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No Laughing Matter: Intranasal Oxytocin Administration Changes Functional Brain Connectivity during Exposure to Infant Laughter

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Infant laughter is a rewarding experience. It activates neural reward circuits and promotes parental proximity and care, thus facilitating parent–infant attachment. The neuropeptide oxytocin might enhance the incentive salience of infant laughter by modulating neural circuits related to the perception of infant cues. In a randomized controlled trial with functional magnetic resonance imaging we investigated the influence of intranasally administered oxytocin on functional brain connectivity in response to infant laughter. Blood oxygenation level-dependent responses to infant laughter were measured in 22 nulliparous women who were administered oxytocin and 20 nulliparous women who were administered a placebo. Elevated oxytocin levels reduced activation in the amygdala during infant laughter and enhanced functional connectivity between the amygdala and the orbitofrontal cortex, the anterior cingulate, the hippocampus, the precuneus, the supramarginal gyri, and the middle temporal gyrus. Increased functional connectivity between the amygdala and regions involved in emotion regulation may reduce negative emotional arousal while enhancing the incentive salience of the infant laughter.

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INTRODUCTION

The laugh of an infant is a uniquely rewarding experience for parents. It provokes feelings of love and happiness and promotes infant survival by eliciting parental proximity and care (Bowlby, 1969/1982; Groh and Roisman, 2009; Mendes *et al*, 2009). Laughter is suggested to be the outcome of a long evolutionary history (van Hooff, 1972), and its production as well as perception might be hardwired in human beings (Owren and Bachorowski, 2003). Although infant smiling is one of the basic attachment behaviors that create closer proximity to a protective caregiver (Bowlby, 1969/1982; Sroufe and Waters, 1976) infant laughter is most easily released by tickling and other forms of rough-and-tumble play (Sroufe and Waters, 1976). The infant's laughter in its turn may activate neural reward centers in the parental brain (Kringelbach, 2005; Kringelbach *et al*, 2008; Strathearn *et al*, 2009) and reinforce parental playful interactions. Oxytocin is a neuropeptide that facilitates the onset of maternal behavior and mother–infant attachment (Carter, 1998; Galbally *et al*, 2011; Insel, 2010) and is involved in the perception of infant vocalizations (Riem *et al*, 2011a, b). Oxytocin might enhance the incentive salience of infant laughter by modulating neural circuits related to the perception of infant cues and thus motivating sensitive responsiveness to infant laughter. To our knowledge, this is the first randomized controlled study to examine the effects of intranasally administered oxytocin on functional brain connectivity in response to infant laughter.

Oxytocin administration studies have shown that it stimulates a range of social behaviors (for a meta-analysis, see Van IJzendoorn and Bakermans-Kranenburg, 2011) including empathy (Bartz *et al*, 2010a), mind-reading (Domes *et al*, 2007), trust (Kosfeld *et al*, 2005), in-group altruism (De Dreu *et al*, 2010), and paternal stimulating play

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(Naber *et al*, 2010). Feldman *et al* (2007) showed that maternal oxytocin levels across pregnancy are predictive of higher quality of postpartum maternal behavior. Oxytocin has anxiolytic and stress-reducing effects in breastfeeding mothers (Heinrichs *et al*, 2001; McCarthy *et al*, 1996) and this might increase mothers' sensitivity to infant signals including infant crying but also infant smiling and laughing. Taylor also suggested that oxytocin modulates stress responses and is implicated in the seeking of affiliative contact in response to stress (Taylor and Samson, 2005; Taylor, 2006). Although infant crying is very different from infant laughter, oxytocin seems to enhance sensitivity to both infant signals. For example, Strathearn *et al* (2009) found that mothers with a strong increase in peripheral oxytocin release while interacting with their infants show more activation in neural reward systems such as the OFC and the ventral striatum during the perception of their smiling infant than mothers with lower oxytocin levels (Strathearn *et al*, 2009). This finding might indicate that oxytocin increases the 'incentive salience' of infant laughter (Berridge, 2007).

One important target of oxytocin is the amygdala (Meyer-Lindenberg *et al*, 2011), a neural structure that is part of the neural network involved in emotional processing. In a previous study we found that oxytocin reduced amygdala responses to infant crying whereas it increased activation of the insula and inferior frontal gyrus (IFG) (Riem *et al*, 2011a), brain regions important for empathy, emotion understanding and maternal bonding (Bartels and Zeki, 2004; Shamay-Tsoory, 2011). The amygdala is also referred to as a neural hub because of its high degree of connectivity, which is critical for the flow and integration of information between regions (Pessoa, 2008). It is strongly connected with other brain regions involved in emotional processing such as the orbitofrontal cortex (OFC), the supra- and subgenual parts of the anterior cingulate cortex (ACC), the brainstem, and the thalamus (Bos *et al*, 2011; Pessoa, 2008).

Several studies have shown that by modulating amygdala activity hormones can shift neural output towards other brain regions within this network. For example, Kirsch *et al* (2005) showed that oxytocin reduces amygdala-brainstem coupling that is important for fear and arousal. Van Wingen *et al* (2010) showed that OFC-amygdala coupling was reduced after testosterone administration. The OFC is involved in reward and hedonic processing and it exhibits a specific neural response to infant stimuli (Kringelbach, 2005; Kringelbach *et al*, 2008; Noriuchi *et al*, 2008). Furthermore, previous studies have shown that the posterior OFC and ACC are involved in the perception of infant crying (Laurent and Ablow, 2011; Swain *et al*, 2008). Although most studies focused on infant crying only, Seifritz *et al* (2003) showed that the ACC was deactivated during both infant laughter and crying, indicating its important role in parent–infant interaction. Both structures are important for emotional regulation, in particular for the reduction of anxiety, by their inhibitory influence on the amygdala (Banks *et al*, 2007; Hahn *et al*, 2011; Meyer-Lindenberg *et al*, 2011; Stein *et al*, 2007; Swain *et al*, 2008). Thus, oxytocin might stimulate mother–infant bonding by modulating connectivity between the amygdala, ACC, and OFC and thereby enhancing the regulation of negative emotions and the experience of reward during mother–infant interaction (Bos *et al*, 2011).

In this study, we examined the influence of intranasally administered oxytocin on neural responses to infant laughter with functional magnetic resonance imaging (fMRI). Whole brain analysis was performed to explore the neural effects of oxytocin on functional activation during infant laughter. We focus our analyses on functional activation of the insula, IFG, and amygdala as a prior study showed that oxytocin modulated activation in these regions during the perception of infant crying (Riem *et al*, 2011a). Moreover, previous fMRI studies indicated that the insula and amygdala are involved in the perception of infant and adult laughter (Sander *et al*, 2003, 2007; Sander and Scheich, 2001, 2005; Seifritz *et al*, 2003). Furthermore, we examined oxytocin effects on the ventral striatum, the ACC, and the OFC because of the suggested significance of these regions in mother–infant bonding and reward processing (Berridge and Kringelbach, 2008; Kringelbach, 2005; Kringelbach *et al*, 2008; Seifritz *et al*, 2003; Strathearn *et al*, 2009). We expected that oxytocin administration would be related to increased activity in the ventral striatum, ACC, OFC, insula, and IFG, and decreased activity in the amygdala. In addition, with psychophysiological-interaction (PPI) analysis we examined whether oxytocin affects amygdala-connectivity during the perception of infant laughter. In region of interest (ROI) analyses we tested whether oxytocin modulated functional connectivity between the amygdala, OFC, and ACC during infant laughter.

MATERIALS AND METHODS

Participants

Participants were selected from a larger study investigating caregiving responses and physiological reactivity to infant crying (Out *et al*, 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 *et al*, 1983) and additional genetic analysis of six polymorphisms; results indicated that 12 twin pairs (6.5% of the sample) classified as monozygotic (MZ) on the basis of the questionnaire were in fact dizygotic (DZ). A group of 44 right-handed females were recruited, 22 from MZ twin pairs and 22 from 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. A between subject-design with twin siblings was used in order to avoid time effects (for example, decreased neural responses to infant laughing due to habituation) and to minimize preexisting differences (for example, age, child-rearing experiences, and genetics) between the oxytocin and placebo group. Two MZ siblings were excluded from the analyses because of excessive head movement during fMRI scanning (peak displacement = 4 mm). Twin siblings of 10 participants did not participate because of MRI contra-indications or other exclusion criteria, resulting in a sample of 30 participants from twin pairs (8 MZ, and 7 DZ) and 12 participants without twin sibling (4 MZ, and 8 DZ). The mean age of the participants was 28.71 years (SD = 6.93, range, 22–49). The majority of the participants (71.4%) 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 (self-reported) menstrual cycle. During the luteal phase, plasma oxytocin levels are lower (Salonia *et al*, 2005) and more responsive to stimulation such as by nipple stimulation (Leake *et al*, 1984). Therefore, effects of oxytocin nasal administration might be more pronounced during the luteal phase. Approximately 40 min before the start of the fMRI data acquisition subjects took nasal spray containing oxytocin or placebo. Time between oxytocin/placebo administration and data acquisition was similar to previous fMRI studies (Marsh *et al*, 2010; Riem *et al*, 2011a; Rimmele *et al*, 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 seven-point Likert scales how much anger, sadness, pleasantness, empathy, happiness, warmth, and calmness they felt. In addition, after fMRI scanning participants rated how healthy the infant laughter sounded, and how much warmth and affection they felt while listening to the laughing sounds. Furthermore, participants rated whether they felt irritated while listening to the control stimuli on five-point Likert scale (one = not irritated, five = irritated).

Experimental Paradigm

Participants listened to intensity-matched infant crying and infant laughter sounds with a duration of 6 s (samples 261 and 110 of the International Affective Digitized Sounds system, Bradley and Lang, 1999). These infant sounds have been used in a previous fMRI study (Seifritz *et al*, 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 recognizable qualities. The infant sounds and control sounds were presented in eight cycles, each cycle consisting of four sounds (cry, cry-control, laughter, laughter-control). The order of presentation of sounds within each cycle was random; the intertrial-interval was 6 s. In this study we focus only on neural responses to infant laughter. Elsewhere we report on the functional activation during the perception of (a different set of) infant crying sounds (Riem *et al*, 2011a).

Oxytocin *vs* Placebo

One sibling from each twin pair was randomly assigned to the oxytocin condition and the other sibling to the placebo condition, resulting in a group of 22 participants who were administered oxytocin and a group of 20 participants who were administered a placebo. Participants without a twin sibling were also randomly assigned to the oxytocin and placebo condition. Because no twin pair was assigned to either the experimental or the placebo condition, data concerning the effects of the experimental administration of oxytocin were statistically independent. The use of twins randomized across conditions enhanced comparability of the groups in areas other than the experimental manipulation. Approximately 40 min before the start of the fMRI data acquisition subjects took six puffs of nasal spray containing 4 IU/puff of oxytocin (24 IU total) or six puffs of a placebo-spray (NaCl solution) under supervision of the experimenter. Drug administration was double-blind. Menstrual phase and use of oral contraceptives were balanced across the placebo and oxytocin group: 11 participants in the oxytocin and 11 participants in the placebo group were in the luteal phase, whereas 8 participants in the oxytocin group and 9 participants in the placebo group were in the follicular phase. In all, 14 participants in the oxytocin group and 16 participants in the placebo group used oral contraceptives, whereas 8 participants in the oxytocin group and 4 participants in the placebo group did not use oral contraceptives.

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 0.875 × 0.875 × 1.2 mm). In addition, a high-resolution EPI scan was obtained (for registration purposes) (TR = 2.2 s; TE = 30 ms, flip angle = 80°, 84 slices, voxelsize 1.96 × 1.96 × 2.00 mm). For fMRI, a total of 185 T2*-weighted whole-brain EPIs were acquired (TR = 2.2 s; TE = 30 ms, flip angle = 80°, 38 transverse slices, voxelsize 2.75 × 2.75 × 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 FSL version 5.98 (FMRIB's Software Library, www.FMRIb.ox.ac.uk/fsl, (Smith *et al*, 2004)). The following pre-statistics processing was applied: motion correction (Jenkinson *et al*, 2002), non-brain removal (Smith, 2002), spatial smoothing using a Gaussian kernel of full-width-at-half-maximum 8.0 mm, and high-pass temporal filtering (highpass filter cutoff = 100.0 s). 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; Jenkinson and Smith, 2001).

In native space, functional activation was examined using general linear model analysis. Each sound (cry, cry-control, laughter, laughter-control) 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 eight regressors. We assessed the contrast laugh > laugh-control

in order to identify regions involved in the perception of infant laughing.

Second, we examined psychophysiological interactions (PPI), that is, condition-dependent changes in the covariation of the response between a seed region and other brain regions (Friston *et al*, 1997). We used the left and right amygdala as seed regions because we were primarily interested in the modulation effects of oxytocin on functional connectivity with the amygdala. We extracted the mean time series for each participant from the left and the right amygdala, defined using the Harvard–Oxford subcortical atlas. These time series were then used as a physiological regressor in the model. We applied two separate models: one to analyze left amygdala connectivity, and one to study right amygdala connectivity. A contrast between laughter and laughter-control (laugh > laugh-control) was created and used as psychological regressor. This regressor was convolved with a double gamma hemodynamic response function and its temporal derivative was added to the model. Furthermore, the cry sound and the cry-control sound were included in the model as two separate regressors, both convolved with a double gamma hemodynamic response function. The temporal derivatives of these two regressors were also added to the model. Finally, the interaction between the psychological regressor and the time series from the left or right amygdala was modeled, giving eight regressors. We assessed the positive and negative contrast of the interaction in order to examine condition-dependent changes in functional connectivity.

All first-level contrast images (laughter > control and PPI) and the corresponding variance images were transformed to standard space and submitted to second-level mixed-effects group whole brain analyses. For functional activation and PPI analysis, 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 *vs* placebo group comparison (oxytocin > placebo and oxytocin < placebo). We included age, 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 in the functional activation and PPI analysis. The statistical images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < 0.05$ (Worsley, 2001).

In addition to the whole brain analyses, ROI analyses were performed in FSL to investigate changes in activation of *a priori* specified regions. For the perception of infant vocalizations these regions are the amygdala, ventral striatum/nucleus accumbens, IFG, and the insula (Bos *et al*, 2011; Riem *et al*, 2011a). These were defined using the Harvard–Oxford (sub)cortical atlas (http://www.fmrib.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, but correcting only for the size of ROI volumes. For PPI, ROIs were the anterior cingulate and the OFC, again defined with the Harvard–Oxford cortical atlas. ROI analyses were only conducted when these regions were not significantly activated in the whole brain analysis. The selection of these ROIs was based on a neural model for the effects of neuropeptides on brain connectivity (Bos *et al*, 2011). The amygdala is strongly connected to the medial and posterior regions of the orbitofrontal and the rostral and caudal regions of the ACC, and it has been suggested that oxytocin shifts neural output towards these brain regions by modulating amygdala activity (Amaral and Price, 1984; Bos *et al*, 2011; Carmichael and Price, 1995; Kringelbach and Rolls, 2004). Mean *Z*-values for significantly activated regions were calculated using Featquery (http://www.fmrib.ox.ac.uk/fsl/feat5/featquery.html) for visualization purposes in figures.

RESULTS

To examine whether oxytocin affected neural responses to infant laughter we contrasted the oxytocin group with the placebo group ($\text{oxytocin}^{\text{laugh}>\text{control}} > \text{placebo}^{\text{laugh}>\text{control}}$ and $\text{oxytocin}^{\text{laugh}>\text{control}} < \text{placebo}^{\text{laugh}>\text{control}}$). There were no significant group differences in the whole brain analysis. ROI analysis showed that, compared with the placebo group, participants who received oxytocin showed reduced activation in the amygdala when they listened to infant laughter compared with control sounds. There was one significant cluster in the left amygdala and one significant cluster in the right amygdala (cluster 1: size = 54, peak $Z = 2.79$, MNI coordinates *x*, *y*, *z* (mm) = −22, −10, −16, cluster 2: size = 22, peak $Z = 2.87$, MNI coordinates *x*, *y*, *z* (mm) = 24, −4, −24) (Figure 1). There were no significant effects of oxytocin in the other regions of interest.

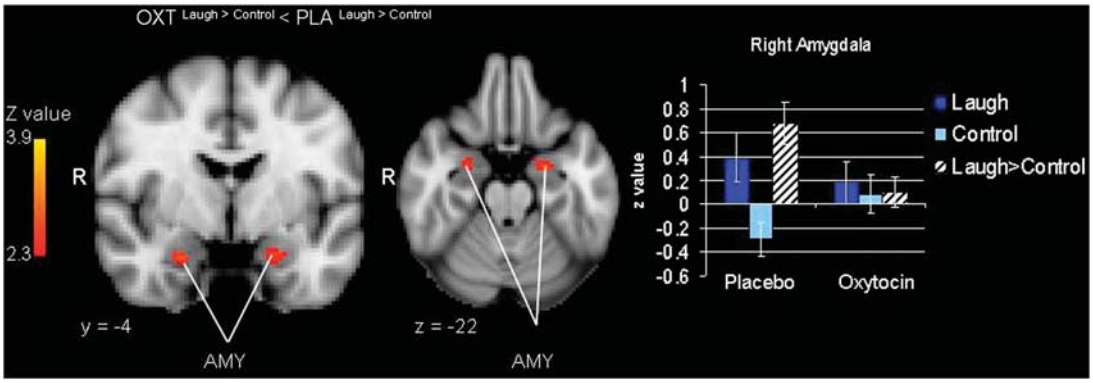

Figure 1 Oxytocin effect on bilateral amygdala (AMY) activation and mean *Z*-values and SEs of right amygdala activation during laugh, laugh-control, and laugh > control in the oxytocin and placebo group. ROI analysis, $p < 0.05$, corrected by cluster threshold ($Z > 2.3$).

In the whole brain analysis of functional activation the contrast of infant laughter *vs* control sound revealed two large clusters of activation in the placebo group with peak voxels in the superior temporal gyri (Cluster 1: size = 10 831 voxels, peak $Z = 6.44$, MNI coordinates x, y, z (mm) = 56, −14, −4, Cluster 2: size = 7295 voxels, peak $Z = 6.30$, MNI coordinates x, y, z (mm) = −58, −12, 0, see Table 1 for an overview of statistics of the local maxima within these clusters). The pattern of activation included the bilateral temporal poles, the bilateral superior temporal gyrus, the bilateral OFC, the bilateral inferior and superior frontal gyrus, the bilateral amygdala, the brainstem, and the right putamen (see top panel Figure 2 for functional activation in the placebo group and lower panel Figure 2 for functional activation in the oxytocin group). ROI analyses indicated that there was no significant activation in the ventral striatum or in the insula during infant laughter compared with control sounds.

In the next step we performed PPI analyses to examine whether oxytocin affected functional connectivity with the amygdala when participants listened to infant laughter compared with control sounds. The whole brain analysis revealed that oxytocin significantly enhanced connectivity between the right amygdala and the left OFC, the bilateral hippocampus, the left precuneus, the right angular gyrus, and the right middle temporal gyrus during infant laughter compared with the control sound (see Table 2 and Figure 3). ROI analyses showed that functional connectivity between the bilateral amygdala and the caudal anterior cingulate was also enhanced by oxytocin during the exposure to infant laughter compared with control sounds (see Figure 3 and Table 2 for an overview of functional connectivity in the oxytocin and placebo group). The average laugh > control

Table 1 MNI Coordinates and *Z*-max Values for Local Maxima Within the Significantly Activated Clusters During Exposure to Infant Laughter Compared with Control Sound in the Placebo Group

Cluster	Region	*Z*	MNI coordinates		
			x	*y*	*z*
2	R superior temporal gyrus	6.44	56	−14	−4
2	R superior temporal gyrus	5.45	66	−24	6
2	R superior temporal gyrus	5.42	50	−4	−18
2	R middle temporal gyrus	4.92	50	−12	−16
2	R middle temporal gyrus	4.55	62	−46	12
2	R precentral gyrus	4.41	60	−2	46
1	L superior temporal gyrus	6.30	−58	−12	0
1	L superior temporal gyrus	6.12	−62	−24	4
1	L planum temporale	5.68	−50	−34	8
1	L planum temporale	5.49	−48	−32	4
1	L superior temporal gyrus	4.88	−66	−38	8
1	L supramarginal gyrus	4.32	−64	−42	18

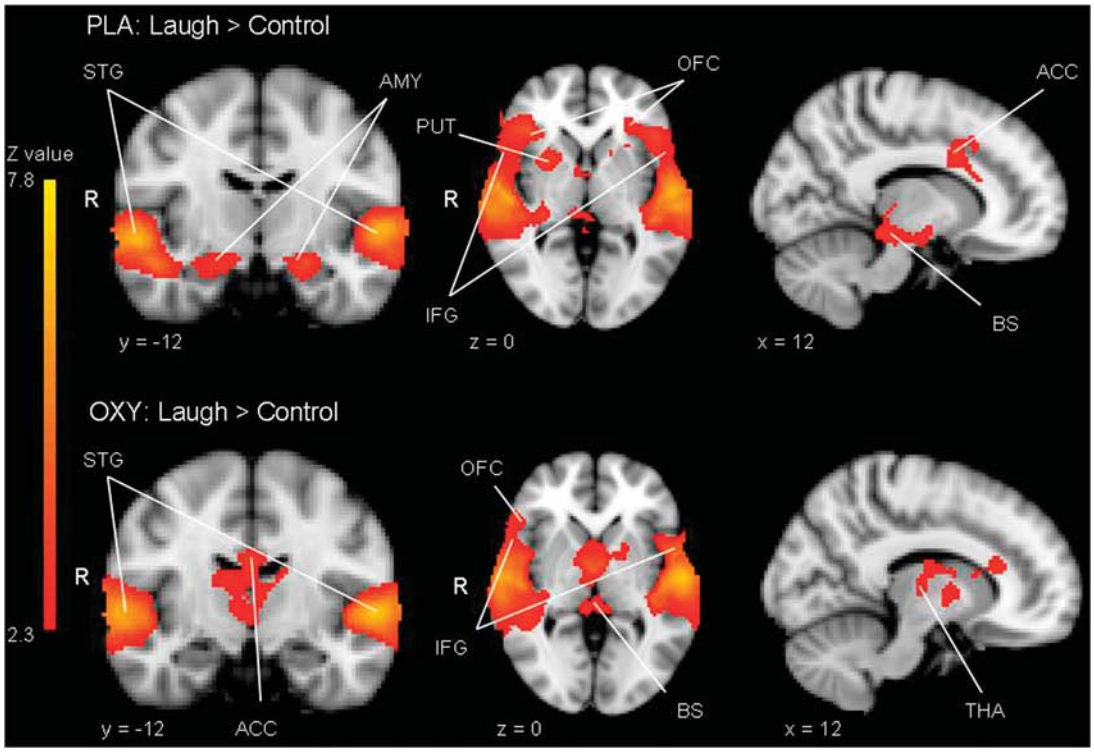

Figure 2 Top panel: significant activation in bilateral temporal poles, the bilateral superior temporal gyrus (STG), the bilateral OFC, the bilateral inferior and superior frontal gyrus (IFG), the bilateral amygdala (AMY), the brainstem (BS), the ACC, and the right putamen (PUT) for the contrast laugh > control in the placebo group. Lower panel: significant activation in bilateral temporal poles, the bilateral superior temporal gyrus, the right OFC, the bilateral IFG, the brainstem, the bilateral thalamus (THA), and the anterior cingulate for the contrast laugh > control in the oxytocin group. Statistical images were thresholded with clusters determined by $Z > 2.3$ and a cluster-corrected significance threshold of $p < 0.05$.

Table 2 Overview of Functional Connectivity During Infant Laughter Compared with Control Sound: MNI Coordinates, Cluster Size, and *Z*-max Values for Significant Clusters of Functional Connectivity

Seed region	Experimental effect	Functional connectivity	MNI coordinates			Cluster size	Peak *Z*
			x	y	z		
R amygdala	$PLA^{laugh<control}$	R intracalcarine cortex	6	−68	16	237	2.95
	$OXY^{laugh>control}$	R brainstem	4	−6	−20	479	3.38
		L orbitofrontal cortex	−46	18	−12	436	3.28
		R supramarginal gyrus	52	−40	34	210	3.30
	$Oxy^{laugh<control}$	R occipital pole	32	−94	−10	398	3.35
	$OXY^{laugh>control} > PLA^{laugh>control}$	L hippocampus	−16	−14	−18	549	3.13
		L precuneus	−16	−44	42	266	3.16
		R middle temporal gyrus	52	−16	−14	233	3.51
		R parahippocampal gyrus	30	−26	−12	201	3.37
		L orbitofrontal cortex	−44	18	−12	185	3.32
		L angular gyrus	−62	−60	26	184	3.24
		L anterior cingulate	−6	10	38	116	3.33[a]
	$OXY^{laugh>control} < PLA^{laugh>control}$	R lateral occipital cortex	18	−86	20	177	3.15
L amygdala	$PLA^{laugh<control}$	R orbitofrontal cortex	34	32	−8	101	3.46[a]
	$OXY^{laugh>control}$	L anterior cingulate	−8	12	36	120	3.33[a]
	$OXY^{laugh<control}$	R middle temporal gyrus	66	−56	−4	491	3.02
		R occipital pole	24	−90	2	358	3.42
		R inferior temporal gyrus	58	−36	−18	233	3.23
	$OXY^{laugh>Control} > PLA^{laugh>control}$	L anterior cingulate	−8	10	38	172	3.70[a]
	$OXY^{laugh>control} < PLA^{laugh>control}$	R lateral occipital cortex	20	−86	18	705	3.32

$p<0.05$, corrected by whole brain cluster threshold ($Z>2.3$). Age, use of oral contraceptives, and menstrual cycle included as confound regressors in the model.
[a]Region of interest analysis, $p<0.05$, corrected by cluster threshold ($Z>2.3$).

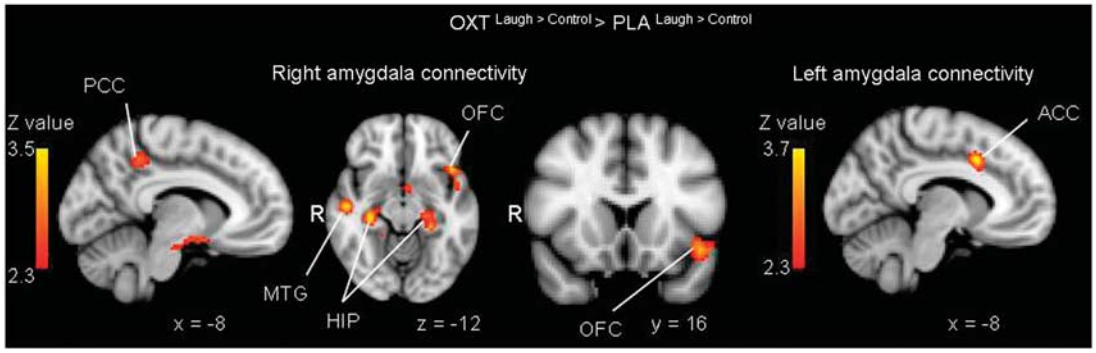

Figure 3 Left panel: oxytocin induced stronger functional connectivity between the right amygdala and the hippocampus (HIP), precuneus (PCC), OFC, and middle temporal gyrus (MTG) during the perception of infant laughter compared with control sound. Right panel: oxytocin also enhanced functional connectivity between the left amygdala and the ACC during the perception of infant laughter compared with control sound. Statistical images were thresholded with clusters determined by $Z>2.3$ and a cluster-corrected significance threshold of $p<0.05$.

connectivity change (or PPI) in the ACC in the oxytocin group was positive, but not significant (peak voxel oxytocin > placebo comparison *x*, *y*, *z* (mm) = −6, 10, 38, $Z=2.30$), whereas it is significantly increased as compared with the placebo PPI (peak voxel oxytocin > placebo comparison *x*, *y*, *z* (mm) = −6, 10, 38, $Z=-2.56$). Thus, there was a significant group difference although the PPI was not significant in the oxytocin group. We performed additional analyses examining whether left amygdala connectivity with the ACC was significantly different from right amygdala connectivity with the ACC. There was no significant difference ($F(1,40)=0.19$, $p=0.89$) and no significant hemisphere × treatment group (oxytocin *vs* placebo) interaction ($F(1,40)=1.07$, $p=0.31$). In sum, oxytocin decreased amygdala activation relative to the placebo condition during exposure to infant laughter and

increased functional coupling between the amygdala and regions implicated in the perception and regulation of emotional cues.

Independent-sample *t*-tests were used to examine the subjective rating of the laughing and control sounds. Participants who received oxytocin experienced more warm feelings ($M = 6.14$, $SD = 1.11$) when listening to the laughing sounds compared with participants in the placebo group ($M = 5.25$, $SD = 1.62$), $t\ (39) = 2.07$, $p < 0.05$ (not significant after Bonferroni correction for multiple comparisons). However, there was no significant group difference in reported affection, $t\ (39) = 1.14$, $p = 0.26$ and no significant group difference in how healthy the participants rated the laughing sound $t\ (39) = 0.49$, $p = 0.63$. Participants did not feel much irritation while listening to the control sounds ($M = 2.05$, $SD = 1.32$) and there was no significant group difference between the oxytocin and placebo group $t\ (39) = 0.94$, $p = 0.35$. To control for nonspecific effects of oxytocin on self-reported mood, we conducted repeated-measures analyses of variance 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 × group interaction effects on any of the mood items: anger $F\ (1,40) = 0.07$, $p = 0.80$, sadness $F\ (1,40) = 0.22$, $p = 0.64$, pleasantness $F\ (1,40) = 0.15$, $p = 0.90$, empathy $F\ (1,40) = 0.00$, $p = 0.99$, happiness $F\ (1,40) = 2.69$, $p = 0.11$, warm feeling $F\ (1,40) = 0.36$, $p = 0.55$, and calmness $F\ (1,40) = 0.01$, $p = 0.91$.

DISCUSSION

Our study demonstrates that oxytocin reduces amygdala activation relative to the placebo condition when individuals listen to infant laughter compared with control sounds. Oxytocin has stress-reducing effects in lactating mothers (Heinrichs *et al*, 2001, 2003), which might enable them to be more sensitive to infant cues. Recent evidence indicates that inhibition of the amygdala, a brain region involved in anxiety and emotional arousal (LeDoux, 2000; Morrison and Salzman, 2010), might be the underlying neural mechanism of these calming oxytocin effects (Gamer *et al*, 2010; Kirsch *et al*, 2005; Riem *et al*, 2011a). In addition, we found that oxytocin increased functional connectivity between the amygdala and neural reward regions, the OFC and the caudal ACC (Berridge and Kringelbach, 2008; Haber and Knutson, 2010; Kringelbach, 2005). Our findings provide empirical support for the neural model on the effects of neuropeptides on brain connectivity proposed by Bos *et al* (2011). Increased functional connectivity between the OFC, ACC, and amygdala may promote mother–infant attachment by enhancing cognitive control over negative emotionality and at the same time increasing the incentive salience of infant laughter (Berridge, 2007; Berridge and Kringelbach, 2008; Bos *et al*, 2011).

Infant laughter is easily released during playful interactions with their parents, which are highly rewarding for both parent and infant (Feldman, 2003; Sroufe and Waters, 1976). Previous studies on oxytocin and parenting showed that oxytocin promotes such playful interactions. For example, Feldman *et al* (2010) showed that fathers with high levels of oxytocin displayed more stimulatory contact during play with their child. In a complementary study, Naber *et al* (2010) found that intranasally administered oxytocin enhances paternal playful interaction. The current study is the first to examine the neural mechanism underlying the effect of oxytocin on the perception of playful infant vocalizations. Future studies should examine the neural mechanisms underlying the rewarding effects of playful parent–infant interactions in a more real-life situation, for example, by studying neural activation and connectivity during the presentation of video fragments of parent–infant playful interactions.

Furthermore, we found that oxytocin increased functional connectivity between the amygdala and the hippocampus, middle temporal gyrus, and precuneus during infant laughter compared with control sound. Although in previous studies the hippocampus has not been directly implicated in parental care, it is known to be affected by parenting experiences, possibly by the altered parental hormonal levels after child birth (Leuner *et al*, 2010). Several studies indicate that amygdala-hippocampus interactions are crucial for emotional memory (Schaefer and Gray, 2007), an important factor in parenting that can be enhanced by oxytocin (Bartz *et al*, 2010b; Guastella *et al*, 2008; Rimmele *et al*, 2009). The middle temporal gyrus and precuneus are part of a network involved in the perception of speech and prosody (Leitman *et al*, 2010; Price, 2010; Turken and Dronkers, 2011) and in aspects of social cognition such as mentalizing and emotion understanding (Atique *et al*, 2011; Leitman *et al*, 2010). Pessoa (2008) suggested that the high degree of connectivity between the amygdala and other regions involved in emotional processing might serve the integration of emotion and cognition, and the evaluation of sensory information. Oxytocin might facilitate evaluation of and responding to emotional stimuli by modulating neural connectivity (Pessoa, 2008; Salzman and Fusi, 2010). This is supported by a study of Gamer *et al* (2010), who showed that oxytocin increased functional coupling between the amygdala and the superior colliculus as well as gaze changes towards the eyes of an emotional stranger in order to facilitate the classification of the emotion.

In the placebo group, we found an increase in activation in the temporal poles, the OFC, the inferior and superior frontal gyrus, the amygdala, the brainstem, and the putamen in response to infant laughter compared with control sounds. Previous fMRI studies on the perception of infant stimuli also reported activation in these regions. For example, Strathearn *et al* (2008) presented mothers with images of their own happy infants and found significant activation in the putamen, a subregion of the ventral striatum, which is important for reward processing. In a previous study on infant crying we also found significant activation in the IFG and the temporal poles (Riem *et al*, 2011a), regions that are involved in theory of mind and empathy (Chakrabarti *et al*, 2006; Decety and Jackson, 2004). However, in contrast with our previous study, the insula was not significantly activated during exposure to infant laughter and oxytocin did not modulate activation in this region. Previous studies have shown that the insula is involved in feeling empathy for others, in particular when

observing others in pain (Lamm *et al*, 2011). For example, Lang *et al* (2011) indicated that the insula was significantly more activated when listening to pain expressions compared with positive stimuli such as laughter, which is in line with our respective results for activation during exposure to infant laughter and infant crying.

One limitation of this study is that the use of a between-subjects design implies the risk of preexisting differences between the oxytocin and placebo group that might have influenced the results. However, most of our participants were MZ and DZ twin pairs, perfectly matched on age and global child-rearing experiences and even on genotype in MZ twin pairs. Second, it should be noted that neural responses to infant laughter might be affected by the infant crying sounds that were also presented during the experimental paradigm because the infant laughter-crying contrast might have enhanced the rewarding experience of infant laughter. In addition, the physiological effects induced by intranasally administered oxytocin are not well-understood and might be different from the effects of endogenous oxytocin secretion. Furthermore, functional connectivity using fMRI is a correlation method that does not allow conclusions about the (direction of the) causal relation between the OFC, ACC, and amygdala during exposure to infant laughter. Several studies suggest however that the OFC and ACC regulate negative emotionality by inhibiting the amygdala (Banks *et al*, 2007; Hahn *et al*, 2011; Stein *et al*, 2007; Swain *et al*, 2008). Furthermore, it should be noted that the regions in which we found significant connectivity changes in the oxytocin-placebo comparison did not all have a significant PPI in the oxytocin group. Finally, our findings can only be generalized to women without children. The perception of infant signals is influenced by parental status (Seifritz *et al*, 2003), possibly because of the altered oxytocinergic system after child birth, lactation, and parent–infant contact (Feldman *et al*, 2010). More research is needed to examine oxytocin effects on functional activation and connectivity during infant signals in parents. Intranasal oxytocin effects might be even more pronounced in parents, because of the emotional and biological significance of their own infant's laughing and crying.

Our findings support neural models on functional connectivity between the amygdala, OFC, and ACC proposed by Kringelbach (2005), Bos *et al* (2011), and Meyer-Lindenberg *et al* (2011). Kringelbach *et al* (2008) showed that the medial OFC exhibits a very early and specific pattern of activity to infant cues. Therefore, it has been speculated that the medial OFC might be the neural base for the innate releasing mechanism described by Lorenz (1943) for affection and care of young infants. The OFC might encode rewarding characteristics of infant stimuli such as 'cuteness' that predispose parents to perceive infant stimuli as special and that elicit nurturing. The medial and posterior OFC, ACC, and amygdala have strong reciprocal connections that are important for the effect of the encoded reward value on subsequent behavior, for example, caregiving responses (Kringelbach, 2005). Although the medial OFC and ACC have been suggested to be important hedonic hot spots of the brain (Berridge and Kringelbach, 2008; Kringelbach, 2005; Parsons *et al*, 2010), they are also involved in emotion regulation by their inhibitory influence on the amygdala, especially the supra- and subgenual parts of the ACC (Banks *et al*, 2007; Hahn *et al*, 2011; Stein *et al*, 2007). Bos *et al* (2011) suggested that oxytocin facilitates social bonding by enhancing cognitive control from prefrontal regions to regulate emotionality, as well as by its effects on the experience of reward during social interaction. Our findings are consistent with this model and suggest that oxytocin promotes parent–infant attachment by reducing negative emotional arousal while increasing the incentive salience of infant cues.

In conclusion, this is the first study to show the effects of oxytocin intranasal administration on functional activation and connectivity to infant laughter. We found that oxytocin decreases amygdala activation to infant laughter and increases functional connectivity between the amygdala and the OFC, ACC, and several other brain regions involved in emotional processing. Our results extend previous findings indicating a central role for oxytocin in parent–infant playful interactions and attachment formation (Feldman, 2003; Feldman *et al*, 2007; Naber *et al*, 2010). Increased functional connectivity between the amygdala, ACC, and OFC may stimulate mother–infant bonding by enhancing the regulation of negative emotions and the experience of reward during parent–infant interaction. Thus, oxytocin increases the incentive salience of infant laughter, which might be one of the mechanisms that lead to enhanced sensitive responsiveness to infant cues and playful parent–infant interaction.

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DISCLOSURE

The authors declare no conflict of interest.

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