Toward a neuroscience of parenting : adult attachment and oxytocin affect neural and behavioral responses to infant attachment signals

Hendricx - Riem, M.M.E.

5 Pity or Peanuts? Oxytocin affects neural response to sick and bored infant crying

Madelon M.E. Riem, Alexandra Voorthuis, Marian J. Bakermans-Kranenburg, & Marinus H. van IJzendoorn, manuscript submitted for publication.

Abstract

The neuropeptide oxytocin plays an important role in mother-infant bonding. However, recent studies indicate that the effects of oxytocin on prosociality are dependent on perceived social context. Using functional magnetic resonance imaging, we examined differential effects of intranasally administered oxytocin on neural responding to 500 and 700 Hz crying that was indicated as emanating from a sick infant and 500 and 700 Hz crying emanating from a bored infant. We found that oxytocin significantly increased insula and inferior frontal gyrus responding to sick infant crying, but decreased activation in these brain regions during exposure to crying of an infant that was labeled as bored. In addition, oxytocin decreased amygdala responding to 500 Hz crying, but increased amygdala responding to 700 Hz crying. These findings indicate that oxytocin enhances the salience of the context and of the acoustics of crying, thus facilitating the interpretation of the cry and the selection of an adequate caregiving response.

Introduction

Infant crying is evolutionary adaptive because it elicits parental proximity and care, and because it conveys information about the health condition of the child (Soltis, 2004). Specific neural circuits may have evolved in caregivers to facilitate perception and evaluation of infant crying (Seifritz et al., 2003). In a previous study, we found that the neuropeptide oxytocin sensitizes caregivers to variations in cry signals by modulating these neural circuits and enhancing sensitive responsiveness to crying (Riem et al., 2011). Other studies have shown that intranasally administered oxytocin stimulates a range of social behaviors, including trust, empathy, and emotion understanding (for a review see De Dreu, 2012). However, recent studies also indicate that the effects of oxytocin on prosociality are dependent on social context (De Dreu, 2012) and personal history (Van IJzendoorn, Huffmeijer, Alink, Bakermans-Kranenburg, & Tops, 2011), possibly because oxytocin increases salience of social information (Graustella & MacLeod, 2012). Using functional magnetic resonance imaging (fMRI), we examined differential effects of oxytocin on neural responding to infant crying with varying information on the context of crying.

Infant crying has been described as a graded signal that changes as a function of the level of distress of the infant (Gustafson, Wood, & Green, 2000). For example, infants who are in pain cry at higher fundamental frequencies than infants who are hungry (Soltis, 2004). In addition to the acoustics of the cry, a range of other factors may influence parental responses to infant crying, such as infant facial expressions, gestures, and contextual information. Indeed, maternal responses to crying have been shown to be delayed when the infant has just been fed, indicating that knowledge of the infant's recent caregiving history influences behavioral responses to crying (Bernal, 1972; Leger, Thompson, Merritt, & Benz, 1996). Caregiving context has also been shown to influence caregiving responses to crying in an experimental setting: Adults who had been told that an infant needed sleep waited longer to respond to infant crying than those without this information (Wood and Gustafson, 2001). Thus, parents are not only sensitive to acoustic variations in crying but also to contextual information, and both sources of information are used to select a caregiving response (Soltis, 2004).

An important role in sensitive parenting is attributed to the neuropeptide oxytocin. Feldman et al. (2007) showed that maternal oxytocin levels across pregnancy are predictive of higher quality of postpartum maternal behavior. Oxytocin has shown anxiolytic and stress-reducing effects in breastfeeding mothers (Heinrichs et al., 2001) and this might promote parents' sensitivity to infant crying. Indeed, in a previous study we found that intranasal oxytocin may facilitate sensitive responding to crying by decreasing activation of the amygdala (Riem et al., 2011), a brain region involved in the experience of anxiety and aversion (LeDoux, 2000). Oxytocin also enhanced activation in the insula and inferior frontal gyrus (IFG), brain regions important for empathy and emotion understanding (Lamm, Decety, & Singer, 2011).

However, oxytocin might not enhance social behavior similarly for everyone and under all circumstances. For example, we found that intranasal oxytocin

decreased the use of excessive handgrip force in response to infant crying, but only in individuals with supportive family backgrounds, indicating that prosocial effects of oxytocin were moderated by harsh caregiving experiences (Bakermans-Kranenburg, Van IJzendoorn, Riem, Tops, & Alink, 2012). Other studies indicate that the social context may be crucial in shaping the effects of oxytocin on social cognition (Bartz, Zaki, Bolger, & Ochsner, 2011). For example, the trust-enhancing effects of oxytocin disappear when partners are unknown (Declerck, Boone, & Kiyonari, 2010). Some studies even point to negative effects of oxytocin on prosocial behavior. De Dreu et al. (2010) found that oxytocin enhanced in-group trust but also promoted defensive aggression toward individuals perceived as out-group members. Thus oxytocin might drive a "tend and defend" response (Carter, 1998), especially when out-group threat is high (De Dreu, Greer, Handgraaf, Shalvi, & Van Kleef, 2012).

One mechanism that might underlie these contextual and personal history influences on oxytocin effects is increased salience of social information (Graustella & MacLeod, 2012). Several studies indicate that oxytocin improves processing of social information and increases attention towards social cues (e.g., Rimmele, Hediger, Heinrichs, & Klaver, 2009). Increased salience of social information might explain the differential effects of oxytocin on behavior in different social contexts. Social context has a stronger influence on behavior when one is more aware of the contextual social cues. More specifically related to infant crying, oxytocin might increase the salience of the context of crying, thereby affecting the perception of and responding to the infant cry. Increased attention towards the context of the cry would be highly adaptive, as it facilitates the interpretation of the infant's crying and helps in selecting an adequate caregiving response. Thus, oxytocin may promote mother-infant bonding by increasing vigilance to contextual cues, which in turn leads to caregiving responses that are fine-tuned to the context of infant crying.

To our knowledge, this is the first study to investigate the influence of intranasally administered oxytocin on the perception of infant crying in systematically varied contexts. We examine differential effects of oxytocin on neural responding to crying that was indicated as coming from a sick infant and crying coming from a bored infant. We focus on neural responses to infant crying at different frequencies, because infant cries range from 500 Hz in normal, healthy infants to 700 Hz and even higher in infants in pain or with medical conditions. We were specifically interested in amygdala, insula and IFG responses to crying, since these regions were affected by intranasal oxytocin during exposure to crying in a previous sample (Riem et al., 2011). We expected to find enhanced neural responding to crying of a sick infant compared to crying of a bored infant, as crying related to sickness may be more alarming to parents, and more important from an evolutionary perspective (Soltis, 2004). Since oxytocin has been shown to enhance attention towards social information, we predicted that intranasal oxytocin would lead to increased processing of the contextual cues, leading to more pronounced differences in neural responding to sick infant crying compared to bored infant crying.

Method

Participants
A total of 343 female undergraduate students from the departments of education and child studies, and psychology at Leiden University participated in the first phase of the study. In this phase, the participants completed online questionnaires on their perception of parenting by their mothers, and some demographic details. One participant was excluded due to random responses. Five females with children of their own were also excluded. One hundred eighty six students participated in the second phase of the study, which was designed to examine behavioral and cardiac responses to infant crying. Fifty-four participants with scores ranging from low to high on a parenting questionnaire were selected to participate in the third phase of the study, consisting of a computer game designed to study prosocial helping behavior towards an excluded adult and for the current fMRI study. Participants were screened for MRI contraindications, psychiatric or neurological disorders, hearing problems, pregnancy, and alcohol and drug abuse. Four participants were excluded from the fMRI study because of hearing problems, resulting in a total sample size of 50 participants for the current study. They were randomly assigned to the oxytocin or the placebo condition. (n = 26 oxytocin, n = 24 placebo). The mean age of the participants was 19.66 years (SD =1.47, range 18-27). The majority (70 %) of the participants used oral contraceptives. Permission for this study was obtained from the Ethics Committees of the Institute of Education and Child Studies of Leiden University and of the Leiden University Medical Centre.

Procedure
Participants were invited for the fMRI study preferably in the luteal phase of their menstrual cycle in order to control for influences of menstrual cycle. For two participants it was not possible to determine menstrual phase, because of use of Mirena intrauterine device.

Approximately 35 minutes before the start of fMRI data acquisition participants took 6 puffs of nasal spray containing oxytocin (16 IU total) or 6 puffs of a placebo spray under supervision of the experimenter. Effects of 16 IU of oxytocin on social behavior and neural activity have been reported in previous studies (Riem et al., 2011; Van IJzendoorn, Bhandari, Van der Veen, Grewen, & Bakermans-Kranenburg, in press). Drug administration was double-blind. After nasal spray administration, the participants were familiarized with the task during practice trials outside the MRI scanner. Before drug administration and after fMRI scanning participants completed a mood questionnaire in order to track mood changes (see Supplementary Material).

Cry paradigm
Participants listened to cry and control sounds at 500 and 700 Hz (see Supplementary Material). Effects of oxytocin on neural responding to these crying sounds (and crying at 900 Hz) were found in a previous study (Riem et al., 2011). A bright green star was presented for 1 s in order to attract participants' attention

to the center of the screen (see Figure 1). Information about the context of the sound that would follow was presented on the computer screen for maximum 2 s. Context information consisted of information about the reason why the infant was crying: sickness ("This infant is sick") or boredom ("This infant is bored"). Context information was also presented for the control sounds at 500 and 700 Hz and consisted of neutral information about the sound: "This is a saw". In order to ensure that participants were attentive to the context information, they were instructed to press different buttons on a MRI compatible button box during the presentation of the three context conditions (sick, bored, saw). The task was self-paced. That is, the context information was followed by a cry or control sound when one of the buttons had been pressed. The crying sounds at 500 Hz and 700 Hz were presented in the sick as well as the bored crying condition. Cry and control sounds were presented in eight cycles, each cycle consisting of 6 trials. The order of presentation of conditions and sounds within each cycle was random; the intertrial interval was 4.5 to 7.5 s (M = 6 s, randomly jittered). A fixation cross was presented on the screen during intertrial intervals and sound presentation.

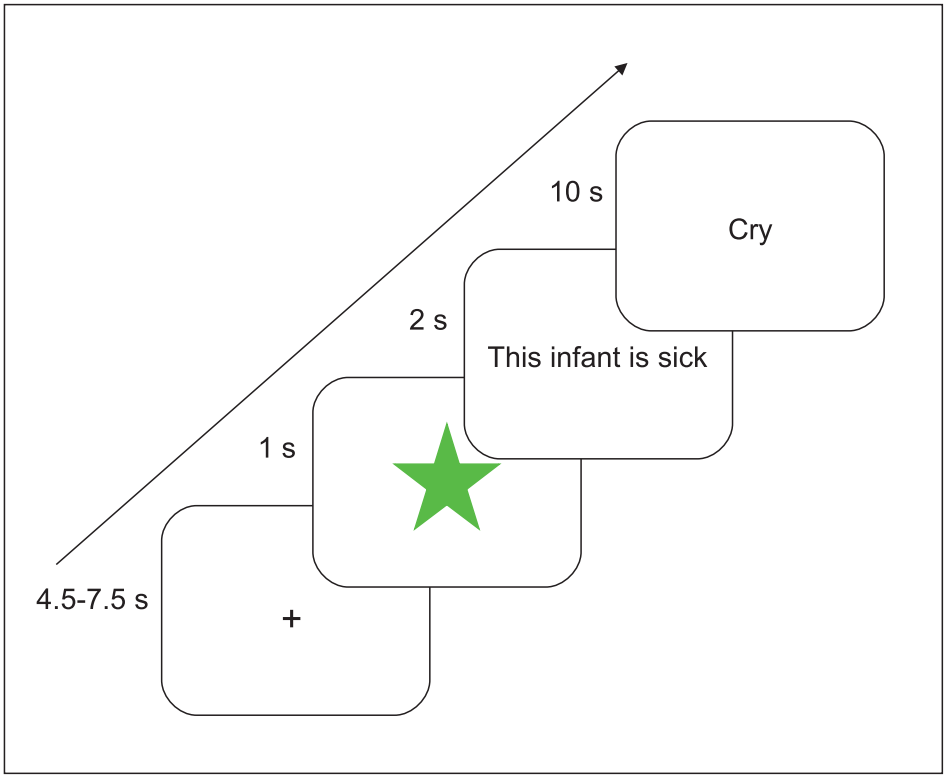

Figure 1. The cry paradigm. Participants' attention was attracted to the center of the screen by presenting a green star, followed by the context information. Context information ("This infant is sick", "This infant is bored", "This is a saw") was presented for maximum 2 s and was followed by the cry or control sounds after a button had been pressed. A fixation cross was presented on the screen during intertrial intervals and sound presentation.

fMRI data acquisition

Scanning was performed with a standard whole-head coil on a 3-T Philips Achieva TX MRI system (Philips Medical Systems, Best, the Netherlands) in the Leiden University Medical Center. First, a T1-weighted anatomical scan was acquired (flip angle = 8°, 140 slices, voxel size .875 x .875 x 1.2 mm). For fMRI, a total of 422 T2*-weighted whole-brain echoplanar images were acquired (repetition time = 2.2 s; echo time = 30 ms, flip angle = 80°, 38 transverse slices, voxel size 2.75 x 2.75 x 2.75mm (+ 10% interslice gap)). Participants listened to the sounds through MRI-compatible headphones.

fMRI data analysis

Data analysis was carried out using FEAT (FMRI Expert Analysis Tool) version 5.98, part of FSL (Smith et al., 2004). The following pre-statistics processing was applied: motion correction (Jenkinson, Bannister, Brady, & Smith, 2002), non-brain removal (Smith, 2002), spatial smoothing using a Gaussian kernel of full-width-at-half-maximum 5.0 mm, and high-pass temporal filtering (highpass filter cutoff = 90.0s). Functional scans were registered to the high-resolution EPI-images, which were registered to the T1-weighted images, which were registered to standard space (Jenkinson et al., 2002).

In native space, functional activation was examined using general linear model analysis. Each sound condition (sick infant crying 500 Hz, sick infant crying 700 Hz, bored infant crying 500 Hz, bored infant crying 700 Hz, control sound 500 Hz, control sound 700 Hz) was modeled separately as a square-wave function. The star and the context information were also modeled as square-wave functions. Each predictor was then convolved with a double gamma hemodynamic response function and its temporal derivative was added to the model, giving 16 regressors. To examine regions involved in the perception of infant crying in context we assessed six contrasts: 1) sick infant crying 500Hz > control sound 500Hz, 2) sick infant crying 700Hz > control sound 700Hz, 3) bored infant crying 500Hz > control sound 500Hz, and 4) bored infant crying 700Hz > control sound 700Hz, 5) sick infant crying 500Hz > bored infant crying 500Hz, 6) sick infant crying 700Hz > bored infant crying 700Hz.

All first-level contrast images and the corresponding variance images were transformed to standard space and submitted to second-level mixed-effects group whole brain analyses. Group means were tested using one-sample t-tests and we tested for group differences using two-sample t-tests on these contrasts with the oxytocin versus placebo group comparison (Oxytocin > Placebo and Oxytocin < Placebo). We included menstrual cycle (follicular or luteal phase) and use of oral contraceptives as confound regressors in the model in the analyses of the group means and group differences. The statistical images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < .05$.

Mean *Z*-values for *a priori* specified regions of interest were calculated for the first four contrasts using Featquery. These regions were the left insula, left inferior frontal gyrus pars opercularis and the right amygdala (Bos, Panksepp, Bluthé, & Honk, 2012; Riem et al., 2011), anatomically defined using the Harvard–

Oxford (sub)cortical atlas (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#ho). In order to investigate interactions between treatment and conditions, repeated measures analyses of variance were conducted with mean *Z*-values of the insula, inferior frontal gyrus and amygdala as dependent variables, context (sick versus control sound, bored versus control sound) and frequency (500 Hz, 700 Hz) as within-subject factors, and treatment (oxytocin, placebo) as between-subject factor. Use of oral contraceptives and menstrual cycle were included as between-subject factors in the analyses in order to control for influences of these variables. The mode of menstrual cycle (luteal phase) was assigned to the two participants with unknown menstrual cycle phase.

Results

In a series of repeated measures analyses of variance we tested treatment (oxytocin versus placebo) and context effects (bored versus sick) on a priori selected brain areas: the insula, inferior frontal gyrus, and amygdala. For the results of the whole brain analysis see Supplementary Material (Figure s1).

Insula. The repeated measures analysis of variance with insula activation as dependent variable showed a significant main effect of context ($F(1,42) = 10.32$, $p < .01$, partial $\eta^2 = .20$). There was increased activation in the insula during exposure to crying of a sick infant (versus control sound), but decreased activation during exposure to crying of a bored infant (versus control sound), see Figure 2. This main effect was qualified by a significant interaction between treatment and context ($F(1,42) = 7.06$, $p = .01$, partial $\eta^2 = .14$). The effect of context was significant in the oxytocin group ($F(1,22) = 19.75$, $p < .001$, partial $\eta^2 = .47$), increasing insula activation during exposure to crying of a sick infant, and decreasing activation during exposure to crying of a bored infant (see Figure 3), whereas in the placebo group there was no significant difference between the sick and bored condition ($F(1,20) = 0.14$, $p = .72$, partial $\eta^2 = .01$). There were no significant main effects of treatment ($F(1,42) = 0.43$, $p = .52$) and frequency ($F(1,42) = 0.18$, $p = .68$). Neither were there significant interactions between treatment and frequency ($F(1,42) = 1.04$, $p = .31$), frequency and context ($F(1,42) = 2.95$, $p = .09$) or between treatment, frequency, and context ($F(1,42) = 1.65$, $p = .21$).

Inferior frontal gyrus. The repeated measures analysis of variance with IFG activation as dependent variable revealed a significant effect of context ($F(1,42) = 9.53$, $p < .01$, partial $\eta^2 = .19$). The IFG was significantly more activated during exposure to crying of a sick infant (versus control sound) compared with crying of a bored infant (versus control sound), but this main effect was qualified by a significant interaction between treatment and context ($F(1,42) = 7.09$, $p = .01$, partial $\eta^2 = .14$). The effect of context was highly significant in the oxytocin group ($F(1,22) = 24.24$, $p < .001$, partial $\eta^2 = .52$), but there was no significant difference between the sick and bored condition in the placebo group ($F(1,20) = 0.07$, $p = .80$, partial $\eta^2 = .00$). Again, oxytocin increased activation in the IFG during exposure to crying of a sick infant, but decreased activation during exposure to crying

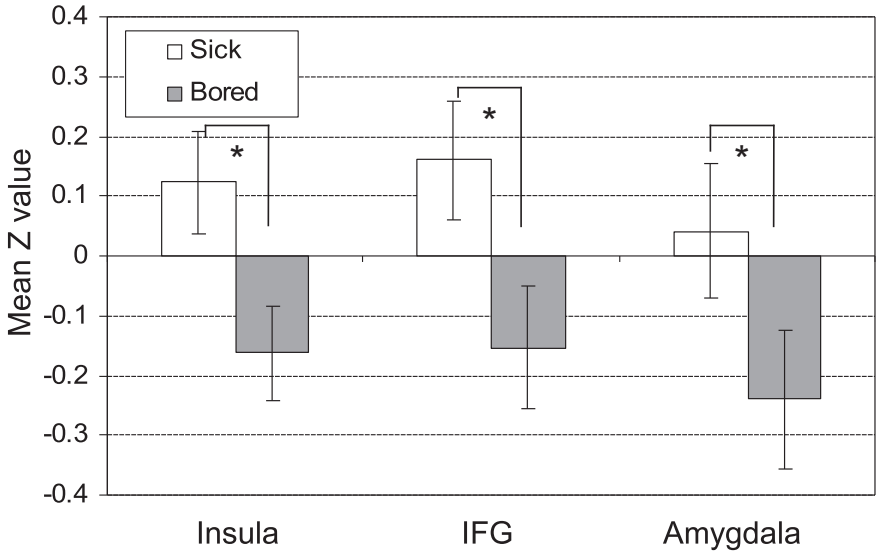

Figure 2. Z-values (*M, SE*) of left insula, left inferior frontal gyrus (IFG), and right amygdala activation during crying of a sick infant (versus control sound, 500 and 700 Hz) and crying of a bored infant (versus control sounds, 500 and 700 Hz). $n = 50$, $^*p < .01$

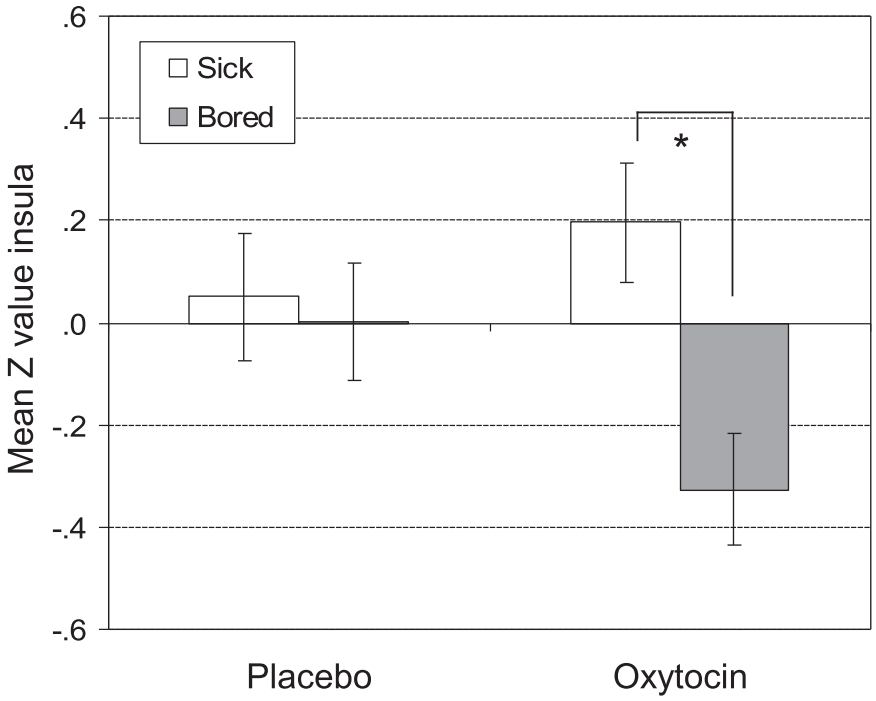

Figure 3. Z-values (*M, SE*) of left insula activation during crying of a sick infant compared with control sounds (500 and 700 Hz) and crying of a bored infant compared with control sounds (500 and 700 Hz) for individuals in the oxytocin and placebo condition. $^*p < .001$

of a bored infant, with similar effects absent in the placebo group, see Figure 4. There were no significant main effects of treatment ($F(1,42) = 0.01$, $p = .94$) and frequency ($F(1,42) = 0.09$, $p = .76$) and no interaction between treatment and frequency ($F(1,42) = 0.78$, $p = .38$), frequency and context ($F(1,42) = 1.00$, $p = .32$), or between treatment, context, and frequency ($F(1,42) = 0.23$, $p = .64$).

Amygdala. The repeated measures analysis of variance with amygdala activation as dependent variable showed a significant effect of context ($F(1,42) = 8.01$, $p < .01$, partial $\eta^2 = .16$). There was increased activation in the amygdala during exposure to crying of a sick infant (versus control sound), but decreased activation during exposure to crying of a bored infant (versus control sound), see Figure 2. Again, the effect of context was only significant in the oxytocin group ($F(1,22) = 6.70$, $p = .02$, partial $\eta^2 = .23$) and not significant in the placebo group ($F(1,20) = 1.81$, $p = .19$, partial $\eta^2 = .08$), but the interaction between treatment and context was not significant ($F(1,42) = 1.42$, $p = .24$). However, there was a significant interaction between treatment and frequency ($F(1,42) = 7.20$, $p = .01$, partial $\eta^2 = .15$). Oxytocin significantly decreased amygdala activation during exposure to 500 Hz crying, but increased amygdala activation during exposure to 700 Hz crying, with similar effects absent in the placebo group (see Figure 5). There were no significant main effects of frequency ($F(1,42) = 1.24$, $p = .27$) and treatment ($F(1,42) = 0.10$, $p = .76$). Neither were there significant interactions between frequency and context ($F(1,42) = 1.74$, $p = .20$) or treatment, context, and frequency ($F(1,42) = 1.31$, $p = .26$).

We examined the potential moderating influence of experiences with parental rejection but results were not significant (data available on request).

Discussion

In this study we examined the influence of oxytocin on neural responses to crying that was indicated as coming from a sick infant and crying coming from a bored infant. We found that intranasally administered oxytocin led to more pronounced differences in neural responding to sick infant crying compared with bored infant crying, indicating enhanced processing of the contextual information. Oxytocin significantly increased insula and IFG responding to crying of a sick infant, but decreased activation in these brain regions during exposure to crying of an infant that was labeled as bored. In addition, we found that oxytocin decreased amygdala responding to crying at 500 Hz, but increased amygdala responding to crying at 700 Hz. These findings indicate that oxytocin enhances the salience of the context and of the acoustics of crying, thus facilitating the interpretation of the infant's crying and the selection of an adequate caregiving response.

Infant crying has often been described as a paradoxical signal (Soltis, 2004). It enhances infant survival by eliciting care and by conveying information on the health condition of the child, but also evokes aversive and angry feelings in parents and can trigger child abuse and neglect (Barr, Trent, & Cross, 2006). The likelihood of using such harsh caregiving responses is increased when infants are sick, possibly because sick, high-pitched crying is perceived as more aversive (Soltis, 2004). Consistent with previous results (Riem et al., 2011), we found that

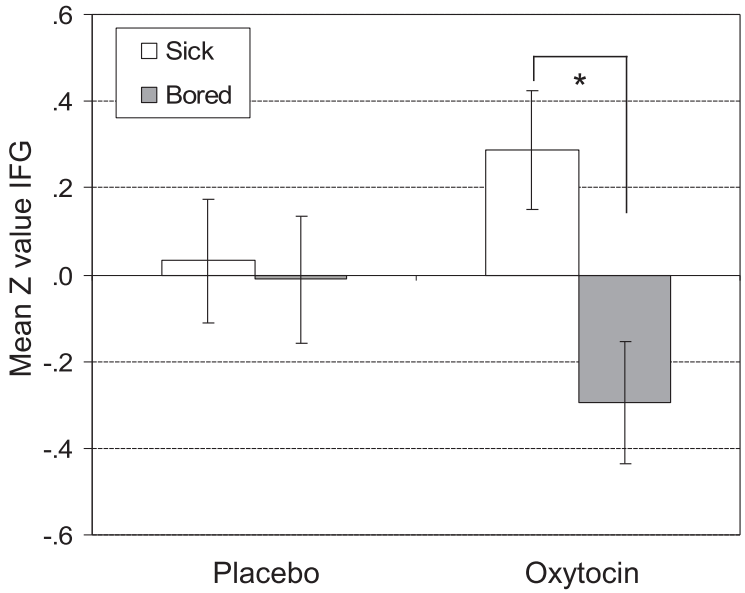

Figure 4. Z-values (*M, SE*) of left inferior frontal gyrus (IFG) activation during crying of a sick infant compared with control sounds (500 and 700 Hz) and crying of a bored infant compared with control sounds (500 and 700 Hz) for individuals in the oxytocin and placebo condition. *$p < .001$

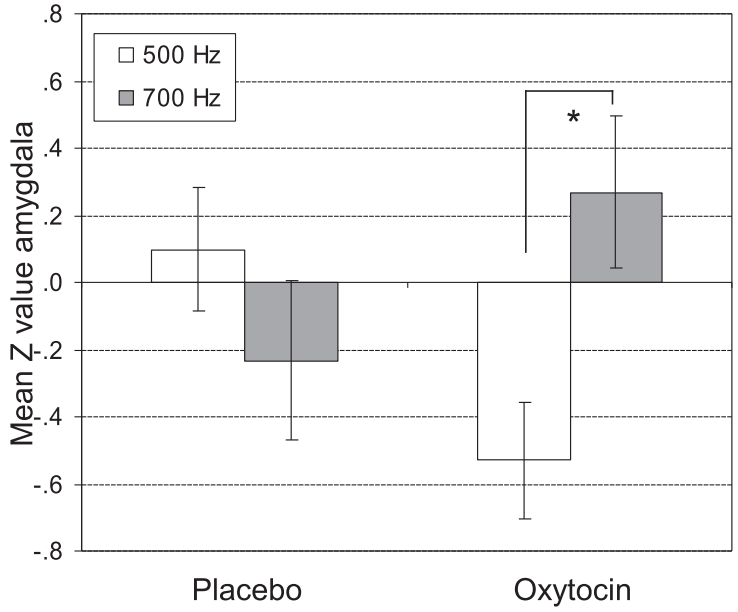

Figure 5. Z-values (*M, SE*) of right amygdala activation during crying (sick and bored infants) at 500 Hz compared with control sounds and crying (sick and bored infants) at 700 Hz compared with control sounds for individuals in the oxytocin and placebo condition. *$p < .01$

oxytocin increased activation in empathy-related brain regions during exposure to sick infant crying, thus facilitating prompt and sensitive responses to sick infants' crying. Increased empathic feelings may enhance the motivation to alleviate the infant's distress in a sensitive way, and decrease harsh caregiving responses that are only aimed at stopping the infant's crying because it is aversive.

Whereas sick infant crying requires a prompt response, a more delayed response may be adequate in case of mild distress, such as fussiness due to boredom. Hubbard and Van IJzendoorn (1991) found that delay of maternal response reduced the number of crying bouts during the first half year of life. The concept of differential responsiveness, which implies that mild distress should not be interpreted in terms of the infant's attachment needs, and that only severe distress requires a very prompt response, may explain these findings. A delayed response to a fussy infant might even be more sensitive because it enables the infant to learn to cope with situations of mild distress. Interestingly, we found that oxytocin reduced activation in the insula and IFG during exposure to bored infant crying. This may indicate that oxytocin reduces concern and empathic feelings for a bored infant, thereby lowering the perceived urgency of this type of crying and stimulating a delayed (in that context sensitive) response to infant fussiness.

Furthermore, we found that oxytocin decreased amygdala responses during exposure to 500 Hz crying, but it increased amygdala responses to 700 Hz crying. This is partly in line with a previous study that showed that oxytocin decreased amygdala activation during exposure to the same infant sounds (and 900 Hz crying) but without context information (Riem et al., 2011). The amygdala is involved in the perception of infant stimuli and has been associated with the experience of fear and the salience of stimuli (Davis & Whalen, 2001; LeDoux, 2000). Several studies have shown that reduced amygdala activation is one of the mechanisms underlying the anxiolytic effects of oxytocin (Domes et al., 2007; Kirsch et al., 2005). Under normal circumstances, reduced amygdala activation might promote sensitive responding to crying by preventing parents from being overwhelmed by negative emotions (Riem et al., 2011). However, reduced levels of arousal might be maladaptive in the case of high-pitched crying, since this type of crying generally signals that the infant is sick or in pain. The finding that oxytocin enhances amygdala responding to high-pitched crying might reflect increased vigilance to signals indicating that the infant is in danger. This interpretation is consistent with a study by Domes et al. (2010) who found that oxytocin enhanced amygdala reactivity to fearful and angry faces in women, thus facilitating the detection of threat signals and triggering reactions to protect the child from adult strangers with frightening faces.

The limitations of our study should be acknowledged. First, we used a between-subjects design to study the effects of oxytocin, which implies the risk of pre-existing differences between the oxytocin and placebo group that might have influenced the results. Randomization and double-blind application have decreased this risk substantially. Moreover, meta-analytic findings indicate no significant differences in outcomes of studies using between- or within-subject designs to examine intranasal oxytocin influences (Van IJzendoorn & Bakermans-

Kranenburg, 2012). Second, the results of this study can only be generalized to women without children. Furthermore, we did not include neural responses to infant crying without context information, which makes it difficult to relate the present findings with the results of our previous study (Riem et al., 2011).

In sum, the findings of our study indicate that the effects of oxytocin are dependent on perceived context, which is in line with previous research showing that the neural and behavioral effects of oxytocin are shaped by social context (Bartz et al., 2011). We found that oxytocin enhanced insula, IFG and amygdala responding to sick or high-pitched infant crying compared with crying of a bored infant, thus enhancing vigilance to signals indicating that the infant is in danger. This is the first study to show that intranasal administration of oxytocin leads to more pronounced differences in neural responding to sick infant crying compared to bored infant crying. Our findings indicate that oxytocin enhances the processing of contextual cues and the acoustics of crying, thus facilitating sensitive responding to infant crying in various manifestations.

Supplementary material to: Pity or Peanuts? Oxytocin affects neural response to sick and bored infant crying

fMRI data acquisition. Cushions were placed between the head coil and the participant to prevent head movement. All anatomical scans were examined by a radiologist and no anomalous findings were reported.

Sounds. Cry sounds were derived from the spontaneous crying of a healthy 2-day old infant. A 10-sec portion of the sustained period of crying was selected. The peak fundamental frequencies (Peak F0) of the entire cry were 515 ± 15 Hz. A new 10-sec cry sound with overall Peak F0 of 714.5 Hz (700 Hz cry) was created by digitally increasing the pitch of the original cry. Neutral auditory control stimuli were created identical to the original auditory stimuli in terms of duration, intensity, spectral content, and amplitude envelope but lacking an emotional meaning.

Whole brain analysis. The contrasts sick 500 Hz > control 500 Hz, sick 700 Hz > control 700 Hz, bored 500 Hz > control 500 Hz, and bored 700 Hz > control 700 Hz revealed significant activation in brain regions involved in auditory information processing, including the bilateral superior temporal gyrus, planum temporale, and Heschl's gyri in the oxytocin and placebo group (see Figure s1 for activations in the placebo group). There were no significant differences in activation between the sick 500 Hz and bored 500 Hz conditions or between the sick 700 Hz and bored 700 Hz conditions in the oxytocin and placebo group. Furthermore, there were no significant effects of oxytocin on activation during sick infant crying compared with control sounds at 500 or 700 Hz, bored infant crying compared with control sounds at 500 or 700 Hz, or during sick infant crying compared with bored infant crying at 500 or 700 Hz.

Mood. Participants rated on five-point Likert scales how much irritation, fear, enthusiasm, and alertness they felt. We conducted repeated measures analyses of variance with reported irritation, fear, enthusiasm, and alertness as dependent variables, treatment (oxytocin and placebo) as between-subject factor and time (time 1: before drug administration, and time 2: after scanning) as within-subject factor to test for effects of oxytocin on self-reported mood. There were no significant effects of treatment (ps > .09) and no significant interactions between treatment and time (ps > .33).

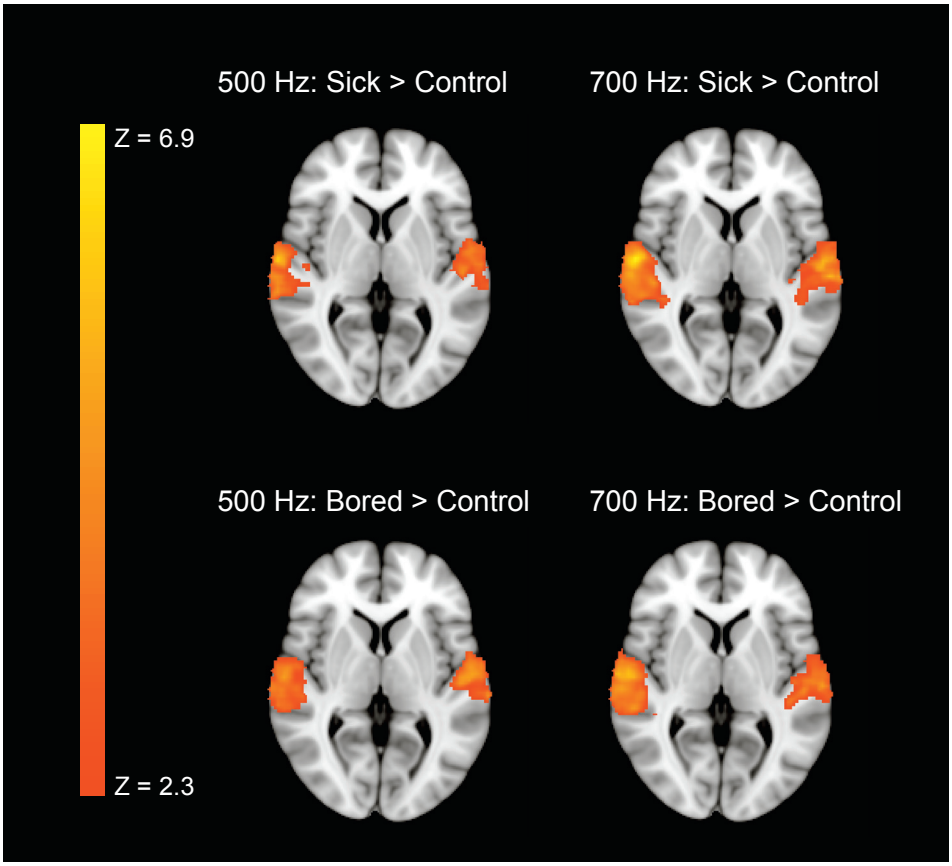

Figure S1. Significant activation in the bilateral superior, planum temporale and Heschl's gyri for the contrasts Bored > Control and Sick > Control at 500 and 700 Hz in the placebo group. Statistical images were thresholded with clusters determined by Z > 2.3 and a cluster-corrected significance threshold of $p < .05$. The right side of the brain corresponds to the left hemisphere and vice versa, z = 4.