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

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Oxytocin modulates amygdala, insula and inferior frontal gyrus responses to infant crying: A randomized controlled trial

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ABSTRACT

Oxytocin facilitates parental caregiving and mother-infant bonding and might be involved in responses to infant crying. Infant crying provides information about the infant's physical status and mood, and elicits parental proximity and caregiving. Oxytocin might modulate the activation of brain structures involved in the perception of cry sounds, specifically the insula, the amygdala and the thalamocingulate circuit, and thereby affect responsiveness to infant crying. In a randomized controlled trial we investigated the influence of intranasally administered oxytocin on neural responses to infant crying using functional Magnetic Resonance Imaging (fMRI). Blood oxygenation level dependent (BOLD) responses to infant crying were measured in 21 women who were administered oxytocin and 21 women who were administered a placebo. Experimentally induced oxytocin levels reduced activation in the amygdala and increased activation in the insula and inferior frontal gyrus pars triangularis. Our findings suggest that oxytocin promotes responsiveness to infant crying by reducing activation in the neural circuitry for anxiety and aversion, and increasing activation in regions involved in empathy.

INTRODUCTION

Infant crying alerts parents to the needs of the infant and elicits parental proximity and caregiving (Bowlby, 1969; Zeifman, 2001). Since young infants are fully dependent on their parents, correct perception and evaluation of infant crying by caregivers is crucial for infant survival. Several brain structures are involved in cry perception, specifically the insula and the thalamocingulate circuit that are activated when listening to infant crying (Bos, Hermans, Montoya, Ramsey, & Van Honk, 2010; Seifritz et al., 2003). Oxytocin is a neuropeptide that facilitates parental caregiving and mother-infant bonding in various species, including humans (Carter, 1998; Feldman, Weller, Zagoory-Sharon, & Levine, 2007; Insel, 2010). Reflecting its important role in maternal behavior, oxytocin might sensitize caregivers to variations in cry signals by modulating neural circuits related to the perception of infant crying, and thus enhance caregivers' responsiveness. In this study, we examine the effects of experimentally elevated levels of oxytocin on neural responses to infant crying. As crying has been found to be one of the major triggers of child abuse and neglect (Reijneveld, Van der Wal, Brugman, Sing, & Verloove-Vanhorick, 2004), examining the mechanisms that are involved in adults' reactions to infant crying is crucial.

Animal studies have shown that oxytocin is involved in lactation, pregnancy and the onset of maternal behavior (Carter, 1998; Insel, 2010). Recent research also suggests an important role of oxytocin in human caregiving. Higher maternal oxytocin levels across pregnancy predict higher quality of postpartum maternal behavior (Feldman et al., 2007). In addition, intranasally administered oxytocin has been shown to stimulate a range of social behaviors, including empathy (Bartz et al., 2010; Hurlemann et al., 2010), mind-reading (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007), trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), and in-group altruism (De Dreu et al., 2010). Carter (1998) argued that oxytocin may stimulate sensitive parenting in humans and other mammals by promoting acceptance of the newborn through reduction of fear to novelty and through enhancing prosocial behavior. This is in line with Heinrichs and Domes' suggestion that oxytocin plays an important role as an underlying neurobiological mechanism for the anxiolytic/stress-protective effects of positive social interaction (Heinrichs & Domes, 2008). On the genetic level individuals with the potentially more efficient variant (GG) of the oxytonergic receptor gene (OXTR rs53576) show reduced levels of stress and increased levels of empathy (Rodrigues, Saslow, Garcia, John, & Keltner, 2009), as well as more sensitive parental interactions with toddlers (Bakermans-Kranenburg & Van IJzendoorn, 2008).

An important component of parental sensitive caregiving is responsiveness to infant crying behavior. Infant crying provides information about the infant's physical health and mental state, and the intensity of distress can be derived from the acoustics of the cry sound (Gustafson, Wood, & Green, 2000; Murray, 1979). The association between oxytocin and increased parental sensitivity may be partly due to the influence of oxytocin on responses to infant crying (Riem, Pieper, Out, Bakermans-Kranenburg, & Van IJzendoorn, 2011). Oxytocin

might facilitate responsiveness to infant crying by modulating brain structures involved in cry perception, such as the thalamocingulate circuit, the insula, amygdala and superior temporal gyrus (Lorberbaum et al., 2002; Seifritz et al., 2003; Swain et al., 2008). The thalamus is considered important for mammalian mother-infant attachment behavior (MacLean, 1990). The insula is involved in maternal bonding and an important region implicated in empathy and emotion understanding (Bartels & Zeki, 2004), and it has been suggested that oxytocin is involved in the neurochemical mechanism underlying emotional empathy (Hurlemann et al., 2010; Shamay-Tsoory, 2011). Bos et al. (2010) showed that testosterone administration increased activation in the thalamus and the insula during exposure to infant crying sounds, possibly through the effect of testosterone on the oxytonergic system. Furthermore, vaginal delivery leads to increased oxytocin levels following vaginal-cervical stimulation, and mothers who experienced childbirth by vaginal delivery showed more brain activation in the superior temporal gyrus, the insula and the anterior cingulate gyrus compared to mothers who had a cesarean section delivery (Swain et al., 2008).

While oxytocin seems to increase activation in brain regions involved in empathy (Shamay-Tsoory, 2011), it decreases activation in the neural circuitry for anxiety and disgust (Gamer, Zurowski, & Buchel, 2010; Stark et al., 2003). Kirsch et al. (2005) found that oxytocin reduced amygdala activation during the perception of fear-inducing visual stimuli in men. This finding fits well with previously reported anxiolytic effects of oxytocin (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; McCarthy, McDonald, Brooks, & Goldman, 1996). Mothers experience strong emotional reactions to infant crying, ranging from empathy to anxiety and anger (Dix, 1991; Out, Pieper, Bakermans-Kranenburg, Zeskind, & Van IJzendoorn, 2010). Aversion or other negative emotional reactions may lead to insensitive parenting behaviors such as withdrawal or hostility in order to stop (having to listen to) infant crying (Dix, Gershoff, Meunier, & Miller, 2004); and high-pitched infant crying in particular is an important trigger for child abuse (Out, Pieper, Bakermans-Kranenburg, Zeskind, et al., 2010; Soltis, 2004). As oxytocin decreases activation in the neural circuitry for anxiety and aversion, it might prevent parents from becoming overreactive to the disturbing infant cry sounds. Although several studies have shown that oxytocin decreases amygdala reactivity to fearful stimuli in males, only one study has been conducted on the effects of oxytocin administration in females. Domes et al. (2010) found that in females intranasal oxytocin increased amygdala activation in response to angry and happy adult faces, which is in contrast with reported effects in males (Kirsch et al., 2005). However, oxytocin may reduce amygdala activation in females listening to infant crying which would be in line with the stress-reducing effects of endogenous oxytocin release in breast-feeding females (Heinrichs et al., 2001; Heinrichs, Neumann, & Ehlert, 2002).

To our knowledge this is the first randomized controlled study to examine the association between oxytocin manipulation and neural responses to infant crying. We studied the influence of intranasally administered oxytocin on neural responses to infant crying in women. We focused on neural responses to infant crying at different frequencies since infant cries range from 500 Hz in normal,

healthy infants to 900 Hz (and even higher) in infants in pain or with medical and neurological conditions (Porter, Porges, & Marshall, 1988; Soltis, 2004; Zeskind & Collins, 1987). Blood oxygenation level dependent (BOLD) response to infant crying was measured using functional Magnetic Resonance Imaging (fMRI). Whole brain analysis was performed to explore the neural effects of oxytocin. In particular, we expected that oxytocin administration would be related to increased activity in the thalamocingulate circuit and in the insula, and decreased activity in the amygdala. Regions of interest (ROI) analyses were conducted to examine the effects of oxytocin in these regions.

METHOD

Participants

Participants were selected from a larger study investigating caregiving responses and physiological reactivity to infant crying (Out, Pieper, Bakermans-Kranenburg, & Van IJzendoorn, 2010). The original sample consisted of 50 male and 134 female adult twin pairs. Zygosity was determined on the basis of a zygosity questionnaire (Magnus, Berg, & Nance, 1983) and additional genetic analysis of selected polymorphisms. A group of 43 right-handed females were recruited, 21 from monozygotic (MZ) twin pairs and 22 from dizygotic (DZ) twin pairs, without children of their own, in good health, without hearing impairments and MRI contraindications, pregnancy, psychiatric or neurological disorders, and screened for alcohol and drug use. One dizygotic sibling was excluded from the analyses due to excessive head movement during fMRI scanning (peak displacement = 10 mm). Twin siblings of 10 participants did not participate due to MRI contraindications or other exclusion criteria, resulting in a sample of 32 participants from twin pairs (9 MZ, 7 DZ) and 10 participants without twin sibling (3 MZ, 7 DZ). The mean age of the participants was 29.07 years ($SD = 7.56$, range 22-49). Sixty-nine percent of the participants used oral contraceptives. Permission for this study was obtained from the Medical Ethics Committee of the Leiden University Medical Center and all participants gave informed consent.

Procedure

Participants were invited preferably in the luteal phase of their menstrual cycle. Approximately thirty-six minutes before the start of the fMRI data acquisition ($M = 35.86$, $SD = 5.12$) subjects took nasal spray containing oxytocin or placebo. Time between oxytocin/placebo administration and data acquisition was similar to previous fMRI studies (Marsh, Yu, Pine, & Blair, 2010; Rimmele, Hediger, Heinrichs, & Klaver, 2009). Participants were instructed to comfortably position themselves on the scanner bed. Cushions were placed between the head coil and the participant in order to prevent head movement. Participants were instructed to attend to the sounds they would hear. Before drug administration and after fMRI scanning participants completed a mood questionnaire in order to track mood changes following drug administration. Participants rated on 7-point Likert scales how much anxiety, anger, frustration, empathy, happiness and calmness they felt (Kirsch et al., 2005). In addition, they rated the perceived urgency of

the infant cry sounds on a 5-point Likert scale after fMRI scanning (Zeskind & Marshall, 1988).

Cry paradigm

Cry sounds were derived from the spontaneous crying of a healthy 2-day old infant. A 10-s portion of the sustained period of crying was selected. The peak fundamental frequencies (Peak F0) of the entire cry were $515 \pm 15\text{Hz}$. Two new 10-s cry sounds with overall Peak F0 of 714.5 Hz (700 Hz cry) and 895.8 Hz (900 Hz cry) were created by digitally increasing the pitch of the original cry (Dessureau, Kurowski, & Thompson, 1998; Out, Pieper, Bakermans-Kranenburg, Zeskind, et al., 2010; Schuetze & Zeskind, 2001; Schuetze, Zeskind, & Das Eiden, 2003). 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. Cry and control sounds were presented in 8 cycles, each cycle consisting of 6 sounds (Cry 500 Hz, Cry 700 Hz, Cry 900 Hz, Control 500 Hz, Control 700 Hz, Control 900 Hz). The order of presentation of sounds within each cycle was random; the intertrial-interval was 6 s (see Fig 1).

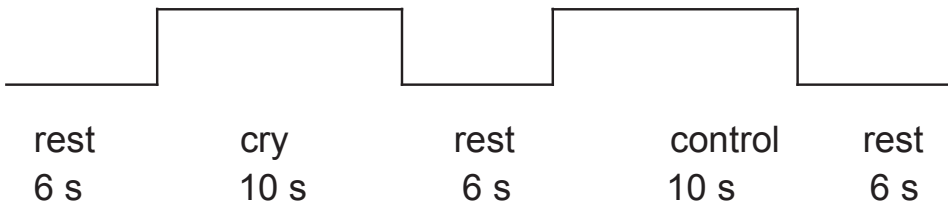


Figure 1. The cry paradigm. Cry sounds and control sounds were presented for 10 seconds, followed by a rest period of 6 seconds.

Oxytocin versus placebo

One sibling from each twin pair was randomly assigned to the oxytocin condition and the other sibling to the placebo condition. Participants without a twin sibling were also randomly assigned to the oxytocin and placebo condition. Approximately thirty-six minutes before the start of the fMRI data acquisition subjects took 6 puffs of nasal spray containing oxytocin (16 IU total, RVG number 03716, Sandoz b.v.) or 6 puffs of a placebo-spray (NaCl solution) under supervision of the experimenter. Drug administration was double-blind.

Image acquisition

Scanning was performed with a standard whole-head coil on a 3-T Philips Achieva 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, voxelsize $.875 \times .875 \times 1.2$ mm). For fMRI, a total of 360 T2*-weighted whole-brain EPIs were acquired (TR = 2.2sec; TE = 30 msec, flip angle = 80° , 38 transverse slices, voxelsize $2.75 \times 2.75 \times 2.75$ mm (+10% interslice gap)). Participants listened to the sounds through MRI compatible headphones.

In accordance with Leiden University Medical Center policy, all anatomical scans were examined by a radiologist from the Radiology department. No anomalous findings were reported.

fMRI data analysis

Data analysis was carried out using FEAT (fMRI Expert Analysis Tool) Version 5.98, part of FSL (fMRIB's Software Library, www.fmrrib.ox.ac.uk/fsl; (Smith et al., 2004)). The following pre-statistics processing was applied: motion correction (Jenkinson & Smith, 2001), 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 = 50.0s). Functional scans were registered to T1-weighted images, which were registered to standard space (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001).

In native space, functional activation was examined using general linear model analysis. Each sound (Cry 500 Hz, 700 Hz, 900 Hz and Control 500 Hz, 700 Hz, 900 Hz) was modeled separately as a square-wave function. Each predictor was then convolved with a double gamma hemodynamic response function and its temporal derivative was added to the model, giving 12 predictors. In order to identify regions involved in the perception of infant crying the following contrasts were assessed: 1) Cry_{combined 500, 700, 900 Hz} > Control_{combined 500, 700, 900 Hz} 2) Cry_{500 Hz} > Control_{500 Hz} 3) Cry_{700 Hz} > Control_{700 Hz} 4) Cry_{900 Hz} > Control_{900 Hz}. These 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_{Cry > Control} > Placebo_{Cry > Control}). Similar to Domes et al. (35) we also examined reduced brain activation in the oxytocin group compared to the placebo group in the reverse contrast (Oxytocin_{Cry > Control} < Placebo_{Cry > Control}). The statistical images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < .05$ (Worsley, 2001).

Additionally, regions of interest (ROI) analyses were performed with FSL to investigate changes in activation of a priori specified regions that were related to the perception of infant crying in the literature. These regions are the amygdala, thalamus, and insula (Bos et al., 2010; LeDoux, 2000; Seifritz et al., 2003) and were defined using the Harvard-Oxford cortical atlas (<http://www.fmrrib.ox.ac.uk/fsl/data/atlas-descriptions.html#ho>). ROI analyses were limited to these search regions, applying the same statistical threshold as for the whole brain analyses, however correcting only for the size of ROI volumes.

We included menstrual cycle and use of oral contraceptives in the whole brain and ROI analyses as confound regressors in the model. To study the possible effect of various, a priori defined, parameters on the observed changes in brain activation we also computed mean parameter estimates of the contrasts that yielded significant activation using Featquery (www.fmrrib.ox.ac.uk/fsl/feat5/featquery.html). This was done for each activated region. Univariate analyses of covariance were performed with the mean parameter estimate as dependent

variable, oxytocin/placebo as between-subjects factor, and age and time between oxytocin/placebo administration and fMRI data acquisition as covariates. In addition, we performed univariate analyses of variance with the mean parameter estimate as dependent variable, oxytocin/placebo as between-subjects factor, and menstrual cycle (follicular or luteal phase), use of oral contraceptives, and monozygotic twin/dizygotic twin/participant without twin sibling (sibling group) as between-subjects factors to examine the influence of potential confounding variables. Mean Z values for regions with a change in brain activation after oxytocin administration were calculated using Featquery for visualization purposes.

RESULTS

Statistical images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < .05$. In addition, we included use of oral contraceptives and menstrual cycle as confound regressors in the model. The main contrast of infant crying (combined 500 Hz, 700 Hz, 900 Hz) versus control sounds (combined 500 Hz, 700 Hz, 900 Hz) revealed stronger bilateral activation in the superior and middle temporal gyrus in the placebo condition (see Table 1 and Fig. 2). ROI analyses were conducted to examine whether there was activation in a priori defined areas of interest (insula, amygdala and thalamus). We found stronger activation in the right amygdala when participants in the placebo group listened to infant crying compared to the control sounds. The thalamus and insula did not show a significant difference in activation during infant crying compared to control sounds.

Similar to the main comparison of total infant crying with control sounds, the contrast of the 500 Hz cry sound versus the 500 Hz control sound (contrast 2) revealed significant activation in the bilateral superior temporal gyrus and the left occipital fusiform gyrus in the placebo condition (see Table 1). ROI analyses did not show significant activation in the thalamus or insula. However, there was significant activation in the right amygdala. In the placebo condition we also found stronger activation in the bilateral superior temporal gyrus during the perception of the 700 Hz cry compared to the 700 Hz control sound (contrast 3). The location of the peak voxel of the cluster in the right hemisphere was located in the middle temporal gyrus. Again, this contrast revealed significant activation in the right amygdala, but not in the insula or thalamus. Lastly, no significantly different activation was observed during the perception of the 900 Hz cry compared to the 900 Hz control sound in the whole brain analysis (contrast 4). The regions of interest analyses revealed significant activation in the right amygdala, but no significant (de-)activation in the insula or thalamus.

To examine whether oxytocin affected neural responses to crying (combined 500 Hz, 700 Hz, 900 Hz) we contrasted the oxytocin group versus the placebo group (Oxytocin_{Cry > Control} > Placebo_{Cry > Control} and Oxytocin_{Cry > Control} < Placebo_{Cry > Control}). These contrasts did not yield significantly different activation in the whole brain analysis. However, ROI analysis showed that compared to the placebo group, participants who received oxytocin showed reduced activation in the

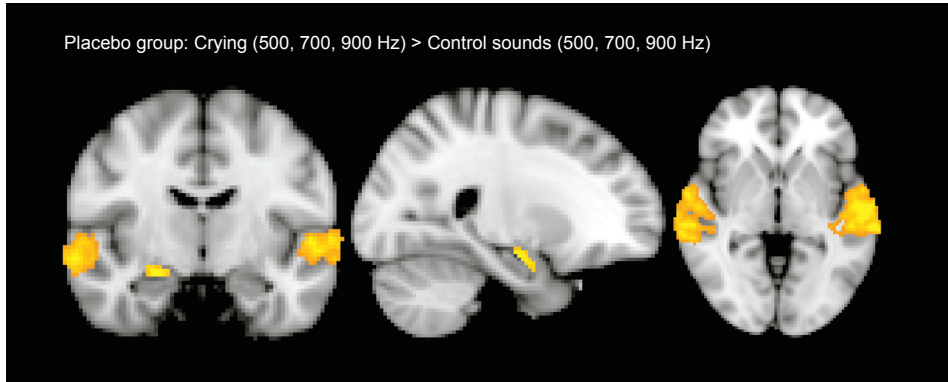


Figure 2. Significant activation in the bilateral superior and middle temporal gyrus and the amygdala for the contrast Crying (500, 700, 900 Hz) > Control sounds (500, 700, 900 Hz). Statistical images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < 0.05$. The amygdala activation was revealed by ROI analysis limited to this search region, applying the same statistical threshold, however correcting only for the size of the ROI volume.

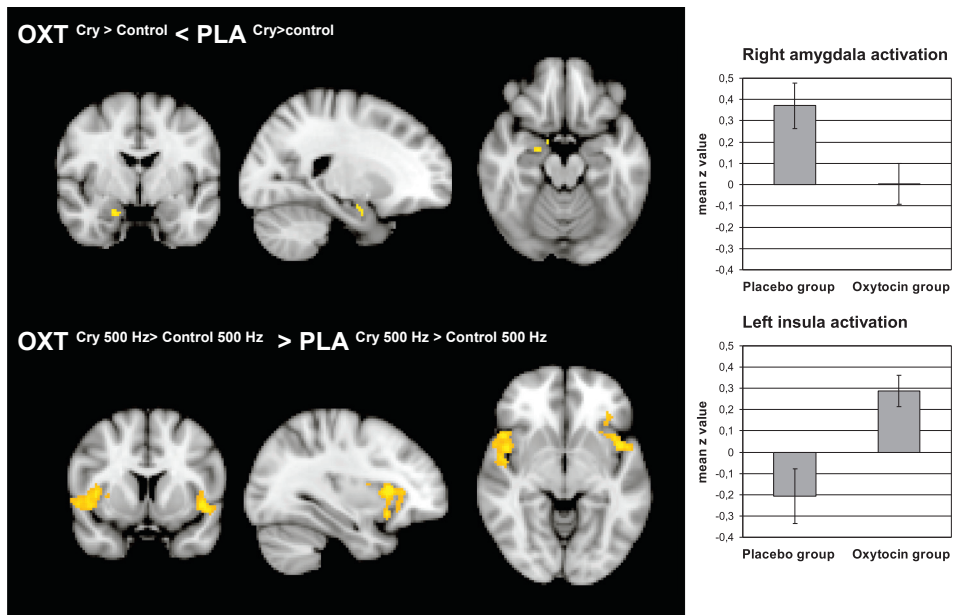


Figure 3. Top panel: oxytocin effect on right amygdala activation and mean Z values and standard errors for the oxytocin and placebo group for the contrast Cry combined > Control combined in the amygdala. Lower panel: oxytocin effect on bilateral insula and inferior frontal gyrus pars triangularis activation and mean Z values and standard errors for the oxytocin and placebo group for the contrast Cry 500 > Control 500 in the left insula. Both statistical images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < 0.05$. The amygdala activation was revealed by ROI analysis limited to this search region, applying the same statistical threshold, however correcting only for the size of the ROI volume.

right amygdala when they listened to infant crying (see Table 1 and top panel Fig. 3). This contrast did not reveal significant activation in the other regions of interest.

We also examined the effect of oxytocin in the 500 Hz condition (Oxytocin^{Cry} 500 Hz > Control 500 Hz > Placebo^{Cry} 500 Hz > Control 500 Hz). Whole brain analysis indicated that oxytocin increased bilateral insula and inferior frontal gyrus pars triangularis activation (Harvard–Oxford cortical atlas: frontal operculum) (see lower panel Fig. 3 and Table 1). The cluster in the right hemisphere extended more laterally and the location of the peak voxel was in the planum polare. The ROI analysis of responses to 500 Hz cry sounds showed that oxytocin increased left insula

Table 1. MNI coordinates, cluster size and Z-max values for significantly activated clusters.

Experimental effect	MNI coordinates			Cluster size	Peak Z
Region	x	y	z		
<i>Main effects in placebo group</i>					
Cry > Control					
L Superior temporal gyrus	-62	-14	0	2314	5.62
R Middle temporal gyrus	62	-26	-4	2367	4.76
R Amygdala	26	-12	-14	136	4.02 ^a
Cry 500 Hz > Control 500 Hz					
L Superior temporal gyrus	-58	-20	0	761	4.94
R Superior temporal gyrus	62	-22	-4	611	3.97
L Occipital fusiform gyrus	-30	-76	-12	520	3.47
R Amygdala	22	-10	-16	27	3.42 ^a
Cry 700 Hz > Control 700 Hz					
L Superior temporal gyrus	-62	-16	2	1797	4.75
R Middle temporal gyrus	72	-34	2	853	3.78
R Amygdala	20	-8	-16	59	2.95 ^a
Cry 900 Hz > Control 900 Hz					
R Amygdala	20	-2	-20	35	3.25 ^a
<i>Sounds x Drug effects</i>					
OXT ^{Cry} > Control < PLA ^{Cry} > Control					
R Amygdala	26	-12	-14	58	3.28 ^a
OXT ^{Cry} 500 Hz > Control 500 Hz > PLA ^{Cry} 500 Hz > Control 500 Hz					
R Planum polare	-52	-8	0	780	3.93
L Inferior frontal gyrus	50	16	-4	747	3.97

$p < 0.05$, corrected by whole brain cluster threshold ($z > 2.3$), use of oral contraceptives and menstrual cycle included as confound regressors in the model.

^a ROI analysis, $p < 0.05$, corrected by cluster threshold ($z > 2.3$)

activation, but there was no significant effect in the thalamus or amygdala. Whole brain and ROI analyses did not show significant effects of oxytocin on neural responses to infant crying at 700 Hz and 900 Hz.

The univariate analyses of (co)variance with age, time between placebo/oxytocin administration and fMRI data acquisition, menstrual cycle, sibling group and use of oral contraceptives showed that none was significantly associated with change in brain activation, neither at whole group level (placebo and oxytocin), nor for the difference between the oxytocin and placebo condition. Whole brain and ROI analyses were repeated after exclusion of four participants who were older than 41 years in order to examine whether advanced age influenced the effects of oxytocin (Al-Azzawi & Palacios, 2009). This did not result in different findings: oxytocin significantly increased inferior frontal gyrus and insula activation and significantly reduced right amygdala activation.

To control for nonspecific effects of oxytocin on self-reported mood and perceived urgency of the cry sounds we conducted repeated-measures ANOVAs with group (oxytocin and placebo) as between-subject factor and time (time 1: before drug administration and time 2: after scanning) as within-subject factor. There were no significant time by group interaction effects on any of the mood items anger ($F(1,40) = 0.02, p = .89$), frustration ($F(1,40) = 0.25, p = .62$), anxiety ($F(1,40) = 3.07, p = .09$), empathy ($F(1,40) = 0.03, p = .86$), happiness ($F(1,40) = 1.08, p = .30$) and calmness ($F(1,40) = 0.40, p = .53$). Moreover, there were no significant effects of oxytocin on perceived urgency of infant crying at 500 Hz ($F(1,39) = 1.58, p = .22$), 700 Hz ($F(1,39) = 2.00, p = .17$) or 900 Hz ($F(1,39) = 2.23, p = .14$).

DISCUSSION

Our study demonstrates that oxytocin administration is related to reduced right amygdala activation and enhanced insula and inferior frontal gyrus activation when exposed to infant crying compared to control sounds. Several studies have shown that the amygdala is involved in the perception of infant stimuli (Bos et al., 2010; Seifritz et al., 2003; Swain et al., 2008) and that oxytocin reduces amygdala activation during the perception of fear-inducing social stimuli (Kirsch et al., 2005; Petrovic, Kalisch, Singer, & Dolan, 2008). Decreased amygdala activation might promote responsiveness to infant crying by preventing parents from being overwhelmed by anxious or aversive feelings. This fits well with findings of stress reducing effects of oxytocin in lactating mothers (Heinrichs et al., 2001; Heinrichs et al., 2002).

Whereas oxytocin reduced neural activation in the amygdala, it increased activation in regions associated with empathy and mother-infant bonding, the insula and the inferior frontal gyrus pars triangularis. The increase in insula and inferior frontal gyrus activation only occurred during the 500 Hz crying condition, possibly because this unaltered cry sound was most naturalistic and characteristic for a normal healthy infant. Previous studies have shown that the insula is involved in the perception of the own infant's sad faces (Strathearn, Fonagy, Amico, & Montague, 2009) and the inferior frontal gyrus is important for affective prosodic comprehension (Leitman et al., 2010). Empathy is an important

prerequisite of parental sensitivity, defined as parents' ability to perceive child signals, to interpret these signals correctly, and to respond to them promptly and appropriately (Ainsworth, Blehar, Waters, & Wall, 1978). Indeed, empathy has been found related to parental responsiveness to infant signals (Feldman, 2007; Gondoli & Silverberg, 1997; Leerkes, 2010). It is based on a neural simulation mechanism that is activated both when subjected to an emotion *and* when observing someone else experiencing the emotion, thus enabling humans to understand others' emotions (Gallese, Keysers, & Rizzolatti, 2004; Iacoboni, 2009). The insula and inferior frontal gyrus are suggested to play an important role in this simulation process (Chakrabarti, Bullmore, & Baron-Cohen, 2006; Decety & Jackson, 2004; Jabbi, Swart, & Keysers, 2007), and oxytocin may facilitate responsiveness to infant crying by increasing activation in brain regions important for empathy. Our findings are in line with results from a study by Bos et al. (2010) who found that testosterone increases insula activation in response to infant crying, possibly by influencing the oxytonergic system. Testosterone has been linked to oxytocin as it is metabolized into estradiol which subsequently influences oxytocin levels (Choleris, Devidze, Kavaliers, & Pfaff, 2008; Cornil, Ball, & Balthazart, 2006).

In the placebo group, we found an increased activation in the bilateral superior and middle temporal gyrus and the occipital fusiform gyrus when listening to infant crying compared to control sounds. These regions are important for language processing and social perception (Baron-Cohen et al., 1999; Leitman et al., 2010). Previous studies have also shown involvement of the superior temporal gyrus and the fusiform gyrus on neural responses to infant stimuli (Strathearn et al., 2009; Swain et al., 2008). In addition, we found increased activation in the amygdala during infant crying compared to control sounds. Amygdala activation was restricted to the right hemisphere. This is in line with previous studies of responsiveness to infant crying (Bos et al., 2010; Lorberbaum et al., 2002; Seifritz et al., 2003). It has been suggested that this right hemisphere dominance has evolved as most women carry their infant on their left arm (Harris, Cardenas, Spradlin, & Almerigi, 2010; Reissland, Hopkins, Helms, & Williams, 2009; Sieratzki & Woll, 1996).

In contrast with our expectations the thalamus did not show significantly increased activation during exposure to infant crying, and no different activation in the oxytocin as compared to the placebo group. It should be noted that previous findings are equivocal, with some studies reporting increased thalamic activation during the perception of infant crying (Bos et al., 2010; Lorberbaum et al., 2002; Swain et al., 2008), and other studies not finding significant thalamic activation to infant cues (Seifritz et al., 2003; Strathearn et al., 2009). These equivocal results might be explained by different characteristics of cry and control stimuli. For instance, in some studies mothers listened to their own infant's crying whereas other studies used cry sounds of unknown infants. Swain et al. (2008) showed that, among other regions, the thalamus was significantly more active when mothers listened to their own infant's cry compared to cry sounds of unknown infants. Several animal studies have shown that the density of oxytocin receptors is high in the thalamus, in particular in social species (Beery, Lacey, & Francis,

2008; Campbell, Ophir, & Phelps, 2009), but the number of studies reporting oxytocin effects on thalamic activation is limited (e.g. Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008). More research is needed to clarify the role of the thalamus in the perception of infant crying and whether it is affected by oxytocin.

Age, menstrual cycle, sibling group, use of oral contraceptives, and time between placebo/oxytocin administration and fMRI data acquisition were not associated with (differences in) brain activation. Although several studies have shown that oxytocin levels fluctuate throughout the menstrual cycle (Altemus, Roca, Galliven, Romanos, & Deuster, 2001; Liedman et al., 2008; Stock, Bremme, & Uvnasmoberg, 1991), it is possible that the effect of intranasally administered oxytocin on neural activity in response to cry sounds was large enough to overrule the effects caused by normal fluctuations. Moreover, the majority of the participants used oral contraceptives dampening menstrual cycle-related hormonal fluctuations (Salonia et al., 2005). Furthermore, our findings of reduced amygdala activation and increased insula activation were not influenced by a general change in mood since oxytocin did not affect self-reported emotional states. These results converge with several other studies that reported no effects of oxytocin on emotional state (Kirsch et al., 2005; Naber, Van IJzendoorn, Deschamps, Van Engeland, & Bakermans-Kranenburg, 2010).

The limitations of our study should be acknowledged. First, the physiological effects induced by intranasally administered oxytocin are not well understood and might be different from the effects of endogenous oxytocin secretion. Second, a between-subjects design implies the risk of pre-existing differences between the oxytocin and placebo group that may have influenced the results. However, the majority of our participants were mono- and dizygotic twin pairs, perfectly matched on age and global child rearing experiences, and even on genotype in monozygotic twin pairs. Third, we suggested that in decreasing amygdala activation oxytocin might inhibit aversive responses to infant crying. In a future study the effects of oxytocin on behavioral responses to infant crying mediated by amygdala activation should be examined. Furthermore, oxytocin might increase stress responses when parents are confronted with threatening stimuli that could harm the infants (De Dreu et al., 2010). Domes et al. (2010) found increased amygdala activation in females in the oxytocin condition in response to fearful or angry adult faces. This finding seems in contrast with the previously reported effects of oxytocin found in men, but it might reflect enhanced vigilance to threat signals evolved in order to protect the child, thus triggering an aggressive reaction to frightening faces of adult strangers (De Dreu et al., 2010). In an ideal future study the Domes et al. (2010) paradigm would be used together with the cry paradigm, preferably with matched male and female respondents. Lastly, our findings can only be generalized to women without children.

In conclusion, this is the first study to show the effect of oxytocin administration on neural responses to infant crying, extending previous findings indicating a central role for oxytocin in parental caregiving and attachment formation (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010; Naber et al., 2010). Our findings suggest that oxytocin promotes responsiveness to infant

crying by reducing activation in the neural circuitry for anxiety and aversion, and by increasing activation in regions involved in empathy. Infant crying may trigger child abuse or neglect (Reijneveld et al., 2004). However, not all parents with irritable infants become abusive, and differences in oxytocin levels may explain why some parents remain sensitive whereas other parents lack the empathic ability to abstain from harsh or even abusive responses to their infant's crying.

