreatment as fixed factors and with the five covariates used in the overall correct analysis. There was a significant main effect of nasal spray on the 40% happy infant, $F(1, 83) = 4.68$, $p = .033$, $\eta^2 = .053$, qualified by a significant interaction between nasal spray and emotional maltreatment, $F(1, 83) = 4.32$, $p = .041$, $\eta^2 = .049$. A similar significant interaction was found for 60% happy infant, $F(1, 83) = 4.47$, $p = .038$, $\eta^2 = .051$. Post hoc analyses with the 40% happy infant showed that participants in the oxytocin group with higher maltreatment scores differed significantly from participants in the placebo group with higher maltreatment scores ($p = .002$). Participants in the oxytocin group with higher maltreatment scores had fewer correct responses ($M = 0.60$, $SD = 0.03$) than the participants in the placebo group with higher maltreatment scores ($M = 0.75$, $SD = 0.04$). For the 60% happy infant, participants in the oxytocin group with higher maltreatment scores differed significantly from participants in the placebo group with higher maltreatment scores ($p = .015$) and participants in the oxytocin group with lower maltreatment scores ($p = .027$). Participants in the oxytocin group with higher maltreatment scores had fewer correct responses ($M = 0.60$, $SD = 0.03$) than the participants in the placebo group with higher maltreatment scores ($M = 0.72$, $SD = 0.03$) and ($M = 0.71$, $SD = 0.03$) for participants in the oxytocin group with lower mal-

treatment scores (figure S3). There was no significant difference between the nasal spray groups with lower or higher maltreatment on their responses to the other infant pairs.

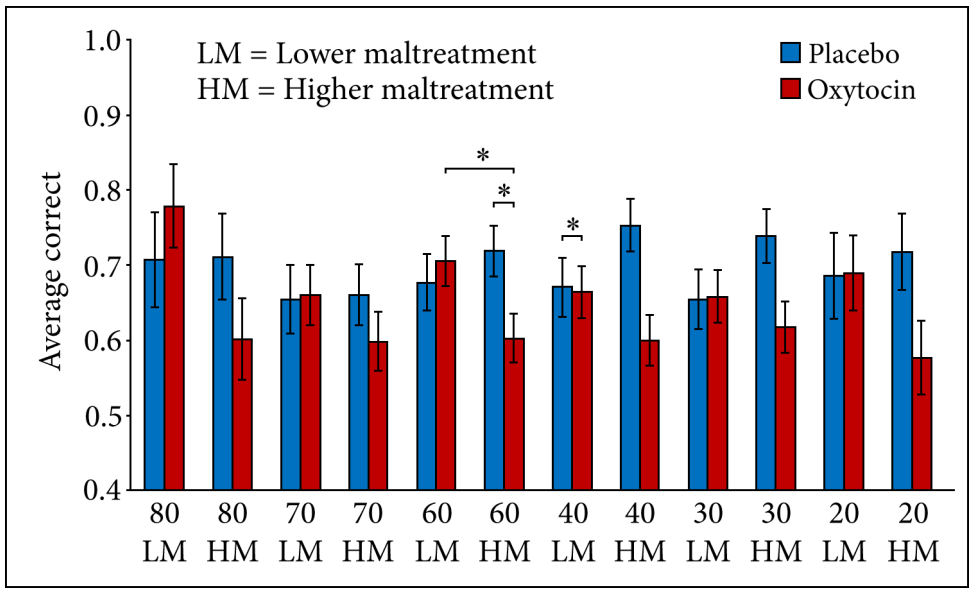



***Figure S3. Correct responses in the testing phase with infant specific pairing.*** *Participants with higher emotional maltreatment scores with oxytocin administration make significantly more incorrect choices as compared to higher emotional maltreatment scores with placebo administration for 60% happy infant and 40% happy infant and lower emotional maltreatment scores with oxytocin administration for 60% happy infant. The scores could range from 0 to 1. Data are plotted as mean ± SEM. * $p < .05$*

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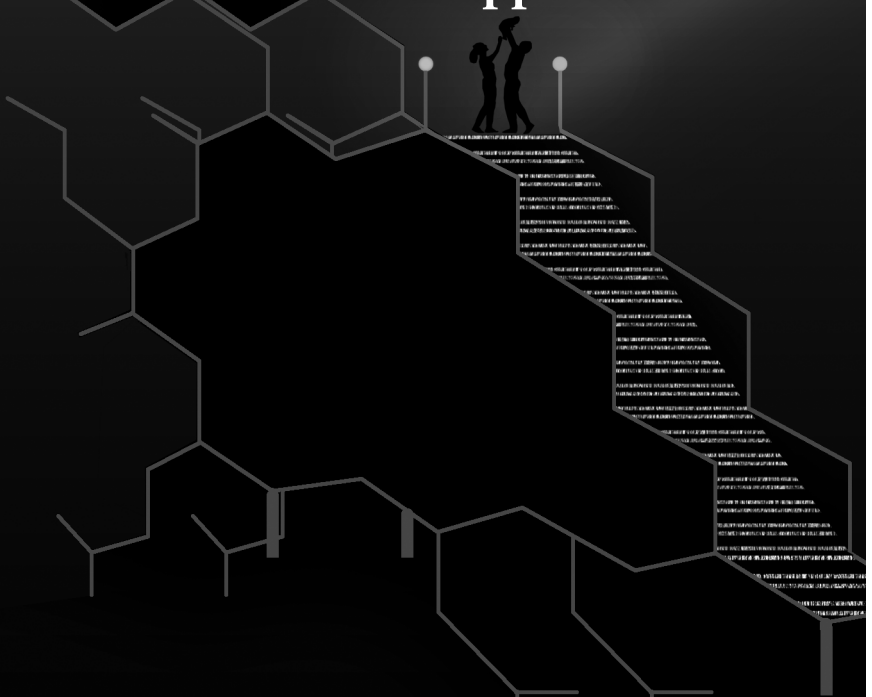
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5

# Temperamental sensitivity moderates the effects of maternal love-withdrawal on perception of infant crying: An interactive infant simulator approach



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## Abstract

Parenting has an impact on the offspring's social and behavioral outcomes. However, not all individuals are affected equally: according to the differential susceptibility hypothesis temperamental traits may moderate the effects of early life experiences. We examined the association between young adults' experiences of maternal love-withdrawal and their perception of infant crying, and the potentially moderating role of temperamental orienting sensitivity. In an ecologically valid but standardized setting, 132 female participants spent two consecutive evenings taking care of an infant simulator. Orienting sensitivity moderated the relation between experienced love-withdrawal and the perception of infant crying: Participants with high orienting sensitivity who experienced low levels of love-withdrawal perceived the crying bouts as less negative than others. We conclude that the long-term impact of early life experiences may be moderated by temperamental characteristics, with implications for individual differences in perceptual responses to infant stimuli in adulthood.

## Keywords

Differential susceptibility, Infant crying, Orienting sensitivity, Infant simulator, Parenting, Temperament.

## Introduction

From an evolutionary point of view crying is one of the most important behaviors shown by pre-verbal infants since it signals the caregiver about a real or potential threat to the infant. Crying elicits caregiving behavior in the parent that results in relieving the infant from the source of discomfort (Murray, 1979; Zeifman, 2001). However, research has also revealed various parental and infant attributes that interfere with this seemingly simple sequence of infant cry - adult caregiving, resulting in various degrees of sensitive to harsh parenting (Crouch *et al*, 2008; McCanne and Hagstrom, 1996; Stith *et al*, 2009). While repetitive and inconsolable crying has been shown to be an important trigger for more harsh and insensitive parenting (Barr *et al*, 2006; Soltis, 2004), individual differences in parents' physiological responses and perception of infant crying might also influence (intended) parenting (Crowe and Zeskind, 1992; Out *et al*, 2010b).

Insensitive parents have been reported to display strong physiological responses to infant cry sounds (Joosen *et al*, 2013; McCanne *et al*, 1996), to perceive cry sounds as more aversive and distressing, and to use more harsh caregiving after listening to experimentally manipulated cry sounds, compared to more sensitive parents (Frodi and Lamb, 1980a, b). Moreover, listening to cry sounds may also have an effect on individuals' mood as seen by increased negative affect ratings (Bruning and McMahon, 2009; Del Vecchio *et al*, 2009). Using a twin design, both environmental factors and genetic make-up have been shown to contribute to individual differences in physiological responses and perception of infant crying (Out *et al*, 2010a).

Parents provide one of the earliest and most continuously experienced environment that helps a child to build schemas (also known as internal working models) of self and others (Bowlby, 1969) including relations with one's own offspring (Bretherton and Munholland, 2008). Individuals might therefore differ in their perceptions and responses to infant crying, based on these early caregiving experiences (Casanova *et al*, 1994). One important class of caregiving experiences pertains to parental discipline. A strategy of withholding love and affection if the child misbehaves or fails at a task is known as the disciplinary strategy of using love-withdrawal. Although this strategy might prove effective in the short run (Garner, 2012), when used excessively it is considered psychological maltreatment (Euser *et al*, 2010), and it may come with considerable costs later in life, such as low self-esteem, low emotional well-being, fear of failure, and more feelings of resentment towards parents (Assor *et al*, 2004; Elliot and Thrash, 2004). Moreover, early life experience of maternal love-withdrawal has been shown to play an important modera-

tor role in the relation between biological factors (e.g., oxytocin) and responses to social cues (Huffmeijer *et al*, 2012; Riem *et al*, 2013; Riem *et al*, in press; Van IJzendoorn *et al*, 2011). For example, intranasally administered oxytocin enhanced pro-social behavior in individuals with few experiences of maternal love-withdrawal but not in individuals with higher exposure to maternal love-withdrawal. Given the associations between love-withdrawal and social behavior and the substantial intergenerational transmission of parenting behaviors (Van IJzendoorn, 1992), exposure to parental love-withdrawal might induce later negativity towards infant signals.

However, all individuals may not be equally influenced by the same environmental factors (Bakermans-Kranenburg and Van IJzendoorn, 2010; Ellis *et al*, 2011). Recent studies have suggested that some individuals are not only more vulnerable than others to adverse environment, but also benefit more from positive environment, and thus should be considered more susceptible for better *and* for worse (differential susceptibility hypothesis; Belsky *et al*, 2007).

Temperament has been proposed as a susceptibility factor, which in interaction with the environment may result in variations in psychological adjustment and physical health (Ellis *et al*, 2011).Van Zeijl *et al*, (2007) found that children with difficult temperament were more susceptible to both negative and positive discipline, compared to children with relatively easy temperament. Data from the large-scale NICHD Study of Early Child Care showed that children with difficult temperament benefit more than children with easy temperament from exposure to sensitive parenting (Bradley and Corwyn, 2008). In the same vein, compared to children with easy temperament, difficult children had more behavior problems early in their school careers when exposed to low-quality child care during infancy or early childhood, but fewer problems when quality was high (Pluess and Belsky, 2009).

Research on infants has been conducted with various temperamental indicators of differential susceptibility, such as difficult temperament (Belsky et al, 1998), temperamental reactivity (Klein Velderman *et al*, 2006), negative emotionality (Kochanska *et al*, 2007), and fearfulness (Gilissen *et al*, 2008). It is important to realize that not only infants but also caregivers may be differentially susceptible to stressors and social experiences (Van IJzendoorn *et al*, 2008). Orienting sensitivity (in terms of variation in depth of processing of sensory information, with more sensitive individuals processing information more thoroughly) has been suggested as a good indicator of differential susceptibility in adults (Ellis *et al*, 2011). In a series of studies on the interaction between orienting

sensitivity and childhood stressors, stronger associations between childhood adversity and self-reported shyness and negative affectivity were found for participants with high scores on sensory processing sensitivity (Aron *et al*, 2005). Orienting sensitivity includes perceptual sensitivity (awareness of slight, low intensity stimulation arising from within the body or the environment), affective sensitivity (awareness of emotional valence associated with low intensity stimuli), and associative sensitivity (reactive cognitive content that is not related to standard associations with the environment) (Evans and Rothbart, 2007, 2008).

High temperamental sensitivity has been shown to interact with (experimentally manipulated) negative environmental factors (adverse parental environment and extremely difficult or impossible assignments, respectively) to predict more negative outcomes (Aron and Aron, 1997; Aron *et al*, 2005). Although this specific result supports a dual risk model, individuals with high orienting sensitivity may be more susceptible not only to negative caregiving experiences but also to positive caregiving experiences than individuals low in orienting sensitivity. To our knowledge there are no published studies that assess the role of caregivers' temperament in moderating the relation between childhood experiences and parenting and caregiving behaviors. In the current study we assess how young adults' temperamental orienting sensitivity moderates the relation between parental love-withdrawal and their perception of infant crying and their mood after taking care of an infant simulator that cries in a lifelike way.

Most of the previous studies measuring physiological and psychological responses to infant crying involved listening to recorded (and manipulated) cry sounds (Crouch *et al*, 2008; Crowe *et al*, 1992). Although these studies have provided us with great insights into physiological and behavioral outcomes, they are of low ecological validity (Bruning *et al*, 2009), as they necessarily fail to approximate the real-life situation of the presence of a crying infant. Moreover, such paradigms lack the controllability component that may give the caregiver a sense of coping and assurance that they are capable of soothing the infant and terminating the crying behavior. Crying infant simulators that can be soothed by the participant, as used in the current study might increase ecological validity in cry research.

The infant simulators were originally developed as a prevention tool for teenage pregnancies, by providing the teenagers a *hands-on* experience of infant caretaking (Roberts and McCowan, 2004; Strachan and Gorey, 1997). Infant simulators have been used in various settings and groups as a part of parenting teaching aid. Research shows

that simulators are taken seriously by the participants (Barnett and Hurst, 2004). In the present study we used the infant simulator in an interactive setting, where the participants over the course of five hours were exposed to a number of cry episodes. During each cry episode they had to figure out the appropriate caregiving to sooth the infant simulator. Appropriate care would result in the termination of the crying. Participants' perception of these cry sounds and participants' mood were assessed after each cry episode. Moreover, as opposed to earlier studies in which infant simulators were used in laboratory settings (Bruning *et al*, 2009), our participants took the infant simulator home to take care of it for two consecutive evenings, increasing the ecological validity of the assessments.

To our knowledge, this is the first study examining the effects of young adults' orienting sensitivity and experienced parenting on perception of infant cry sounds, using an interactive infant-caregiving paradigm. We hypothesized that individuals with high orienting sensitivity will be affected more by their love-withdrawal experiences than individuals with low orienting sensitivity. In individuals with high orienting sensitivity, we expected that less maternal love-withdrawal would be associated with less negative perception and more maternal love-withdrawal would be associated with more negative perception of infant crying. We expected that these associations would be weaker or absent in individuals with low orienting sensitivity. Earlier studies also report a significant increase in negative mood after exposure to infant cry sounds when participants could not do anything to stop the cry sound (Bruning *et al*, 2009), thus increased negative affect may be related to their helplessness rather than to infant crying *per se*. We therefore explore the effects of temperamental sensitivity and experienced parenting on participants' mood after infant crying without a specified expectation of the direction of the effect.

## Method

### *Participants*

A total of 353 undergraduate students from the Institute of Education and Child Studies, and Department of Psychology at Leiden University participated in the first phase of the study. In this phase, the participants completed online questionnaires on their temperament, perception of parenting by their mothers, and some demographic details. One participant was excluded due to random responses. Ten male participants and five females with children of their own were also excluded to avoid gender and experience

effects on any of the outcomes. The final sample consisted of 337 females between 18 and 30 years ($M$ = 19.93, $SD$ = 1.56). More than 90% of the sample was Caucasian.

The participants were then invited for the second phase of the study where they had to take care of a 'life-like' infant simulator for two evenings (in order to examine the effects of familiarity and experience). Forty-two of them (12.61 %) were not willing to participate in the second phase. They did not differ from the rest of the participants on demographics, temperament and maternal parenting dimensions (all $p > .05$). For the current study the first 132 students who participated in the ongoing second phase were selected, since this sample size provided a power of .80 to find a medium-sized (interaction) effect at a significance level of alpha = .05. The mean age of the participants was 20.12 years ($SD$ = 1.74). This group of participants was similar to the initial sample in demographics, temperament and maternal parenting dimensions (all $p > .05$). Ten participants were excluded from the final analyses because of missing values due to technical failure of the instruments used during the sessions. The study was approved by the departmental ethics committee and informed consent was obtained from all participants.

***Procedure***

Participants completed online questionnaires on their temperament, their mothers' parenting strategies and some demographic details. After that they received information about the possibility to take care of a realistic infant simulator. The participants were asked to take care of the simulator for two evenings (5 p.m. - 10 p.m.) as if it were their own baby. The participants used a hand held computer to answer questions about their perception of the cry sounds and their mood after each cry and caretaking episode.

The infant simulator was programmed to start at 5 p.m. every evening and stop at 10 p.m. During these 5 hours, the simulator had various cry episodes such as hunger cry, for diaper change, for burping etc. The infant simulator schedules (cry frequencies, gap between cry episodes etc.) are based on diaries kept by parents of real infants. A "difficult baby" schedule was used in order to have sufficient cry episodes. The simulator could be soothed by responding appropriately, i.e. feeding the simulator for hunger cry, changing the diaper when required etc. After soothing the simulator, the participant completed some questions on the hand held computer about the perception of the cry, such as the urgency and aversiveness of the cry sound. The participants also indicated their mood after each cry episode.

***Measures***

***Love-withdrawal.*** The 11-item scale for love-withdrawal (Huffmeijer *et al*, 2011) was administered in order to assess the use of this disciplining strategy by participants' mothers up until participants were 16 years old. Five items came from the Withdrawal of Relations subscale of the CRPBI (Beyers and Goossens, 2003; Schludermann and Schludermann, 1970), two items were adapted from this same questionnaire, and four items adapted from the Parental Discipline Questionnaire (PDQ; Hoffman and Saltzstein, 1967; Patrick and Gibbs, 2007). These questionnaires have been well validated and the 11-item version was used in previous research (see Huffmeijer *et al*, 2011). Each item (e.g., *My mother was a person who is less friendly with me, if I do not see things her way*) was rated on a 5-point scale ranging from *not applicable* to *fully applicable*. One of the items was inadvertently not visible in some questionnaires due to a technical error. The score for this item was substituted with the mean score of the other items of the love-withdrawal scale. Internal consistency of the scale was high (Cronbach's $\alpha$ = .93).

***Temperament.*** Temperament was assessed using the 77 item Adult Temperament Questionnaire (ATQ-77; Evans *et al*, 2008). Each question (e.g., *I am often consciously aware of how the weather seems to affect my mood*) was rated on a 7-point rating scale ranging from *not at all* to *always*. Four temperament scales, as suggested earlier in literature (Evans *et al*, 2007) were distinguished: *Negative affect*, *Extraversion*, *Effortful control,* and *Orienting sensitivity*. We used orienting sensitivity to test for moderation of the association between maternal love-withdrawal and negative perception of infant crying. Cronbach's $\alpha$ for the orienting sensitivity scale for the current sample was .76.

***Infant simulator.*** The infant simulator (Realityworks, Inc., Virtual Parenting, Coffs Harbour, NSW) is a doll resembling a real infant in physical appearance, size and weight (2.95 kg). The physical features of the simulator are modeled in a way that requires taking care like a real infant. For example, it has a lifelike neck that falls back if not supported. The simulator is programmed similar to an infant with realistic cry sounds (beginning with mild fuss eventually increasing to full-blown crying) as well as breathing, burping and suckling sounds. All the sounds, including cry sounds, are recorded from real infants. Each cry episode requires specific caregiving, such as feeding, burping, diaper change and rocking. Inbuilt sensors in combination with external sensors (in diapers and feeding bottles) register whether correct caregiving was provided or not. The infant simulator responds by being calm again if the appropriate care is provided. The participants were introduced to the simulator by indicating the baby doll's name (e.g.,

Lisa), and they were asked to take care as if it was a real baby. They were instructed to provide proper head support when carrying the baby, and to either feed, burp or change the diaper in order to sooth the crying baby. Feeding bottles, diapers and extra clothing were provided to the participants, as well as a soft baby carrier.

***Perception of infant simulator's crying.*** After each cry episode the participants rated the degree of aversiveness, urgency, sickness and irritability of the cry sounds on a 5-point rating scale. These adjectives have been used in previous cry research as a measure of parents' negative perceptions of the cry sounds (LaGasse *et al*, 2005)2005. The total number of times the participants completed the questionnaires after hearing a cry sound varied among the participants depending on their handling of the simulator. We therefore choose the first 8 cry episodes for constructing the scale for cry perception as approximately 88% of the participants had complete data for 8 cry episodes on both days. As the internal consistency of urgency was low (cry episode 1-8, Cronbach's $\alpha = .40$), this item was not used for further analysis. Factor analysis resulted in one factor based on the remaining three items (aversiveness, sickness and irritability) explaining 50% of the total variance. Higher factor scores indicated more negative perception of the cry sounds.

***Mood.*** Eight items were selected from the Positive Affect Negative Affect Scale (PANAS; Crawford and Henry, 2004; Watson *et al*, 1988) to assess the transient mood of the participant after each cry episode. Each item was rated on a 5- point scale ranging from not *at all* to a *lot*. Two scales, Positive affect ($\alpha$ (day1) = .94, $\alpha$ (day 2) = .96) and Negative affect ($\alpha$ (day1) = .95, ($\alpha$ (day2) = .96) were constructed using the four items for each dimension (cry episode 1-8, separately for day 1 and day 2).

***Response bias.*** Eighteen social desirability items from the Child Abuse Potential Inventory (CAPI; Milner, 1994) were used for assessing the degree of social desirability in participants' responses to the questionnaires. Cronbach's $\alpha$ for the current sample was .64.

***Reality value of the infant simulator.*** Five items were presented to assess the participants' perception of their taking care of the infant simulator as a realistic experience (see e.g., Bath *et al*, 2000). Participants took the simulators seriously as evident from their scores on the items such as, "did you notice yourself talking to the baby" (84 %) and "taking care of the doll was a realistic experience": The mean score on the item asking about the reality value of the infant simulator was $M = 6.21$ ($SD = 1.71$) on a scale from 1 to 10. Cronbach's $\alpha$ for the 5-item overall scale was .74.

## Results

### *Descriptives and Bivariate Correlations*

Distributions of all variables of interest were checked for normality. Table 1 presents descriptive data of maternal love-withdrawal, temperamental orienting sensitivity and their correlations with perception of cry sounds and transient mood after the cry episodes. Since response bias and positive affect on day 2 were modestly correlated ($r$ = .21, $p$ = .02), residual scores for mood and perception of cry (controlling for response bias) were used in the analyses. Negative perception of crying showed stability over the two days, as did positive and negative mood. Regarding the lifelike features of the infant simulator, high reality value of the simulator was correlated to more negative perception of crying on day 2 ($r$ = .19, $p$ < .05).

### *Perception of infant crying: Multivariate approach*

Two repeated-measures analyses of variance were conducted, one for mood and one for the perception of crying. Mood (positive and negative affect) and perception of the cry sounds on day 1 and day 2 of taking care of the infant simulator were within-subjects factors. Love-withdrawal and orienting sensitivity were dichotomized using a median split and were entered as between-subjects factors. For perception of cry, the three-way interaction between day, love-withdrawal, and orienting sensitivity was significant ($F$ (3,118) = 3.17, $p$ = .027, $\eta^2$ = .07). Post hoc analyses were conducted to clarify the interpretation of the significant three-way interaction. Comparison within high and low orienting sensitivity groups showed no significant interaction between day and maternal love-withdrawal in the two groups. A significant main effect of maternal love-withdrawal was present for the participants with high orienting sensitivity ($F$ (1, 60) = 4.57, $p$ = .04; $\eta^2$ = .07) but not for participants with low scores on orienting sensitivity ($F$ (1, 58) = 0.80, $p$ = .38; $\eta^2$ = .01). Inspection of means revealed that individuals with high orienting sensitivity and low exposure to maternal love-withdrawal perceived the infant cry sounds significantly less negative than the other three groups. There was no significant difference in cry perception among the other three groups (see Figure 1).

For positive and negative mood there were no significant main, two-way or three-way interaction effects (all $p$ > .17). None of the predictors contributed or interacted significantly to predict participants' mood after the cry episodes.

***Table 1. Descriptive data and correlations of maternal love withdrawal, orienting sensitivity, perception of cry sounds and mood after cry episodes.***

| | Mean (SD) | Maternal love withdrawal | Orienting sensitivity | Reality value of simulator | Perception of cry Day1 | Positive mood Day1 | Negative mood Day1 | Perception of cry Day2 | Positive mood Day2 | Negative mood Day2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Maternal love withdrawal | 1.66 (0.73) | | | | | | | | | |
| Orienting sensitivity | 4.27 (0.75) | 0.12 | | | | | | | | |
| Reality value of simulator | 6.21 (1.71) | -0.14 | -0.05 | | | | | | | |
| Perception of cry Day1 | -0.04 (0.96) | 0.25** | -0.05 | 0.01 | | | | | | |
| Positive mood Day1 | 3.38 (0.59) | 0.05 | 0.15 | 0.05 | -0.20* | | | | | |
| Negative mood Day1 | 2.01 (0.64) | 0.13 | -0.15 | 0.08 | 0.67** | -0.25** | | | | |
| Perception of cry Day2 | -0.03 (0.97) | 0.03 | 0.11 | 0.19* | 0.45** | 0.05 | 0.37** | | | |
| Positive mood Day2 | 3.49 (0.69) | -0.06 | 0.01 | 0.08 | -0.29** | 0.33** | -0.28** | -0.42** | | |
| Negative mood Day2 | 1.63 (0.61) | -0.04 | 0.00 | 0.18 | 0.38** | -0.05 | 0.55** | 0.66** | -0.35** | |

*n = 122, * p < .05 ** p < .01*

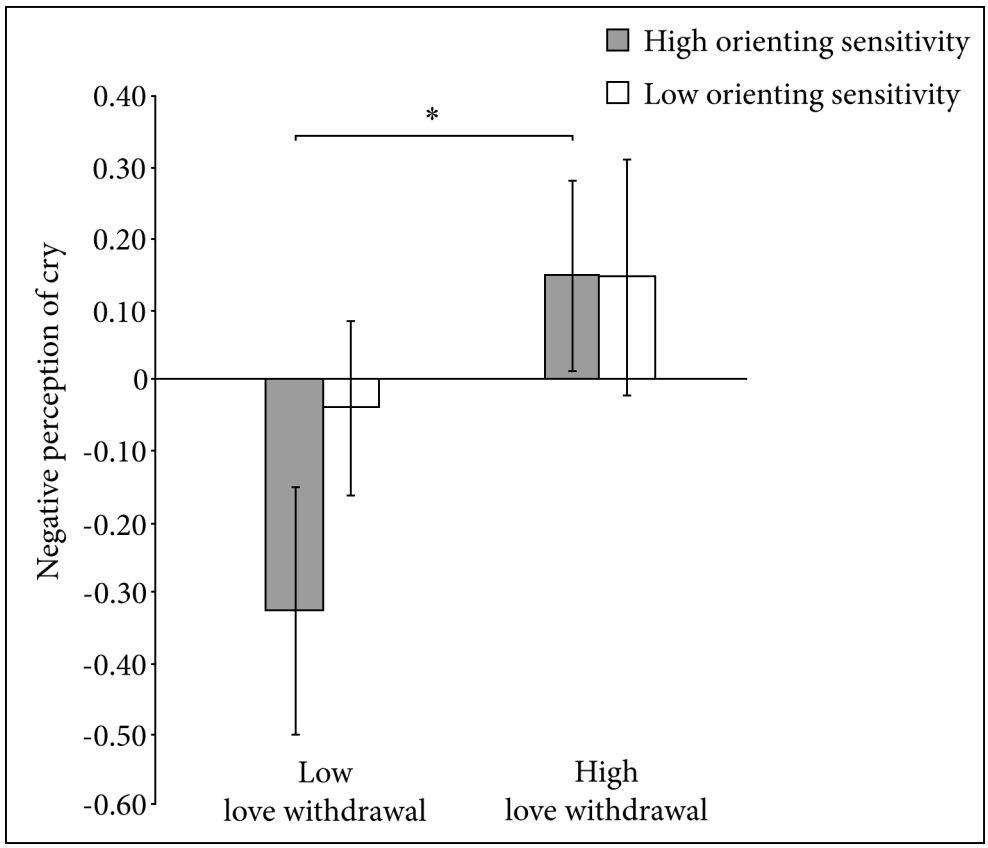



***Figure 1. Effects of love withdrawal and orienting sensitivity on negative perception of cry sounds.*** *Higher values indicate more negative perception of cry sounds. Data are plotted as mean ± SEM. * $p < .05$. Group sizes range from 21 to 39. $\eta^2 = .07$*

## Discussion

We found that temperamentally high-sensitive participants who experienced little maternal love-withdrawal perceived infant crying as significantly less negative than participants who experienced more maternal love-withdrawal. In the low orienting sensitivity group, the perceived negativity in the infant cry sounds did not differ between the high and low love-withdrawal groups.

A positive perception of infant crying as an 'honest' signal (Furlow, 1997) is important for sensitive caretaking and subsequent well-being of the infant (Zeifman, 2003). More negative perception of infant cues renders the infant vulnerable to more negative

and harsh parenting experiences (Lee *et al*, 2007; Leerkes and Crockenberg, 2006; Soltis, 2004). For example, excessive and uncontrollable crying is more often perceived negatively and can trigger parental abuse and neglect (Lee *et al*, 2007). We used the infant simulator with interactive features, which, like in real life, starts with fussing, and cries more intensely over time. The caregiver has to identify the reason for crying and provide appropriate care in order to calm the baby. This sequence mimics real-life caregiving and makes the paradigm more ecologically valid than listening to pre-recorded cry sounds in a lab environment. Indeed, the participants reported that the experience was rather realistic, as evident from the fact that they talked to the babies and mentioned them by their names.

Our results show that temperamentally sensitive individuals with little experience of maternal love-withdrawal perceived infant crying as less negative compared to temperamentally sensitive individuals with more love-withdrawal experiences and individuals low on orienting sensitivity. Complementary to the results of earlier studies which pose temperamental sensitivity as a risk factor (Aron *et al*, 1997), our results show the potential of sensory sensitivity to benefit more from positive circumstances. This is of particular importance since it underscores the difference between a double risk and a differential susceptibility model. While one might argue that our results only partly support the differential susceptibility hypothesis, as temperamentally sensitive individuals with low love-withdrawal experiences perceived infant crying less negative than temperamentally sensitive individuals with high love-withdrawal, but the latter group did not perceive infant crying as more negative compared to individuals with low sensory sensitivity and high love-withdrawal, it is important that our study shows the 'for better' outcomes that are essential for the differential susceptibility model.

One explanation for our pattern of results may be that there was an under-representation of extremely high scores on love-withdrawal in our low-risk sample, which may lead to an under-detection of the complete for better *and* for worse differential susceptibility model. In a more heterogeneous sample including individuals subjected to more extreme levels of love-withdrawal, participants with higher scores on orienting sensitivity might perceive crying as most disturbing of all other groups. In the present study the absence or infrequent use of love withdrawal was an indicator of positive environmental influences. One might argue that the absence of love-withdrawal might not necessarily qualify as an indicator of sensitive and supportive parenting. Future studies might address this shortcoming by assessing a full range of parenting dimensions, including highly positive experiences such as unconditional love (Bradley *et al*, 2008). Other parenting

dimensions such as acceptance by parents and experiences of harsh parenting might also have an effect on the perception of infant crying (Leerkes *et al*, 2006). Future research might demonstrate these effects.

Positive or negative affect might also influence the difference in perception of crying (Forgas, 1995). In our study however, the perception of the infant cry sounds was not mediated by participants' transient mood, as participants' mood in response to infant crying did not differ systematically between high and low love-withdrawal groups with high or low orienting sensitivity. Moreover, given the stability of temperamental characteristics (Kagan and Snidman, 1991), our results suggest an early life interaction between orienting sensitivity and love-withdrawal, leading to the development of individual differences in processing of and reactions to infant stimuli.

Previous research with recorded and manipulated cry sounds shows an increase in negative affect after listening to cry sounds (Bruning *et al*, 2009). However, in these studies the participants could do nothing to stop the crying, which may induce negative affect related to feelings of helplessness rather than due to cry sounds *per se*. This idea is supported by a recent finding, showing that testosterone levels increased in adult males listening to recorded cry sounds, but decreased when the crying infant simulator could be soothed by parenting activities (Van Anders *et al*, 2012).

The participants in the current study were females with ages ranging between 18 and 30 years. This group of participants was chosen so as to increase homogeneity and to avoid any confounding effects of gender and caregiving experiences. Also, most of the earlier research assessed the effect of maternal love-withdrawal on their daughters (Assor *et al*, 2004; Elliot *et al*, 2004). Future research with more diverse groups might test for effects of gender and caregiving experiences and include paternal love-withdrawal as a predictor. Moreover, future research might extend our findings by using a sample including parents and cry stimuli from their own versus unknown infants. Previous research has shown that parents differ from non-parents in response to infant stimuli (Seifritz *et al*, 2003) and own versus unknown infant stimuli might trigger different responses (Strathearn *et al*, 2008).

In sum, this is the first study showing that temperamental orienting sensory sensitivity moderates the association between individuals' early caregiving experiences and their response to infant crying, using an interactive infant simulator paradigm. Our results show the potential of using an infant simulator to assess parenting styles that may

closely reflect real life. We found that temperamentally sensitive individuals were least negative to infant crying when they had experienced supportive parenting in their family of origin. These results suggest the potential of individuals with a highly sensitive temperament to benefit more from positive caregiving experiences than temperamentally less sensitive individuals, in line with the differential susceptibility hypothesis. Moreover, these results indicate that the long-term impact of early life experiences may be moderated by temperamental characteristics, with implications for individual differences in perceptual responses to infant stimuli in adulthood.

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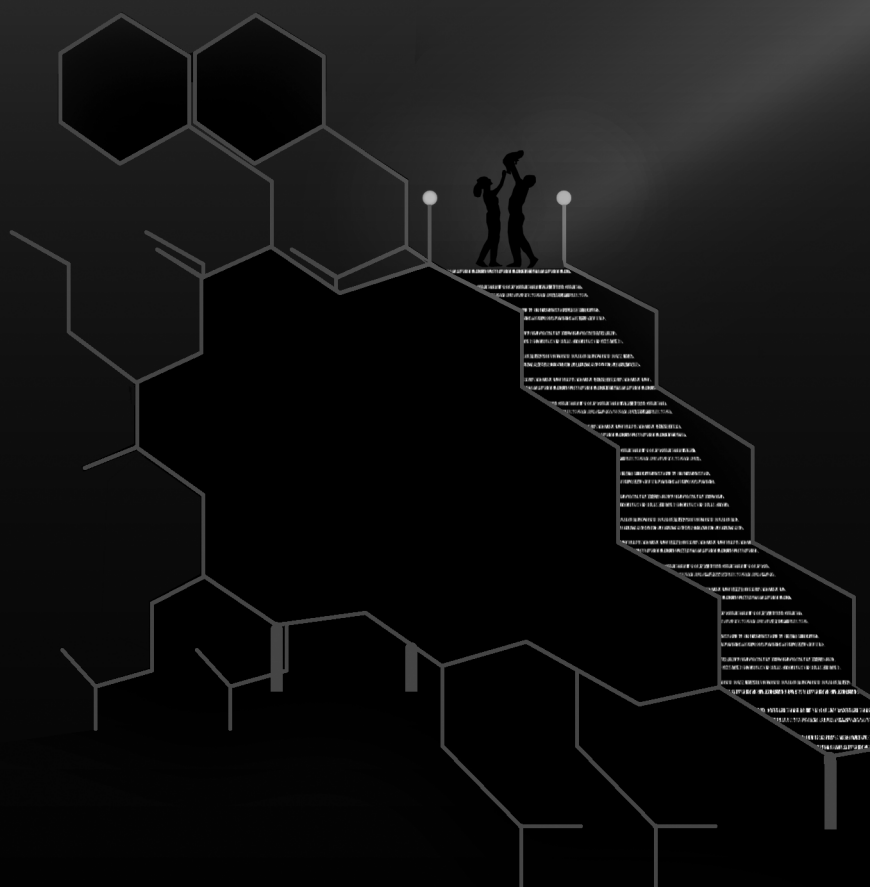
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# 6

# General Discussion



In the studies presented in this thesis we showed that childhood experiences of emotional maltreatment affect the processing of emotional and temperamental infant cues. Moreover, we found evidence for the involvement of the oxytonergic system in the association between early life emotional adversities and behavioral responses to infant stimuli. As described in Chapter 2, we found that emotional maltreatment (via endogenous oxytocin levels) was related to perceived positivity in happy infant faces. More emotional maltreatment experiences were associated with higher salivary oxytocin levels, which in turn were related to a more positive perception of the mood of happy infant faces. Furthermore, we found an association between experienced love withdrawal and perception of negativity in infant crying (Chapter 5). Fewer experiences of love withdrawal were associated with a less negative perception of infant crying, but this effect was most pronounced in individuals with high scores on temperamental orienting sensitivity. In Chapter 3 we presented a validation of the Baby Social Reward Task and we showed that experimentally manipulated infant mood information affected the perceived cuteness and the motivation to view these same infant faces with neutral expressions. Happy infants were rated as more cute, and participants expended more effort to view these infants after receiving the mood information, whereas they expended less effort to view sad infants. In Chapter 4 we reported our findings showing that intranasal oxytocin administration decreased the memory for infant mood information, making the happy and sad infants to be perceived more similar, however, this effect was present only for the group with more experiences of emotional maltreatment.

***Childhood experiences and the oxytonergic system***

Both early life stressful experiences and the oxytonergic system shape some common neural sites. For example, both of these have been shown to affect structural and functional properties of various brain regions such as amygdala (Inoue *et al*, 2010; Riem *et al*, 2011; Van Harmelen *et al*, 2012). In Chapter 5 we reported that participants with experiences of maternal disciplining strategy of love withdrawal rated infant crying as more negative. These results are in line with previous studies showing that experiencing childhood emotional maltreatment is associated with altered neural development, such as reduced prefrontal cortex volumes and enhanced amygdala and neural activation while viewing emotional faces (Huffmeijer *et al*, 2011; Van Harmelen *et al*, 2012; Van Harmelen *et al*, 2010b) as compared to typically developing individuals, which might possibly explain the behavioral differences seen in our studies. With regard to the contribution of oxytocin, in Chapter 2 we reported that higher oxytocin levels were associated with a more positive evaluation of the mood of a happy infant. These findings

corroborate studies showing that oxytocin is released in brain sites responsible for emotion processing, such as the nucleus accumbens, the amygdala, the septum and the bed nucleus of the stria terminalis, which all have high densities of oxytocin receptors (Gimpl and Fahrenholz, 2001). Moreover, these effects of oxytocin on emotion processing are thought to be brought about by decreased amygdala activation while viewing or listening to emotional stimuli such as facial cues or infant crying (Baumgartner *et al*, 2008; Kirsch *et al*, 2005; Riem *et al*, 2011). While experience of maltreatment has been associated with increased amygdala activity in response to emotional information, in individuals with higher oxytocin levels oxytocin might exert its anxiolytic effects and thereby decrease the over-arousal by dampening amygdala activity especially in maltreated individuals.

Next to these common sites of action, adverse childhood experiences have also been shown to directly influence the oxytonergic system. In Chapter 2 we report that early experiences of emotional maltreatment are associated with salivary oxytocin levels, similar to findings reported in previous studies (Heim *et al*, 2008; Pierrehumbert *et al*, 2010). However, the findings of various studies diverge, with some showing a negative relation between adverse experiences and activity of oxytonergic system (Heim *et al*, 2008) and others showing a positive relation (Pierrehumbert *et al*, 2010). We found higher salivary oxytocin levels associated with more self-reported maltreatment, which is in line with a recent study showing increased urinary oxytocin levels in young females with experiences of physical abuse (Seltzer *et al*, 2013). The implications of these observations have still to be elucidated. The effects of maltreatment and stressful life events are complex, affecting various neuro-hormonal systems, and they appear to be moderated by factors such as age and gender (Joels and Baram, 2009). Even within the oxytonergic system, the relation between exposure to stress and oxytocin levels is not yet well understood. Of the two most dominant theories about the interaction between oxytocin and stressful experiences, one theory suggests suppressive effects of oxytocin on the hypothalamic-pituitary-adrenal axis, with suppressed stress reactivity as a result, while the other suggests a greater release of oxytocin as part of stress reactivity (Pierrehumbert *et al*, 2010).

Early maltreatment may not only affect the secreted levels of the hormone, but might also bring about its effects by altering oxytocin receptor density (Francis *et al*, 2000), oxytocin receptor binding (Liberzon and Young, 1997) and/or epigenetic changes (Kumsta *et al*, 2013), a complexity which might be difficult to capture in studies with human subjects. In Chapter 2 we assessed the role of a single nucleotide polymorphism on the oxytocin receptor gene (*rs53576*) in moderating the relation between childhood emotional maltreatment and endogenous salivary oxytocin levels. We did not find a

significant moderating effect of the polymorphism, a finding consistent with a recent meta-analysis (Bakermans-Kranenburg and Van IJzendoorn, 2013). Although this polymorphism has been shown to moderate the effects of intranasal oxytocin administration on social preferences towards infants (Marsh *et al*, 2012) and has been associated with parenting and trust behaviors (Bakermans-Kranenburg and Van IJzendoorn, 2008; Rodrigues *et al*, 2009), the polymorphism is present in an intron of the oxytocin receptor gene and the functional significance of the polymorphism has yet to be demonstrated (Bakermans-Kranenburg *et al*, 2013). Well-designed studies with larger sample sizes and clearly defined ethnic groups are needed to study the effects of oxytocin receptor polymorphisms, as well as experimental work on the functional properties of oxytocin receptor polymorphisms in animals and humans.

The associations between emotional maltreatment and emotion processing, between oxytocin and emotion processing, and between emotional maltreatment and oxytocin have been replicated repeatedly (Marsh *et al*, 2010; Pollak *et al*, 2000; Seltzer *et al*, 2013). However, very few studies (mainly from our research group) have examined the combination of maltreatment and oxytocin in affecting neuro-behavioral outcomes (Huffmeijer *et al*, 2012; Riem *et al*, 2013; Riem *et al*, in press; Van IJzendoorn *et al*, 2011). For instance, individuals who experienced lower levels of love withdrawal by their mothers made more charitable donations when they receive oxytocin, whereas oxytocin administration does not affect donating behavior of their less fortunate peers who experienced high levels of love-withdrawal (Van IJzendoorn *et al*, 2011). While love withdrawal is an important component of emotional abuse and has an impact on the perception of infant cues (Chapter 5), we also studied the broader maltreatment construct with components of emotional abuse and neglect imparted by family members including parents and siblings (Chapter 2 and 4). In these studies we show that the experience of emotional maltreatment affects the development of the oxytonergic system, resulting in individual differences in the perception of infant temperament (Chapter 2). Moreover, the responsiveness of the oxytonergic system to externally administered oxytocin is affected by these negative experiences, resulting in impaired memory for infant temperamental cues only in maltreated individuals (Chapter 4).

***Efficacy and reliability of oxytocin manipulation and assessment measures***

We used intranasal administration to experimentally increase oxytocin levels and observed its effect on memory of infant temperament cues. We also measured endogenous salivary level to assess the association of oxytocin with mood recognition.

While these are currently the best available methods to experimentally increase oxytocin levels and collection of saliva constitutes a noninvasive method to measure physiological levels of oxytocin, there is some debate about the efficacy and reliability of these methods. In humans there is no experimental evidence yet showing that oxytocin can indeed cross the blood brain barrier after intranasal administration, or can reach relevant brain areas through other ways or means. It has been suggested however, that neuropeptides of similar size and structure as oxytocin (e.g., vasopressin) are indeed taken up in cerebrospinal fluid when administered intra-nasally and result in neurobiological and behavioral changes (Born *et al*, 2002). In a recent study we showed that salivary levels of oxytocin remained elevated for at least seven hours after the nasal spray administration (Van IJzendoorn *et al*, 2012). The study used different doses (16 and 24 IU) of oxytocin; these doses did not make a significant difference in salivary oxytocin levels (Van IJzendoorn *et al*, 2012), possibly due to the *saturation* by such high doses (Figure 1). Indeed, other studies using 16, 24 or even 40 IU have shown comparable effects in brain activity (Kirsch *et al*, 2005; Riem *et al*, 2011). One disadvantage of the nasal spray method is the inability to control the dosing amount. Absorption through the mucosal surface might be different among participants due to the specific anatomy of the nose, the structure of the nasal cavity and the environment in the nasal cavity, creating additional individual differences in the bioavailability of oxytocin in the brain (for a review see Guastella *et al*, 2013). More controlled administrations, taking into account any morphological differences might further improve the reliability of the effects on intranasal oxytocin administration in humans (Guastella *et al*, 2013).

Evidence that oxytocin can indeed reach the brain after intranasal administration (or alternatively, trigger a feed-forward reaction causing endogenous release of oxytocin) comes from a recent study conducted in rodents showing an increase in oxytocin levels in brain regions such as the amygdala and the hippocampus. Moreover, an increase in plasma levels of oxytocin after intranasal administration was short lived compared to brain levels (Neumann *et al*, 2013). However, direct experimental evidence showing that this phenomenon also translates to humans still awaits to be presented. Pieces of evidence so far suggest that, similar to animal studies, increased plasma levels of oxytocin after intranasal administration are short lived in humans as well, possibly also providing an indirect evidence for a disconnect between central and peripheral hormone levels (Gossen *et al*, 2012). The route taken by synthetic oxytocin from the nasal cavity to the brain is not known. Of several possible routes that an intranasally administered drug might take, a recent review suggest five most likely routes. These include, absorption and uptake by

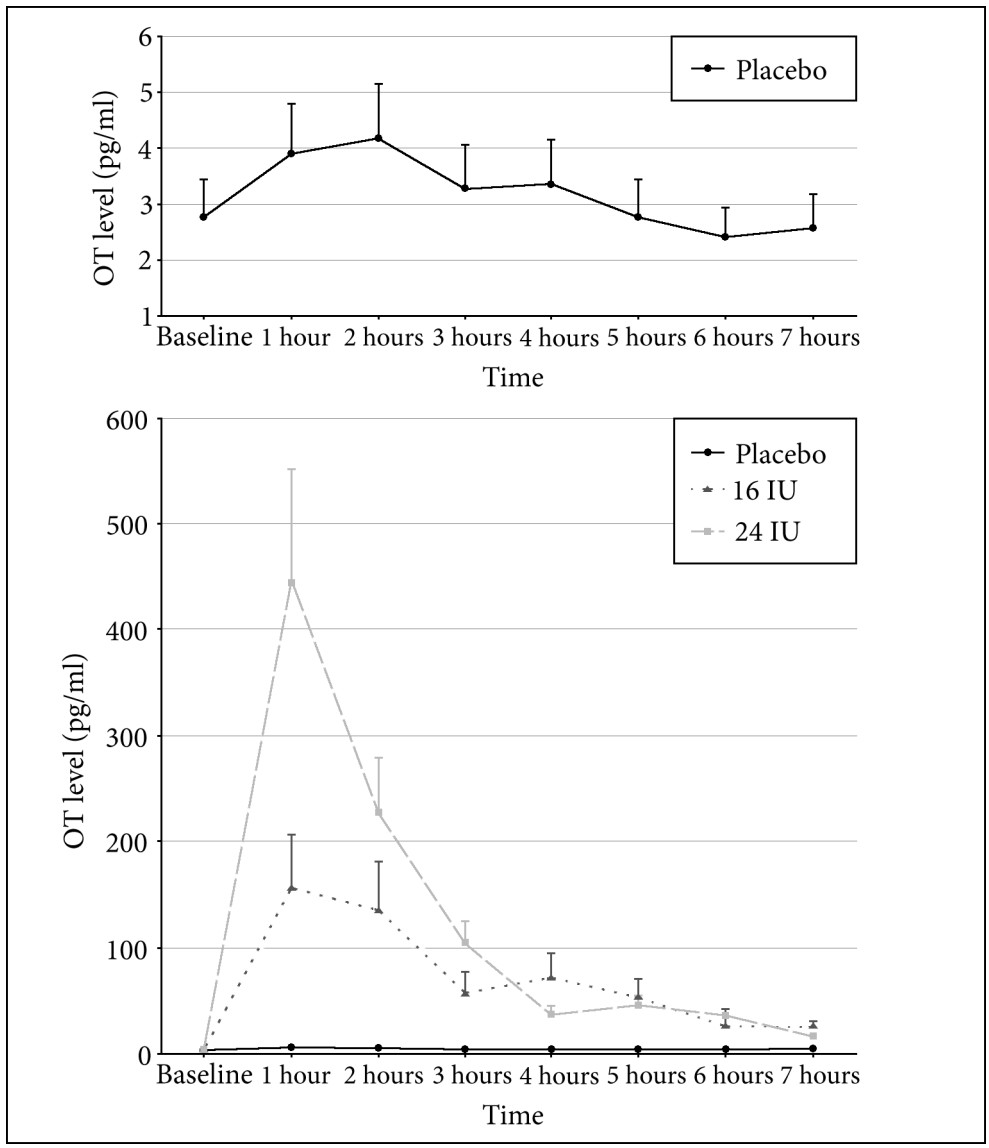



***Figure 1. Salivary oxytocin levels over the day in placebo (A) and after administration of 16 IU or 24 IU oxytocin (B).*** *Administration of oxytocin or placebo through nasal spray directly after the baseline assessment; subsequent assessments every hour after administration of oxytocin or placebo (Van IJzendoorn et al, 2012).*

a) nasal vasculature into the systemic circulation, b) oral mucosa and gastroenterally, c) olfactory bulb pathways, d) trigeminal nerve pathways and e) the paravascular spaces that connect into the interstitial spaces of the brain parenchyma (for a detailed account on the topic see Guastella *et al*, 2013). Unfortunately, there has been no human research regarding the amount of oxytocin that actually reaches the brain, its half-life in the cerebrospinal fluid, and the brain area specific activity as might be assessed by receptor concentration and ligand - receptor binding. Salivary oxytocin levels are suggested to be coordinated with the central nervous system levels of oxytocin (Weisman *et al*, 2012). The study by Van IJzendoorn *et al* (2012) shows increased oxytocin levels in saliva after nasal spray with a gradual decrease until seven hours. Moreover, the stability of oxytocin levels in saliva without any drug administration supports the reliability of the measure. However, whether these measures actually correlate with cerebrospinal levels or not, and the degree of correlation between these two, cannot be implied with certainty. The invasive nature of the confirmatory tests has prevented this very basic but important knowledge required for the correct understanding and interpretation of the findings. At present, intranasal administration and salivary oxytocin levels are the best available, non-invasive tools in oxytocin research, the results should however be interpreted with caution.

***Evolutionary significance of altered oxytonergic system with maltreatment experiences***

Abusive and neglectful experiences have been related to interpersonal difficulties and problems in creating stable and secure attachments, both romantic and to one's offspring (Cyr *et al*, 2010; Hornor, 2012). Our findings might suggest that alterations in the oxytonergic system due to maltreatment experiences might be adaptive for some individuals, possibly by preparing them for more positive interactions with potential new attachment partners (as also argued by Seltzer *et al*, 2013). This argument might be supported by a study showing an increase in oxytocin concentration following physical contact with biologically unrelated children but not with related children (Bick and Dozier, 2010). It has been argued that this might be explained by the role of oxytocin in initiation (but not continuation) of maternal behaviors as also shown in rodent studies (Bick *et al*, 2010; Insel, 1997). In a similar vein we found that oxytocin was related to the perception of positivity in infant faces (Chapter 2) and that intranasal oxytocin decreased the perception gap between positive and negative infant temperamental cues, possibly to increase approach behavior towards infants with more negative temperaments, especially in the *at risk* maltreated group (Chapter 4).

***Alternative mechanisms for modifying perception of infant cues***

Infants' perceived cuteness, due to its rewarding nature, has also been associated with more sensitive parenting by their mothers (Langlois *et al*, 1995). This bias is inherently unfair and it is thus important to see whether perceptions of infant cuteness can be changed for the better. In Chapter 3 we show that experimental modulation of infant mood to create a more positive perception of temperament resulted in increased cuteness ratings and more effort to view them. For negatively perceived temperament, the cuteness ratings were not affected, but participants expended less effort to view these infants. In the human brain, reward processing is distinguished as having two components: liking and wanting (Kringelbach and Berridge, 2012). While rating the infants as cuter is a part of the liking response, expending energy to view the infant represents the wanting part of reward (Parsons *et al*, 2011). Some studies are now identifying different brain areas involved in the liking and wanting part of reward processing (Berridge and Kringelbach, 2013). Our results suggest that infant temperament has clear consequences for how adults perceive infant cues, with effects on both the liking and wanting components. Perception of infant cuteness is not based on physical facial features alone, and is modifiable through experience with that very infant.

***Experimental tasks***

The advantages of experimental manipulation over real life observational studies have been noted in literature, such as more controlled environmental conditions and the possibility of identifying causality. However, in highly controlled settings, the ecological validity of the stimulus is sometimes lost, and the generalizability of the findings to real life may be difficult. For validity of the experimental study, the researcher has to maintain the controlled environment while still allowing real life similarities to find their way (e.g., in real life, a crying sound is always accompanied by the presence of an infant). In this regard, the following two manipulations used in our studies deserve being mentioned.

***Baby Social Reward Task (BSRT).*** The BSRT was used in Chapter 3 and 4 in order to manipulate the mood of infants to give the participants an idea of the temperament of the infant. Most of the experimental studies, both with adults and infants, use facial cues (Guastella *et al*, 2008; Marsh *et al*, 2010) or sounds (Out *et al*, 2010; Riem *et al*, 2011). While some studies have also used videos (Sitnikova *et al*, 2003), the controllability of these paradigms might be limited due to the complexity related to depth and movement. These attributes recruit various different brain areas (Jong *et al*, 1994)

and therefore might hamper the unequivocal interpretation of the data. Moreover, in brain imaging studies the results might be more complicated to interpret. In the BSRT, we coupled infant emotional facial cues with corresponding sounds in order to increase the ecological validity. We manipulated the mood of the infant, and by using more than one trial we aimed to create an infant with a specific temperament. Moreover, like in real life, the same infant showed both happy and sad moods. For example, an infant manipulated to be perceived as happy most of the time still cried in some trials. Similarly, an infant aimed to be perceived as difficult cried on most of the trials and showed happy mood in fewer trials. These manipulations were meant to make the task as more valid while still preserving a controlled environment as required for the experimental setting.

***Infant Simulator.*** Most of the research on responses to cry sounds is done by using recorded and manipulated cry sounds of real infants, without the presence of an infant (Joosen *et al*, 2013). Moreover, in many studies with recorded cry sounds, participants cannot act to the crying by providing appropriate care. In Chapter 5, we used the infant simulator which is a *doll* resembling a real infant. Confronted with the infant *doll's* crying, participants have to figure out the reason for the cry and provide care such as feeding, changing the diaper, or burping. The participants were then asked to rate the perceived negativity of the cry. This whole setup mimics a natural caregiving event and allows us to capture caregivers' perception of infant cues similar to real life situation. Moreover, the variations in the caregiver's perception due to the frequency and pitch of crying can be controlled experimentally, which presents as an advantage over studies with real infants.

***Limitations and future directions***

We note some limitations of the studies presented in this thesis. The participants of all studies were adult females without offspring, and they had no daily experiences of caring for an infant. Research suggests heightened neuronal plasticity due to various hormonal and neurochemical processes during pregnancy, resulting in drastic changes in the maternal brain (for a review see Kinsley and Amory-Meyer, 2011). Oxytocin is one of the hormones which plays a major role during parturition. Moreover, mothers differ from females without children of their own in their responses to infant cues (Zeskind, 1980). Taken together this suggests that replicating our work in mothers would be helpful in understanding the significance of these neuronal and behavioral alterations. In a similar vein, mothers' responses to own versus unknown infants might differ too (Strathearn *et al*, 2008). The differences in maternal perception towards own versus genetically

unrelated infants might be of interest. Moreover, research has also reported gender differences both in oxytonergic system functioning and responses to infant cues (Parsons *et al*, 2011; Weisman *et al*, 2013). For example, gender has been shown to moderate the relations between oxytocin levels and anxiety ratings. Males with higher oxytocin levels score lower on trait anxiety but no such associations were seen for females (Weisman *et al*, 2013). Specifically in parenting behaviors, mothers' oxytonergic system (genes and hormones) was shown to be associated with children's social reciprocity towards peers but fathers' oxytonergic system was not associated with children's reciprocity (Feldman *et al*, 2013). The study of gender differences in oxytonergic system responses to infant cues therefore might shed more light on the different roles played by fathers and mothers in infant upbringing.

In the present studies, we used self-report measures of experienced maltreatment and maternal discipline strategies. Self-report measures might suffer from specific disadvantages such as biases due to current mood and personality of the respondents. Other biases such as social desirability tendencies might also result in biased information about the actual experiences of maltreatment. However, the questionnaires used in the present studies are reliable and well validated (Bernstein *et al*, 2003; Huffmeijer *et al*, 2011) and have been used in various studies to measure experienced maltreatment (Van Harmelen *et al*, 2012; Van Harmelen *et al*, 2010b). Future studies might however use other methods such as extensive interviews or eye witness reports to increase the accuracy of the reported experiences.

The present sample consisted of university students, with an under-representation of extreme cases of emotional abuse. Future studies may include the full range of maltreatment to clearly understand alterations in various neural and behavioral systems with extreme versus less extreme cases of abuse and neglect. Emotional maltreatment has been reported to co-occur with other forms of maltreatment. For example, a recent maltreatment prevalence study conducted in the Netherlands showed that of all children reported to be maltreated, only 55% of the children experienced one type of maltreatment, 30% experienced two different types, 13% experienced three types, and 2% experienced four or more types of maltreatment (Euser *et al*, in press). Another Dutch study assessing structural differences in brain's grey and white matter volumes in relation to experiences of emotional maltreatment reported that of the individuals suffering from childhood emotional abuse and neglect, 31% also reported physical abuse, and 29% also reported sexual abuse. In addition, 38% of all individuals reporting sexual abuse also reported physical abuse (Van Harmelen *et al*, 2010a). In the current sample, we did not

differentiate between individuals with experiences of emotional maltreatment and those having additional experiences of physical or sexual abuse. Our results might thus represent a combined effect of different types and frequency of maltreatment, and not reflect the effects of only emotional maltreatment.

***Implications and Conclusions***

In sum, we found that the perception of infant cues differs between individuals with fewer versus more experiences of emotional maltreatment (Chapter 5). These adverse experiences seem to change the activity and responsiveness of the oxytonergic system, such that higher levels of oxytocin are secreted to allow for a more positive evaluation of happy infant mood (Chapter 2). Intranasal administration decreases the negative perception of sad infant expressions and decreases the memory for negative infant cues in individuals who experienced emotional maltreatment during their childhood years (Chapter 4). Our results might suggest that developmental changes in the oxytonergic system might help maltreated individuals to be open to new, potentially positive relationship experiences and to facilitate new attachments. Moreover, we suggest that reward training might be helpful in changing individuals' perception of an infant for the better and to support parents to spend more energy to stimulate their child's development (Chapter 3). Overall, our findings might serve as a first step toward identifying cognitive and neurobiological mechanisms that might help to improve (future) parenting.

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# *Nederlandse samenvatting*

Een kind opvoeden is niet gemakkelijk. Een ouder moet de signalen van een kind goed kunnen herkennen en daar op tijd en gepast op reageren om een kind, als het van streek is, weer gerust te stellen (Ainsworth *et al*, 1978). Maar mensen verschillen in hun perceptie van kindsignalen en in hun vermogen om daar goed op te reageren (Montoya *et al*, 2012). In dit proefschrift hebben we individuele verschillen in de perceptie van kindsignalen onderzocht, en gekeken of negatieve ervaringen in de kindertijd daarop van invloed zijn. Daarnaast hebben we onderzocht of de perceptie van kindsignalen kan veranderen door experimentele interventies, zoals computertraining of toediening van oxytocine.

Verschillen tussen ouders in hoe ze op kindsignalen reageren kunnen worden veroorzaakt door genetische kenmerken en door verschillen in levenservaringen. Zulke individuele verschillen hebben mogelijk een effect op hoe ouders signalen van een kind waarnemen (Crouch *et al*, 2008; Out *et al*, 2010). Zo zijn moeders positiever en sensitiever in de omgang met hun kinderen wanneer ze meer sociale steun ervaren (Crockenberg, 1988; Lee *et al*, 2009). In dit proefschrift hebben we het effect van ervaringen met emotionele mishandeling in de kindertijd op de perceptie van kindsignalen onderzocht. We hebben getoetst of ervaringen met emotionele verwaarlozing en *love withdrawal* als disciplineringsstrategie (het onthouden van liefde en aandacht als een kind niet doet wat de ouder wil) gerelateerd zijn aan de perceptie van kindsignalen zoals lachen en huilen.

Daarnaast is er nog veel onbekend over de onderliggende biologische mechanismen die verantwoordelijk zijn voor het effect van vroege ervaringen op de latere perceptie van kindsignalen. Om meer zicht te krijgen op één zo'n neurobiologisch mechanisme hebben we de betrokkenheid van het oxytocinesysteem bij de perceptie van kindsignalen onderzocht.

In Hoofdstuk 2 wordt de relatie onderzocht tussen ervaringen van emotionele mishandeling in de kindertijd en de perceptie van de stemming van baby's met blije of verdrietige gezichtsuitdrukkingen. In Hoofdstuk 5 doen we dat met behulp van een babypop die een verrassende gelijkenis heeft met een echte baby als het op huilen aankomt. We vonden dat emotionele mishandeling geassocieerd was met hogere oxytocine niveaus in speeksel, die op hun beurt weer leidden tot een positievere perceptie van de stem-

ming van blije kindergezichten (Hoofdstuk 2). Minder ervaring met love withdrawal was gerelateerd aan een minder negatieve perceptie van de huilende babypop, en dat effect was het sterkst voor participanten met hoge scores op de temperamentstrek 'gevoeligheid voor indrukken uit de omgeving' (Hoofdstuk 5). Deze resultaten laten zien dat vroege ervaringen met emotionele mishandeling effect hebben op het waarnemen en verwerken van emotionele kindsignalen. Daarnaast laat onze studie zien dat het oxytocinesysteem betrokken is bij de relatie tussen gebrek aan vroege emotionele steun en latere reacties op kinderen.

Omdat endogene oxytocineniveaus gerelateerd bleken aan de perceptie van kindergezichten en het toeschrijven van een gemoedstoestand aan een kind, hebben we vervolgens onderzocht of het geheugen voor kindsignalen kon worden beïnvloed door het oxytocineniveau experimenteel te verhogen (door oxytocine via een neusspray toe te dienen). Daartoe hebben we (in samenwerking met onderzoekers van Oxford University) een nieuwe leertaak ontwikkeld, de Baby Social Reward Taks (BSRT). We hebben de BSRT als instrument om de stemming van kinderen te manipuleren gevalideerd door te laten zien hoe vaker of minder vaak huilen de perceptie van een kind als makkelijk of moeilijk beïnvloedt (Hoofdstuk 3). Kinderen die minder vaak huilden en vaker lachten werden eerder 'schattig' en gemakkelijk gevonden en participanten waren bereid meer inspanning te doen om hun foto te zien, zelfs als ze op die foto een neutrale gezichtsuitdrukking hadden. Deze resultaten suggereren dat de perceptie van de stemming van een kind een effect heeft op de kenmerken die volwassenen aan een kind toeschrijven en op hoeveel moeite een volwassene bereid is te doen om het kind te zien. Belangrijk is ook dat de perceptie van schattigheid van een baby niet alleen gebaseerd blijkt op fysieke gezichtskenmerken, maar ook afhankelijk is van (huil-)ervaringen met die baby.

In Hoofdstuk 4 beschrijven we de resultaten van een studie waarin gebruik gemaakt is van de gevalideerde BSRT om te testen of het toedienen van oxytocine via een neusspray effect heeft op het geheugen voor het temperament van een kind. Ook hebben we getoetst of vroege ervaringen met emotionele mishandeling dit effect modereren. Het toedienen van oxytocine via de neus verminderde het geheugen voor informatie over het temperament van het kind (of het een kind was dat relatief veel of relatief weinig huilde). Maar dit effect vonden we alleen voor participanten die emotionele mishandeling hadden meegemaakt. Participanten die meer emotionele mishandeling hadden meegemaakt, waren na de oxytocine neusspray minder accuraat in het herkennen van kinderen die relatief veel of juist relatief weinig huilden. Eerder onderzoek liet zien dat toediening van oxytocine de afkeer van babyhuilen vermindert (Riem *et al*, 2011). Een consequentie kan

zijn dat het verschil tussen baby's die vaker en minder vaak huilen kleiner wordt, waardoor participanten ze als gelijker beschouwen. Aan de andere kant kan oxytocine het maken van welwillende beslissingen vergemakkelijken (De Dreu *et al*, 2012), en dat zou kunnen verklaren waarom baby's die vaker huilen toch een positieve connotatie krijgen.

De uitkomsten van onze studies zijn in lijn met eerdere onderzoeken die de relatie tussen emotionele mishandeling en emotieverwerking, tussen oxytocine en emotieverwerking, en tussen emotionele mishandeling en oxytocine hebben laten zien (Marsh *et al*, 2010; Pollak *et al*, 2000; Seltzer *et al*, 2013). Maar er zijn slechts weinig studies waarin het gecombineerde effect van mishandeling en oxytocine op gedrag en neurobiologische uitkomsten is onderzocht (de paar studies die er zijn, zijn met name in onze onderzoeksgroep uitgevoerd, zie bijvoorbeeld (Huffmeijer *et al*, 2012; Riem *et al*, 2013; Riem *et al*, in press; Van IJzendoorn *et al*, 2011). De studies beschreven in dit proefschrift laten zien dat het meemaken van emotionele mishandeling invloed heeft op de ontwikkeling van het oxytocinesysteem, en dat dat weer van invloed is op individuele verschillen in de perceptie van het temperament van een kind (Hoofdstuk 2). Daarnaast wordt het effect van het toedienen van oxytocine beïnvloed door deze negatieve ervaringen, waardoor alleen mensen die te maken hebben gehad met emotionele mishandeling na toediening van oxytocine een minder goed geheugen hebben voor het huilen van het kind. Onze resultaten geven ondersteuning aan het idee dat het oxytocinesysteem bij mishandelde personen de functie kan hebben om hen te helpen om open te staan voor nieuwe, mogelijk positieve relaties en om nieuwe gehechtheidsrelaties aan te gaan. Deze resultaten zijn een eerste stap om cognitieve en neurobiologische mechanismen te identificeren waardoor (toekomstig) opvoeden positief beïnvloed kan worden.

Tot slot leiden onze resultaten tot vele nieuwe vragen: (a) Gelden onze bevindingen ook voor moeders, vaders en personen die geen ouder zijn? (b) Is er een verschil in de ontwikkeling van het oxytocinesystem tussen mensen met ernstige (klinische) ervaringen van mishandeling en minder ernstige ervaringen? (c) Welke biologische mechanismen zijn verantwoordelijk voor de veranderingen in de ontwikkeling van het oxytocinesystem als gevolg van mishandeling en welke mechanismen zorgen vervolgens voor veranderingen in de reactie op signalen van het kind? Antwoorden op deze vragen kunnen ons helpen meer inzicht te krijgen in de neurobiologische veranderingen die gepaard gaan met vroege negatieve levenservaringen en in de gelijktijdig ontwikkelende mechanismen die daarvoor kunnen compenseren en zo de negatieve effecten bij het opvoeden van de volgende generatie kunnen relativeren.

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*Ritu Bhandari*

# *Curriculum Vitae*

*Ritu Bhandari was born on the 21st of June 1984 in Bhilwara, Rajasthan, India. In 2002, she completed Senior Secondary education from Mahila Ashram Secondary School, Bhilwara. She received her Bachelor's degree in Biology in 2005 and her Master's degree in Biotechnology in 2007. She conducted basic neuroscience research in various international research centers in India. These projects included 'Comparative Neuro-proteomics of adult rat hippocampus, in response to acute and chronic stress' at the Department of Biological Sciences, Tata Institute of Fundamental Research, Mumbai, India and 'Differential regulation of specific genes in response to Prion infection and its involvement in pathogenesis, in an in vitro model', conducted at National Brain Research Centre, Gurgaon, India. In the period between 2007 and 2008, she also worked as a lecturer, teaching Master's and Bachelor's students studying Biotechnology. In 2010 she moved to Amsterdam and participated in the project entitled 'Role of acetylcholine for cognition in visual and frontal cortex' at the Netherlands Institute for Neuroscience, University of Amsterdam, as a visiting fellow. In November 2010, she started her doctoral research in the Department of Child and Family Studies at Leiden University. Her doctoral research focused on the relation between experienced emotional maltreatment during childhood and the oxytonergic system and their effects on processing of emotional infant cues.*