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Oxytocin Modulates Neural Reactivity to Children's Faces as a Function of Social Salience

Dina Wittfoth-Schardt*[,1,2], Johanna Gründing[1,2], Matthias Wittfoth[2,3], Heinrich Lanfermann[1,2], Markus Heinrichs[4], Gregor Domes[4], Anna Buchheim[5], Harald Gündel[6] and Christiane Waller[6]

[1]Institute of Diagnostic and Interventional Neuroradiology, Hannover Medical School, Hannover, Germany; [2]NICA—NeuroImaging and Clinical Applications Hannover, Hannover, Germany; [3]Clinic of Neurology, Hannover Medical School, Hannover, Germany; [4]Department of Psychology, Laboratory for Biological and Personality Psychology, University of Freiburg, Freiburg, Germany; [5]Department of Psychology, Clinical Psychology, University of Innsbruck, Innsbruck, Austria; [6]Clinic of Psychosomatic Medicine and Psychotherapy, University Clinic Ulm, Ulm, Germany

Oxytocin (OT) enhances social behaviors such as attachment and parental caretaking. Neural correlates of maternal attachment are found in reward-related brain regions, for example, in the globus pallidus (GP). The present work investigates the effects of OT on the neural correlates of parental attachment. Fathers viewed pictures of their own child (oC), a familiar child (fC), and an unfamiliar child (uC) after intranasal application of OT *vs* placebo. OT reduced activation and functional connectivity of the left GP with reward- and attachment-related regions responsive to pictures of the oC and the uC. The present results emphasize the key role of OT in human parental attachment and suggest that OT reduces neural reactivity to social cues as a function of social salience. Our results together with previous findings speak to a selective reduction of neural reactivity to social stimuli, irrespective of their valence. We argue that one major pathway by which OT exerts its positive effects on affiliative and social behaviors is the attenuation of automatic neural responses, which in turn leads to increased approach behaviors and decreased social avoidance.
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INTRODUCTION

The close link between the neuropeptide oxytocin (OT) and affiliative behaviors has been established in a number of studies in both humans (Bartz *et al*, 2011; Buchheim *et al*, 2009; Heinrichs and Domes, 2008; Meyer-Lindenberg *et al*, 2011) and other mammals (McGraw and Young, 2010; Young and Wang, 2004). When OT is intranasally administered in humans, it influences various social behaviors: for example, it increases trust (but not risk behavior) in economic games (Baumgartner *et al*, 2008; Kosfeld *et al*, 2005) and reduces the behavioral and physiological signs of stress during couple conflict (Ditzen *et al*, 2009) or psychosocial stress (Heinrichs *et al*, 2003). Modulations of the central processing of affective stimuli were also related to OT, such as for example the reduction of amygdala activation to face stimuli with negative valence (Domes *et al*, 2007; Kirsch *et al*, 2005; Petrovic and Ingvar, 2002).

*Correspondence: Dr D Wittfoth-Schardt, Institute of Diagnostic and Interventional Neuroradiology, NICA Hannover, Hannover Medical School, Feodor-Lynen-Strasse 35, 30625 Hannover, Germany, Tel: +49 511 532 7292, Fax: +49 511 532 5876,
E-mail: wittfoth-schardt.dina@mh-hannover.de
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Due to its relevance in affiliative behaviors, OT has also received increasing attention with respect to its effects on human parenting behaviors. In fathers, higher plasma OT levels were associated with increased father–infant affect synchrony across the first 6 months of fatherhood (Gordon *et al*, 2010b). Moreover, the level of paternal plasma OT correlated with the degree of stimulatory parenting behaviors such as proprioceptive contact or object presentation (Gordon *et al*, 2010a), and increased with high levels of stimulatory contact with their infant (Feldman *et al*, 2010). In line with this, fathers of children between 1.5 and 5 years of age who received intranasal OT stimulated more explorative behaviors in their children during play (Naber *et al*, 2010).

The effects of OT on complex human social behaviors are not surprising given that OT binding sites are abundant in the brain regions that are involved in reward and attachment, for example, the striatum, the globus pallidus (GP), the medial orbitofrontal cortex (mOFC), and the ventral tegmental area (VTA). Other areas with high OT receptor density include the insula, amygdala, and superior temporal cortex involved in primary affective and emotional processing (Davidson and Irwin, 1999; Loup *et al*, 1991; Panksepp, 2009). In line with these findings, previous research has pinpointed the striatopallidal region, the mOFC, and the medial and lateral temporal cortices as

key regions of attachment, for example, during a mother's perception of her own child (oC) (Bartels and Zeki, 2004; Leibenluft *et al*, 2004; Strathearn *et al*, 2008) or more generally during the processing of the faces of loved ones (Acevedo *et al*, 2011; Bartels and Zeki, 2000; Gundel *et al*, 2003; O'Connor *et al*, 2008).

Despite the well-documented involvement of OT in human parental care, there is to date no study investigating its effects on the neural correlates of parent–child attachment. Furthermore, the cortical network related to the attachment between father and child remains unexplored. The present study is the first to disentangle the neural correlates of paternal attachment, and the effects of intranasal OT on these neural responses by means of functional imaging.

To this end, we first compared the brain activation of fathers while viewing pictures of their oC, a familiar child (fC), and an unfamiliar child (uC). Due to the tight coupling between the neuroendocrine responses involved in attachment and reward (Bartels and Zeki, 2004; Insel, 2010), we hypothesized that the fathers' oC would recruit a set of regions rich in dopamine and/or OT, for example, the striatopallidal region, mOFC, VTA, and hippocampus, similar to previous findings in mothers (Bartels and Zeki, 2004; Leibenluft *et al*, 2004; Strathearn *et al*, 2008). Second, we aimed to elucidate the effects of intranasal OT on the neural network underlying the perception of children's faces. Since OT influences neural and behavioral aspects of attachment (Buchheim *et al*, 2009; Guendel *et al*, 2009; Meinlschmidt and Heim, 2007), we expected that OT would reduce neural activation in frontal and temporal areas, as reported previously for fearful, angry, and happy faces in males (Domes *et al*, 2007; Kirsch *et al*, 2005). Furthermore, we expected OT to modulate neural responses as a function of the amount of attachment in each condition in reward/attachment-related regions (Bartels and Zeki, 2004; Leibenluft *et al*, 2004; Strathearn *et al*, 2008).

MATERIALS AND METHODS

Participants

Twenty-one right-handed healthy biological fathers of at least one kindergarten child (3–6 years) participated in the study. Participants were screened to exclude acute or past neurological, psychiatric or endocrine illness, and use of psychotropic/endocrine medication. Written informed consent was obtained before the experiment, and subjects received a financial reward for their participation. The study protocol was approved by the local ethics committee in accordance with the Declaration of Helsinki. One participant dropped out before completion of the study, and the data of another participant had to be excluded due to scanner artifacts. In total, 19 participants (mean age ($\pm$ SD) 39.3 ± 6.2 years) were included in the final analysis. The mean age of the own children (nine girls) was 55.74 ± 12.27 months. All fathers cohabited with their child and its mother. On average, they spent 33 ± 12.71 h per week with their child and reported very high feelings of closeness with their child (93 ± 7 on a scale from 0 to 100).

Study Design

Each father attended two functional imaging sessions within 2–4 weeks at similar times of day. The double-blind administration of OT and placebo (PL) was counterbalanced across participants in a within-subjects design. Thirty minutes before scanning, 24 IU of OT (Syntocinon; Novartis, Basel, Switzerland) or PL (ingredients equivalent except for the peptide) were intranasally administered in three puffs per nostril with 4 IU each (Bartz *et al*, 2011; Born *et al*, 2002; Domes *et al*, 2007, 2009). Before and after each scanning session, participants filled in questionnaires to assess drug-related changes in mood, alertness, calmness (MDBF Multidimensional Mood Questionnaire (Steyer *et al*, 1997)), or state anxiety (STAI—State-Trait Anxiety Inventory—State version (Laux *et al*, 1981)). Mean scores were subsequently compared across time points (pre-fMRI, post-fMRI) and sessions (OT, PL) to rule out generalized effects of OT on these measures.

At the beginning of the first appointment, fathers filled in a self-report questionnaire regarding the quality of their acquaintance with the fC. On four-point Likert scales they stated how well (not well–very well) and for how long (<6 months to >1 year) they know the fC, how they feel about contact with the fC (pleasant–unpleasant) and how often they spend time with the fC (never–several times/week). After the functional run, fathers also rated how close they felt to each of the three children on a visual analog scale from 0 to 200 mm. Closeness ratings were compared across sessions (OT, PL) and familiarity conditions (oC, fC, and ufC).

During a third visit, 17 fathers completed the Adult Attachment Projective Picture System (AAP) to assess their adult attachment representation (George and West, 2001). Classification of attachment representation was coded by an experienced rater (AB) based on the verbatim narratives (secure $N=9$, insecure $N=8$).

Digital photographs of the father's oC, a fC (a friend of their child's) and a uC were taken within 1–12 weeks before the experiment. Within each set, all three children were of the same gender and age. For the fC, most fathers reported medium (21.1%) or low (63.2%) levels of familiarity, but contact with the fC was rated as neutral (47.4%) or pleasant (52.6%). Most participants knew the fC for >1 year (68.4%) and rarely (52.6%) or never (42.1%) spent time with the fC during play times.

We chose six photographs per condition where the child was looking directly at the camera with a friendly facial expression. The stimuli were matched for luminance and color temperature, and masked with an oval shape to reveal only the face of the child. In cases where the parents agreed, oC and fC stimuli served as uC stimuli for other participants. Each stimulus was presented 10 times over the course of the experiment, amounting to a total of 180 stimuli. Using a rapid event-related design, the stimuli were presented for 2 s on a gray background. We used the same pseudo-randomized order for each participant to avoid more than two consecutive trials of the same condition. Within the pseudo-randomized sequence, the respective stimuli were randomly drawn from each picture set (oC, fC, and ufC). A central fixation was presented for 4 ± 0.7 s after each stimulus as a low-level baseline. Before

each scanning session, participants were instructed to attentively view each picture. Since even low-level cognitive tasks such as performing a gender discrimination (Mitchell *et al*, 2007; Pessoa *et al*, 2005) or rating facial expressions (Drabant *et al*, 2009; Hariri *et al*, 2000) are known to reduce emotional responses, we deliberately chose a passive viewing instruction to limit the amount of cognitive processing and allow the initial emotional and attachment-related responses to each of the children to unfold naturally.

Functional Image Acquisition and Analyses

Functional imaging data were acquired with a 12-array head coil on a 1.5-T Siemens Avanto (Siemens, Erlangen, Germany) using a T2*-weighted echo-planar imaging sequence. We acquired 35 interleaved 3 mm slices with a 25% gap (in-plane resolution $3 \times 3 \times 3.75\,mm^3$, FA $= 90^\circ$, FOV $= 192$ mm, 64×64 matrix) axially along the AC–PC plane at a TR/TE of 2100/30 ms known to produce good quality functional images by increasing the sampling time points and reducing susceptibility artifacts (Deichmann *et al*, 2002). The Siemens iPat (integrated parallel acquisition technique) mode (Sodickson and Manning, 1997) was used together with GRAPPA (generalized autocalibrating partially parallel acquisition) with an acceleration factor of 2 (Griswold *et al*, 2002).

Functional data were analyzed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm) after the first two volumes of each session were discarded to allow for a stable T1 saturation. The images were realigned to the first volume within each session and unwarped to remove variance induced by interactions of movement and field inhomogeneity. The second session was coregistered with the first session to correct for inter-session differences in head position. All volumes were normalized to the standard EPI template and smoothed with a 9-mm isotopic Gaussian kernel.

In the first-level, fixed-effects model for each participant, regressors were created for the experimental conditions, the fixation, and the instruction in each treatment session. Boxcar regressors modeled the actual length of each event in seconds and were convolved with the canonical hemodynamic response function implemented in SPM8. A first order autoregressive model (AR1) corrected for serial autocorrelations and low-frequency signals were removed using a high-pass filter (128 s). Predetermined effects of each experimental condition *vs* fixation were calculated, resulting in six *t*-statistics for each subject (OT [oC > fix], OT [fC > fix], OT [uC > fix], PL [oC > fix], PL [fC > fix], PL [uC > fix]).

In a second-level random effects group analysis, the individual condition effects were compared using a within-subject 2×3 ANOVA with factors treatment (OT, PL) and familiarity (oC, fC, and ufC). Within this ANOVA, we first compared familiarity conditions only in the PL session to elucidate the effects of the familiarity conditions on brain activation in fathers under native conditions. Subsequently, the effect of OT was assessed across sessions and between familiarity conditions. The intensity threshold for the whole-brain analyses was set to $p < 0.001$ (uncorrected) with an extent cluster threshold correction that was calculated by the SPM8 software ($k \geqslant 7$ voxels). This method refers to the estimated smoothness of the images. After determining of the number of resels, the expected Euler characteristic is calculated. This is used to provide the correct threshold (number of voxels) that is required to control for false positive results.

Additional region of interest (ROI) analyses were performed at a corrected $p_{FWE} < 0.05$ using anatomical masks based on the AAL database within the WFU-PickAtlas (Maldjian *et al*, 2003, 2004; Tzourio-Mazoyer *et al*, 2002) for the GP and the hippocampus, which showed both a familiarity effect under PL and a treatment effect after intranasal OT on the whole brain level.

Activated clusters from the whole brain analysis are reported in MNI space and labeled using the AAL database within the WFU-Pickatlas (Maldjian *et al*, 2003, 2004; Tzourio-Mazoyer *et al*, 2002). In cases where we found significant results also within the anatomical ROI, the reported activation corresponds to the results from this analysis.

As the left GP was the only region where we found familiarity effects under PL and the interaction of treatment and familiarity both on the whole brain level and in the more stringent ROI analysis, we conducted further analyses specifically in this region.

For the 17 fathers for which attachment representations were available, mean contrast estimates from the left GP cluster were compared between attachment representation groups in a repeated-measures ANOVA with factors attachment representation (secure, insecure), treatment (OT, PL) and familiarity (oC, fC, and uC) at a threshold of $p < 0.05$.

In addition, we also conducted psycho-physiological interaction analyses (PPI) to investigate functional connectivity with the left GP, which showed an interaction of treatment and familiarity in the categorical analysis. From every subject, we extracted the first eigenvariate from the seed region in the left pallidum ROI and calculated two first-level models containing the left GP time course as the physiological variable. The first model investigated the contrast oC > fC under OT and PL as the psychological variable, while the second model investigated the contrast uC > fC. The interaction term between the physiological variable and the respective psychological variable was entered into each model, and the resulting contrast weights for the two treatment sessions were then fed into two separate random effects analyses to compare left GP coupling between OT and PL for the oC (OT [oC > fC] and PL [oC > fC]) and the uC (OT [uC > fC] and PL [uC > fC]) at an intensity threshold of $p < 0.005$ uncorrected (uncorrected) with an extent cluster threshold correction as calculated by SPM8 ($k \geqslant 8$ voxels).

RESULTS

Drug Effects on Behavioral Data

We observed no effects of OT administration on mood, alertness, calmness, or state anxiety (interaction treatment × time point: mood $p = 0.54$, alertness $p = 0.09$, calmness $p = 0.68$, state anxiety $p = 0.71$). VAS closeness ratings in the three familiarity conditions were highest for the oC, intermediate for the fC, and low for the ufC (familiarity $F[2,36] = 169.38$, $p < 0.001$). However, closeness ratings were unaffected by OT (treatment × familiarity

$p = 0.25$). Mean mood and anxiety scores and closeness ratings are reported in Supplementary Tables S1 and S2.

Effects of Familiarity Under PL

In response to pictures of their oC compared with fC pictures (PL [oC > fC]), fathers showed activations in the left GP, the left hippocampus, the right mOFC, as well as in the bilateral inferior frontal gyrus/anterior insula (Figure 1; Supplementary Table S3). oC pictures also activated the right GP, the left VTA, the left mOFC, and the left inferior frontal gyrus/anterior insula compared with pictures of an uC (PL [oC > uC]; Figure 1; Supplementary Table S3). Comparing pictures of the uC with fC pictures (PL [uC > fC]), we observed activation in the left hippocampus, the left posterior insula, and the left superior temporal gyrus (Figure 1; Supplementary Table S3). No activated voxels were found comparing fC pictures with oC pictures (PL [fC > oC]) or pictures of a uC (PL [fC > uC]), or comparing pictures of the uC with oC pictures (PL [uC > oC]).

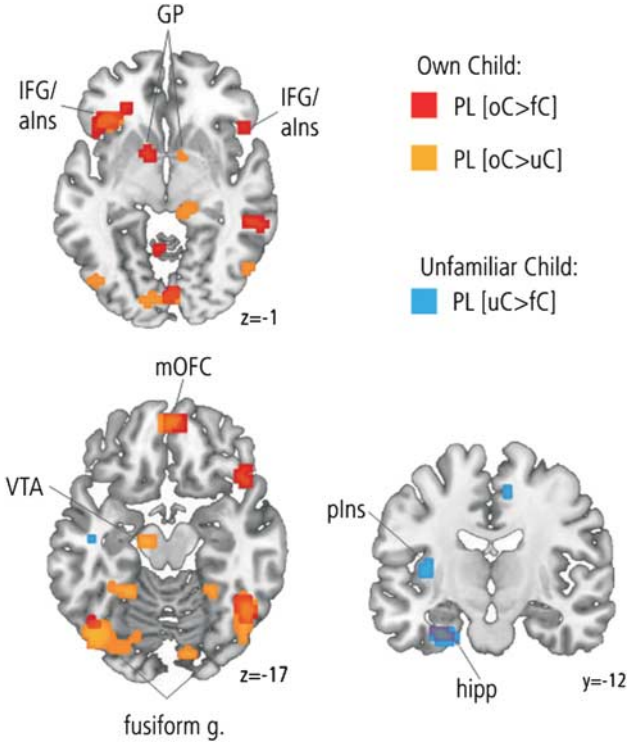

Figure 1 Activation in response to own child pictures. Increased activations in response to oC > fC pictures under PL (red) were observed in the left GP, the mOFC, the left hippocampus, and the bilateral inferior frontal gyrus/anterior insula and fusiform gyrus. In response to oC > uC pictures under PL (yellow), a similar pattern of activations was observed including the right GP, mOFC, bilateral inferior frontal gyrus/anterior insula and fusiform gyrus, as well as the left VTA. The comparison of uC > fC pictures under PL (blue) revealed activations in the left posterior insula and the left hippocampus. Activated clusters are significant at $p_{uncorr} < 0.001$ with a cluster extent threshold of $k \geqslant 7$ voxels. alns, anterior insula; fC, familiar child; hipp, hippocampus; IFG, inferior frontal gyrus; mOFC, medial orbitofrontal cortex; oC, own child; PL, placebo; pIns, posterior insula; uC, unfamiliar child; VTA, ventral tegmental area.

Interaction of Familiarity and Treatment

OT modulated activations in the GP and in the caudate when fathers viewed pictures of their oC. Moreover, OT modulated activation in the GP, medial and lateral temporal cortices when fathers viewed pictures of a uC. More precisely, we found a signal reduction to oC pictures compared with fC pictures under OT in the left GP (PL [oC > fC] > OT [oC > fC]). For oC pictures compared with pictures of a uC OT increased activation in the left caudate body (OT [oC > uC] > PL [oC > uC]). For pictures of a uC compared with fC pictures, OT decreased neural response in the left GP, the left hippocampus, and the left superior and middle temporal gyri (PL [uC > fC] > OT [uC > fC]). All activated clusters for the above-mentioned contrasts are reported in Table 1.

Region of Interest Analyses

As stated above, the amount of neural activation in the PL session varied as a function of familiarity.

In contrast to the whole brain analysis, no voxels were activated in the comparison of oC with uC pictures in the hippocampus ROI for the PL session. When pictures of the uC were contrasted with pictures of the fC, two voxels in the left hippocampus (−24 −9 −27, $p_{FWE} = 0.001$) survived threshold.

In response to oC pictures, the left GP showed increased activation compared with pictures of the fC (−12 6 −6, $k = 7$, $p_{FWE} = 0.008$), while the right GP showed increased activation in comparison with pictures of a uC (12 3 −3, $k = 1$, $p_{FWE} = 0.033$).

Investigating the interaction of treatment and familiarity within the hippocampus ROI, we found one voxel in the left hippocampus, which showed a reduced difference between the unfamiliar and the fC under OT compared with PL (−24 −9 −27, $p_{FWE} = 0.021$).

In the left GP, the intranasal application of OT reduced activation in response to oC pictures (−12 6 0, $k = 5$, $p_{FWE} = 0.017$) and to pictures of a uC (−12 3 3, $k = 6$, $p_{FWE} = 0.006$). No modulatory effects of OT were observed in response to fC pictures in the left GP, and no interaction of familiarity and treatment was observed in the right GP ROI. Mean signal change values within the entire left GP region of interest are given in Figure 2 for the three familiarity conditions in the OT and PL sessions, respectively.

For the 17 fathers who completed the AAP, the extracted mean contrast estimates from the left GP were additionally compared across attachment representation groups (secure *vs* insecure). In this analysis, we found that attachment representation did not explain the interaction of familiarity and treatment in the left GP (attachment representation × treatment × familiarity $p = 0.88$).

OT Modulation of Left GP Functional Connectivity

To elucidate the interactive effects of OT and familiarity, we compared functional connectivity of the left GP seed region for the oC and the uC in the OT and PL sessions, since it was the only region which reliably showed both an effect of familiarity under PL and an interaction of treatment and

Table 1 Interaction Effects of Familiarity and Treatment

Region	Right/left	Brodmann area	Cluster size (voxels)	*Z*-score	*p*-value (uncorr.)	MNI-coordinates		
						x	y	z
Neural activation: familiarity × treatment								
Decrease by oxytocin: own child > familiar child (PL [oC>fC] > OT [oC>fC])								
Globus pallidus*	L		8	3.56	<0.001	−12	6	0
Increase by oxytocin: own child > unfamiliar child (OT [oC>uC] > PL [oC>uC])								
Caudate body	L		8	3.48	<0.001	−15	6	21
Decrease by oxytocin: unfamiliar child > familiar child (PL [uC>fC] > OT [uC>fC])								
Globus pallidus*	L		17	3.85	<0.001	−12	3	3
Precentral gyrus	L	6	8	4.45	<0.001	−63	3	18
Hippocampus*	L	35	1	3.58	<0.05	−24	−9	−27
Middle temporal gyrus	L	22	7	3.60	<0.001	−45	3	−21
	R	21	10	3.97	<0.001	63	−9	−24
Superior temporal gyrus	L	21	10	3.59	<0.001	−45	−18	−12
Supramarginal gyrus	L	40	7	3.54	<0.001	−45	−33	33

The whole-brain analysis was thresholded at an uncorrected $p<0.001$ with a cluster extent threshold of $k=7$ voxels. *Significant at $p<0.05$ corrected for multiple comparisons within the anatomical ROI. fC, familiar child; oC, own child; OT, oxytocin; PL, placebo; uC, unfamiliar child.

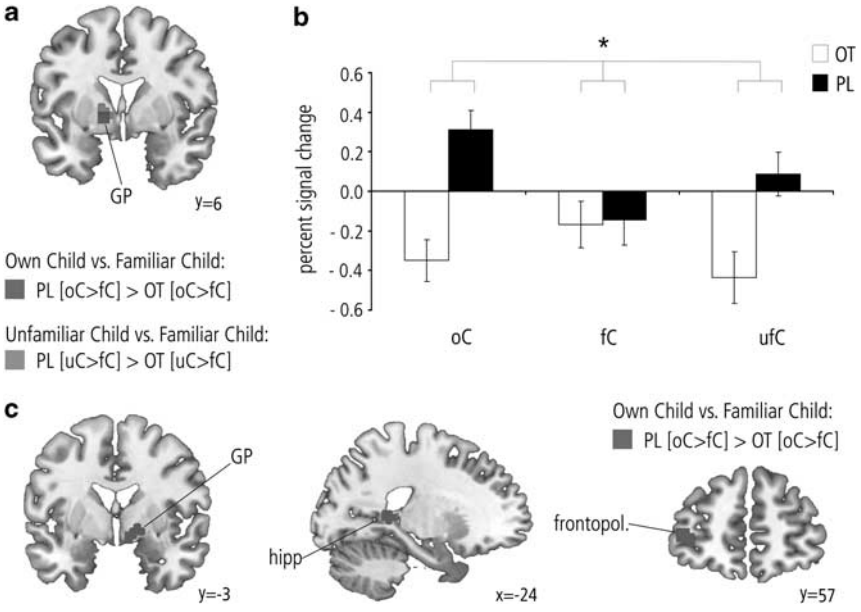

Figure 2 Oxytocin modulates contrast functional activation and connectivity to own and unfamiliar child pictures. (a) Modulation of neural activation in the left GP under OT ($p_{FWE}<0.05$) for the oC>fC (red) and for the contrast uC>fC (blue). (b) Mean signal change values (±SEM) from the left GP show that OT reduced neural responses to the oC and the ufC, while no changes were observed for the fC. (c) OT also reduced functional connectivity between the left GP seed region and the right GP, the left hippocampus and the left frontopolar cortex for the contrast oC>fC. Activated clusters are significant at $p_{uncorr}<0.001$ with a cluster extent threshold of $k\geqslant 8$ voxels. fC, familiar child; frontopol, frontopolar cortex; GP, globus pallidus; oC, own child; OT, oxytocin; SEM, standard error of mean; uC, unfamiliar child. The color reproduction of this figure is available on the *Neuropyschopharmacology* journal online.

familiarity for oC and uC pictures in the whole brain and in the ROI analyses.

For oC pictures compared with fC pictures (PL [oC>fC]>OT [oC>fC]) we found that OT decreased functional connectivity between the left GP and the right GP, the left hippocampus, and the left frontopolar cortex (Figure 2; Table 2). Conversely, OT did not modulate left GP functional connectivity for pictures of a uC compared

Table 2 Regions Showing Lower Connectivity with the Left GP for the Own *vs* the familiar Child (oC > fC) Under OT

Region	Right/left	Brodmann area	Cluster size (voxels)	*Z*-score	*p*-value (uncorr.)	MNI-coordinates		
						x	y	z
Left GP functional connectivity: familiarity × treatment								
Decrease by oxytocin: own child > familiar child (PL [oC > fC] > OT [oC > fC])								
Globus pallidus	R		42	3.66	< 0.001	15	−3	−6
				3.20	0.001	6	3	−12
Middle frontal gyrus	L	10	29	3.56	< 0.001	−39	57	3
Hippocampus	L		26	3.71	< 0.001	−24	−42	6
Superior parietal lobule	R	5/7	75	3.81	< 0.001	30	−63	63

The whole-brain analysis was thresholded at an uncorrected $p < 0.001$ with a cluster extent threshold of $k = 8$ voxels. fC, familiar child; GP, globus pallidus; oC, own child; OT, oxytocin; PL, placebo; uC, unfamiliar child.

with fC pictures (PL [uC > fC] > OT [uC > fC]). We also found no regions with increased left GP connectivity under OT in either contrast (OT [oC > fC] > PL [oC > fC]; OT [uC > fC] > PL [uC > fC]).

DISCUSSION

In the present study, we were able to show that (1) fathers activate reward- and attachment-related brain regions, specifically in the left GP when they see pictures of their oC and that (2) OT reduces the activation in and the functional connectivity of the left GP in response to pictures of the oC and a uC.

Familiarity Effects in Fathers Under PL

In line with previous studies, the oC activated the GP among other regions in our group of fathers. The GP processes reward-related signals in general (Hong and Hikosaka, 2008), and specifically those related to one's oC (Bartels and Zeki, 2004; Leibenluft *et al*, 2004). Fathers in our study also showed increased activation to the oC in other reward-related regions in the mOFC (Kringelbach, 2005) and the VTA (D'Ardenne *et al*, 2008). Consistent with our results, these regions were also identified in studies investigating the neural correlates of maternal attachment (Bartels and Zeki, 2004; Leibenluft *et al*, 2004; Strathearn *et al*, 2008), suggesting that one's oC activates reward- and attachment-related regions such as the GP both in mothers and in fathers.

We also observed activations in the hippocampus, the superior temporal cortex, and the posterior insula in response to a uC as opposed to a fC. A similar activation pattern to unfamiliar compared with familiar children was also reported in mothers (Leibenluft *et al*, 2004), which suggests that both mothers and fathers activate regions that are associated with the perception of facial movements and emotional expressions when they see the face of a uC (Gobbini *et al*, 2004; Haxby *et al*, 2000).

In contrast to mothers who showed increased activations in response to familiar as opposed to unfamiliar children (Leibenluft *et al*, 2004), we did not observe activation increases in response to the fC compared with the unfamiliar or the oC in our group of fathers. One possible explanation arises from the fact that the fathers in our study spent little time looking after the fC, while mothers usually attend their child and its friends quite frequently during play times. Indeed, fathers in the present study reported low or medium levels of familiarity with the fC despite being acquainted for 1 year or longer. Since previous work exclusively investigated mothers (Leibenluft *et al*, 2004), the described activations associated with the fC might be related to a greater familiarity with the fC in mothers compared with our study group. In line with this hypothesis, Leibenluft *et al* (2004) reported increased activations, for example, in the posterior cingulate-precuneus, the medial prefrontal cortex, and the posterior superior temporal sulcus, suggesting the engagement of autobiographical memories and representations of the mental states of others when mothers see familiar compared with unfamiliar children (Frith and Frith, 2003; O'Connor *et al*, 2008).

Effects of OT on Neural Responses as a Function of Social Salience

Integrating the above findings with the changes in functional activation and connectivity induced by OT in the present study suggests that the neuropeptide is effective in reducing neural responses to social stimuli as a function of their salience. The high salience of the oC can readily be explained by its self-relevance due to its rewarding quality and high attachment value, and is reflected in activations of the GP and other regions associated with reward and attachment under PL (Bartels and Zeki, 2004; Northoff and Hayes, 2011). Since there is no attachment with the uC, the salience of the uC can be interpreted in terms of novelty, as indicated by increased activations in a network of regions processing the faces of strangers in response to the uC under PL (Gobbini *et al*, 2004; Haxby *et al*, 2000). In direct comparison between the oC and the uC, OT increased the BOLD signal for the oC in the right caudate, which might reflect an up-regulation of the rewarding aspects of parental attachment over novelty (Bartels and Zeki, 2004; Leibenluft *et al*, 2004; Strathearn *et al*, 2008). However, the interpretation of this OT effect in the caudate is only tentative, since we did not find activation in this region comparing the oC

with the uC in the PL session as would be expected from previous findings.

Taken together, the above-mentioned findings nevertheless suggest that the salience of the stimuli constitutes the common feature of the oC and the uC in the present design: the salience of the oC is related to its reward and attachment value, while the uC is salient because it is novel. In keeping with this view, OT reduced the activation of the left GP and other regions in the two salient conditions (ie, the oC and the uC), but not in the fC condition. On the one hand, OT decreased functional connectivity within a fronto-pallido-hippocampal network in response to the oC, suggesting that the neuropeptide is effective in modulating reward processing and reward-based behavioral flexibility in the self-relevant, attachment- and reward-related oC condition (Boorman *et al*, 2009; van der Meer and Redish, 2011). On the other hand, and in line with previous studies postulating a common neural mechanism of novelty and reward in the GP (Bunzeck *et al*, 2010; Guitart-Masip *et al*, 2010), we also observed an OT-related decrease of activation in the left GP, as well as the hippocampus and lateral temporal regions, indicating changes in the processing of novel, unfamiliar faces (Gobbini *et al*, 2004; Haxby *et al*, 2002; Kanwisher and Yovel, 2006).

Reduction of Attachment- and Novelty-Related Brain Responses Under OT

But why does OT reduce—and not increase—activation and functional connectivity within the fronto-pallido-hippocampal network? A recent interactionist model by Bartz *et al* (2011) posits that the social effects of OT in humans dependent both on context and on inter-individual differences. Moreover, Campbell (2010) states that one main function of OT is the down-regulation of physiological responses to salient cues that are directly related to somatic or psychological well-being. For example, OT is capable of reducing the physiological and behavioral responses to stress (Ditzen *et al*, 2009; Heinrichs *et al*, 2003) and pain perception (Singer *et al*, 2008), thus promoting physiological well-being.

One major pathway by which OT facilitates social approach behaviors—the basis for the formation of any stable social bond—is linked to a reduction of betrayal aversion or social avoidance both on the behavioral and on the neural level. In monetary transaction games, the intranasal application of OT increased trusting behaviors mirrored by higher investments (Baumgartner *et al*, 2008; Kosfeld *et al*, 2005); a behavior that remained unaffected even after repeated breaches of the investors' trust (Baumgartner *et al*, 2008). Neurally, this finding was corroborated by reduced post-(negative)-feedback activations in the amygdala and caudate, regions involved in fear and feedback processing necessary for reward learning and subsequent behavioral adaptation (Baumgartner *et al*, 2008). In line with these findings, OT also increased behavioral ratings of trustworthiness for neutral faces of unknown others (Theodoridou *et al*, 2009), and reduced neural activation to fearful faces (Domes *et al*, 2007; Kirsch *et al*, 2005), and also to happy faces in men (Domes *et al*, 2007). In line with these results and the findings from the present study, the facilitation of social interactions ascribed to OT may be related to an attenuation—rather than an augmentation—of automatic (neuro-)physiological responses specifically to socially salient cues under OT, irrespective of their valence. Increased approach tendencies and reduced social avoidance might thus open up the possibility to form new social bonds and experience social support, which in turn promotes somatic and physiological well-being.

Future Perspectives

The close relationship between the positive, rewarding aspects of social interactions and the oxytocinergic system is underscored by activations in the GP and other reward-related brain regions in response to pictures of one's own child in our study and others (Bartels and Zeki, 2000, 2004; Leibenluft *et al*, 2004) and by the high density of OT receptors in reward-related regions including the GP (Lim *et al*, 2004; Loup *et al*, 1991). Nevertheless, OT has also caused detrimental effects on recollections of early attachment in anxiously attached individuals (Bartz *et al*, 2010b) and on trust and cooperation in patients suffering from borderline personality disorder (Bartz *et al*, 2010a). These findings emphasize the importance of specifying the exact conditions under which OT exerts its positive effects on social interactions, especially in individuals with impaired social functioning (Bartz *et al*, 2011; Meyer-Lindenberg *et al*, 2011). Future studies should thus aim to systematically elucidate the effects of OT with respect to stimulus valence, social salience, attachment value, and novelty/familiarity.

CONCLUSIONS

The present results support the view that OT plays a key role in the orchestration of neural responses associated with human parental attachment. In line with previous findings, OT was capable of selectively attenuating functional brain responses and connectivity to self-relevant social cues in regions associated with attachment, reward, and novelty processing. OT may thus be effective in paving the way for stable social bonds by increasing the rewarding aspects of attachment and reducing the general apprehension with strangers.

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DISCLOSURE

The authors declare no conflict of interest.

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