Psychoneuroendocrinology (2009) xxx, xxx–xxx

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

# Effects of intranasal oxytocin on emotional face processing in women

Gregor Domes [a,b,1,*], Alexander Lischke [b,1], Christoph Berger [b], Annette Grossmann [c], Karlheinz Hauenstein [c], Markus Heinrichs [a], Sabine C. Herpertz [d]

[a] Department of Psychology, University of Freiburg, Germany
[b] Department of Psychiatry and Psychotherapy, University of Rostock, Germany
[c] Department of Radiology, University of Rostock, Germany
[d] Department of General Psychiatry, Heidelberg University, Germany

Received 10 April 2009; received in revised form 10 June 2009; accepted 12 June 2009

**KEYWORDS**
Oxytocin;
Neuropeptides;
Facial emotions;
Women;
Amygdala;
Functional magnetic-resonance imaging

**Summary** The neuropeptide oxytocin (OXT) has previously been found to reduce amygdala reactivity to social and emotional stimuli in healthy men. The present study aimed to investigate the effect of intranasally administered OXT on brain activity in response to social emotional stimuli of varying valence in women. In a functional magnetic-resonance imaging study, sixteen women were presented with fearful, angry, happy and neutral facial expressions after a single dose of 24 IU OXT or a placebo administration in a within-subject design. Group analysis revealed that the blood-oxygen-level-dependent (BOLD) signal was enhanced in the left amygdala, the fusiform gyrus and the superior temporal gyrus in response to fearful faces and in the inferior frontal gyrus in response to angry and happy faces following OXT treatment. This effect was independent of fixation pattern to specific sections of the facial stimuli as revealed by eye tracking and independent of basal plasma levels of OXT, estradiol, and progesterone. The results are at odds with the previously reported effects found in men. Future studies should include both sexes to determine a possible sexual dimorphism in the neural effects of OXT, considering gonadal steroids and OXT receptor affinity.
© 2009 Elsevier Ltd. All rights reserved.

## 1. Introduction

Over the last decades, numerous animal studies have shown that the neuropeptide oxytocin (OXT) is crucially involved in the regulation of reproduction related behavior in female mammals (Insel et al., 1997). OXT is a nine amino acid peptide that is synthesized in the magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus and released through the posterior pituitary in the periphery. In addition, it is released from the paraventricular nuclei into the brain, where it acts on a specific class-1-G-protein-coupled receptor phosphatidylinositol–calcium second messenger system (Kimura et al., 1992), thus enabling

* Corresponding author at: Department of Psychology, University of Freiburg, Stefan-Meier-Strasse 8, D-79104 Freiburg i. Br., Germany.
*E-mail address:* domes@psychologie.uni-freiburg.de (G. Domes).
[1] Shared first authorship.

0306-4530/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2009.06.016

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016

this neuropeptide to directly influence behavior (Landgraf and Neumann, 2004). OXT is especially involved in mating, pair bonding, and mother–offspring attachment in mammals (Insel and Young, 2001; Young and Wang, 2004). In rodents, behaviorally relevant expression of OXT receptors in the central nervous system has been found in the amygdala (Huber et al., 2005), the hippocampus (Tomizawa et al., 2003), the paraventricular nucleus of the hypothalamus (Blume et al., 2008), and other brain regions including the basal ganglia and the prefrontal cortex (Gimpl and Fahrenholz, 2001). Although these studies might suggest that these areas are also the primary sites of OXT action in humans, marked species differences have been established for different mammals including humans (Tribollet et al., 1992). Critically, the expression of OXT receptors in the living human brain remains to be investigated, for example using positron emission tomography. In humans, OXT is traditionally viewed as a female hormone that is primarily associated with labor, as it induces uterine contraction during parturition and stimulates the letdown reflex during breastfeeding. Based on the animal literature, it has been postulated that beyond these peripheral actions, central OXT modulates cognition in the context of social interactions, thus promoting positive sociality (Donaldson and Young, 2008).

To date, most of the studies in humans on the effects of OXT social cognition and behavior have been conducted with men (Heinrichs and Domes, 2008). The majority of these studies used intranasal applications of synthetic OXT. In sum, these studies have provided accumulating evidence for the involvement of OXT in human social cognition and behavior (Heinrichs et al., 2009). In particular, recent experiments have shown that OXT promotes trusting behavior (Baumgartner et al., 2008; Kosfeld et al., 2005), enhances facial emotion recognition (Domes et al., 2007b) and memory for positive social information (Guastella et al., 2008b; Rimmele et al., 2009), reduces social stress (Heinrichs et al., 2003), improves social cognition in socially impaired individuals with autism (Hollander et al., 2007), and alters dysfunctional cognitions in social phobia (Guastella et al., 2009). Functional imaging studies have just begun to elucidate the underlying neural correlates of these pro-social effects. A number of studies have provided evidence that the amygdala might be a key structure for the mediation of the social cognitive effects of OXT (Domes et al., 2007a; Kirsch et al., 2005; Petrovic et al., 2008; Singer et al., 2008). A first study by Kirsch et al. (2005) has shown that a single dose of OXT reduced amygdala reactivity to pictures of aversive scenes and faces with negative valence. Recent studies extended this finding by showing that the amygdala responding is also reduced to positive facial expressions (Domes et al., 2007a), aversively conditioned emotional response to social stimuli (Petrovic et al., 2008), and to pain (Singer et al., 2008).

As noted above, all of these studies investigated OXT effects in healthy men, in order to rule out possible interactions with circulating gonadal steroids in women. Thus, it is not yet clear whether the results obtained in male samples may be generalized to women. This is of particular interest as there are obvious functional differences of OXT in men and women, and significant sex differences in neuropeptidergic functioning have been repeatedly found in animal studies (Carter, 2007). In animals a number of studies have investigated the sexual dimorphism of the OXT system. For example, OXT plasma levels tend to be higher in females (Kramer et al., 2004) and synthesis as well as OT receptor affinity appears to be modulated by gonadal steroids such as estradiol and progesterone (Gimpl et al., 2002). On the behavioral level, several studies have shown sexual dimorphisms of neuropeptides in different species. For example, in prairie voles, female parenting behavior is more dependent on OXT, whereas male parenting behavior is associated with AVP (Bales et al., 2004). Another study demonstrated that aggression is associated with OXT in females, but not in males (Bales and Carter, 2003). Sex differences in OXT receptor binding depend on the brain area and the species. For example, female prairie voles show higher binding of OXT receptors in the medial prefrontal cortex (PFC) (Smeltzer et al., 2006), whereas in female rats, higher OXT binding was found in the hypothalamus but not in the central amygdala (Uhl-Bronner et al., 2005). Given these sex differences in the central OXT system and the sexual dimorphisms with regard to the behavioral consequences in rodents, behavioral effects of OXT previously found in men may not be generalized to women.

In the present study, we thus investigated a group of young healthy women using intranasal administrations of OXT before assessing neural activity in response to emotional faces of varying valence during functional magnetic-resonance imaging (fMRI). Specifically, we focused on potential effects of OXT on amygdala activity in response to negative affective stimuli. In addition, we expected modulatory effects of OXT on neural activity in brain areas involved in the processing of emotional information from facial expressions, i.e. the inferior occipital lobe, the fusiform gyrus (FG), the superior temporal lobe and the inferior frontal gyrus (IFG) (Adolphs, 2002; Gallese et al., 2004).

## 2. Methods

### 2.1. Participants

Sixteen healthy adult women (mean age $\pm$ s.d., $24.2 \pm 2.5$ years) were enrolled for participation in this study through announcements on the institutional bulletin board. All participants were right-handed, free of psychoactive and endocrinologically relevant medication (including oral contraceptives), had normal or corrected to normal vision, and did not report a history of neurological or endocrine disease. All participants gave written-informed consent to the study procedures which were in accordance with the Declaration of Helsinki and had previously been approved by the ethics committee of the medical faculty of the University of Rostock.

### 2.2. Procedure

On the scanning days, participants were instructed to abstain from smoking, caffeine, and analgesic medication. Subsequently, participants completed a set of questionnaires and were familiarized with the imaging procedures, the administration of the neuropeptide, and the stimuli during scanning.

In order to rule out possible interactions of exogenous OXT with fluctuations of gonadal steroids over the menstrual

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016

cycle, all sessions were conducted in the mid-luteal phase as assessed by participants self-report and validated by blood assays obtained on the day of fMRI scanning. The experimental sessions were conducted in a double-blind, placebo-controlled within-subject cross-over design, with an interval of about one month to ensure that all sessions were conducted during the same cycle phase.

Each experimental session started with a screening of current somatic and mental illness and exclusion criteria for MRI. Thereafter, participants completed a multidimensional mood questionnaire, the MDBF (Steyer et al., 1997). OXT or the placebo was administered intranasally 45–60 min before functional MRI scanning (Born et al., 2002). Following a standardized protocol, the participants self-administered three puffs of OXT per nostril (Syntocinon-Spray, Novartis, Switzerland; each puff with 4 IU OXT) or placebo (PLA; containing all ingredients except for the peptide) under the supervision of the study coordinator (A.L.). MRI scanning began with the functional scans followed by an anatomical scan. The total time of an experimental session was 3 h, with approximately 40 min in the scanner. All participants received monetary compensation after completion of the study.

## 2.3. Hormonal assessment

In order to control for baseline differences in peripheral neuropeptide levels of OXT, and as a manipulation check, blood samples were collected before nasal spray administration and approximately 45 min after the administration before fMRI scanning.

For OXT analysis, 5 ml of blood was drawn into EDTA vacutainer tubes and immediately cooled in ice-chilled water at 4° C. The sample was then centrifuged at 4° C at 4000 rpm for 5 min, aliquoted and stored at −20 °C. After completion of the experiments, the plasma was shipped on dry ice to the Department of Behavioral and Molecular Neuroendocrinology at the University of Regensburg, Germany. After extraction, the samples were analyzed using a radioimmunoassay (Landgraf, 1981). The assay detection limit was 0.1 pg/sample, and cross-reactivity with other related neuropeptides was <0.7%. The coefficient of variation for intra-assay precision was 7–10%, whereas inter-assay variation was eliminated by measuring all samples within the same assay.

For basal progesterone and estradiol analysis, another 5 ml of blood was collected in EDTA vacutainer tubes and analyzed at the Institute for Clinical Chemistry and Laboratory Diagnostics of the University of Rostock, Germany using electrochemiluminescence immunoassays (ECLIAs; Roche, Risch, Switzerland). The detection limit of each assay was 0.03 ng/ml and 5 pg/ml for progesterone and estradiol, respectively. The cross-reactivity of both assays with other related compounds was minimal. The coefficients of variation for intra-assay and inter-assay precision were <6% and <7% for estradiol and <3% and <6% for progesterone, respectively.

## 2.4. Stimuli and scanning procedure

Photographs of 10 different individuals (5 male/5 female) with three basic facial emotions (anger, fear, happiness) and neutral facial expression were taken from a standardized database of faces (N.C. Ebner, M. Riediger, U. Lindenberger, FACES-A database of facial expressions in young, middle-aged, and old women and men: development and validation. Unpublished manuscript, Max Planck Institute for Human Development, Berlin, Germany). The pictures of a particular valence were randomly presented in blocks of 13.9-s duration. Each picture was presented for 1300 ms with an interstimulus interval of 100 ms. Following each block, the participants were asked to rate the presented stimuli on a 4-point scale of "emotional arousal" presented for 3 s on the screen ranging from 0 (very low) to 3 (very high). Ratings were obtained by a button press on a four-button device. A total number of 16 blocks were presented in randomized order with inter-block intervals of 10 s (total time of the stimulation: 7:20 min). Stimulus presentation and response registration was controlled using Presentation 12.1 (Neurobehavioral Systems, Albany CA, USA).

## 2.5. Eye tracking

For the assessment of fixation pattern on the presented stimuli, we recorded eye-movements during scanning with an MRI-compliant eye-tracker (Resonance Technology, Los Angeles, USA). Raw data were collected at a rate of 30 Hz and with a typical spatial resolution of 0.15°. Due to technical artifacts, data from two participants had to be removed, leaving fourteen datasets for eye-tracking analysis. After filtering of the raw data, fixations were coded when the gaze remained for a least 100 ms within an area with a diameter of 14 pixels. In each condition, the mean number of fixations and the mean fixation time was calculated for the whole face and the eye region of the facial stimuli using stimulus-specific templates that defined the areas of interest. For statistical analysis, we calculated the relative number of fixations and the relative fixation duration for the face compared to the rest of the picture and for the eye region compared to the face.

## 2.6. Magnetic-resonance imaging

Images were acquired on a 1.5 T Scanner (Siemens Avanto) equipped with high-speed gradients and the standard head matrix coil (Siemens, Erlangen, Germany). Head movements were minimized using foam cushions. Visual stimuli were presented with a pair of stereoscopic MRI compliant goggles (VisuaStim, Resonance Technology, Los Angeles, USA). Using a BOLD-sensitive echo-planar-imaging (EPI) sequence (TE = 40 ms, TR = 2730 ms, flip-angle = 90°, FoV = 214 mm × 214 mm, matrix = 64 × 64), a total of 166 volumes with 36 interleaved axial slices (3 mm thickness with 1 mm gap) covering the whole brain were acquired. After finishing functional scanning, a structural image was acquired using a three-dimensional, T1-weighted, gradient-echo (MPRAGE) sequence (160 sagittal slices, 1 mm slice thickness, TE = 3.9 ms, TR = 1500 ms, flip-angle = 15°, FoV = 256 mm × 256 mm, matrix = 256 × 256).

## 2.7. Image analysis

For image preprocessing and statistical whole brain analysis we used SPM5 (http://www.fil.ion.ucl.ac.uk/spm) imple-

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016

mented in MATLAB (Version 7.5; The Mathworks, Natick, MA, USA). The first four volumes of the functional series were discarded in order to reduce T1 saturation artifacts. Preprocessing included realignment of the images to the first image in the series, co-registration of the functional images and the structural image, spatial normalization to the Montreal Neurological Institute (MNI) standard brain provided with SPM5 and spatial smoothing (Gaussian kernel of 12 mm FWHM) to reduce residual structural inter-individual differences and to enhance signal-to-noise ratio for second-level group analyses (Mikl et al., 2008).

Data analysis started with the modeling of each block of a specific condition as box-car functions convolved with a hemodynamic response function. In order to reduce slow drift artifacts, a high-pass filter with a cut-off period of 128 s was applied to the voxel time courses. Regression coefficients for the resulting conditions were estimated using least squares within SPM5, which were subsequently subject to a random-effects second-level analysis taking inter-subject variance into account.

In a first step, we calculated a 2-way GLM ANOVA with the factors "face valence" and "drug treatment". We contrasted a particular facial valence (fearful, angry, happy) with the neutral category (main effect of facial valence). In addition, the effect of facial valence within each drug condition was calculated (simple main effects). Finally, we calculated the differential effects of drug treatment on the contrasts of facial valence (interaction). The statistical threshold for the main effects was set to $p < 0.001$ (uncorrected) and a cluster size threshold of 20 voxel; for the interaction we applied a more liberal threshold of $p < 0.005$ (uncorrected) and $k > 20$ voxel. For spatial visualization of significant interaction contrasts within the medial temporal lobe, the fusiform gyrus and the superior temporal gyrus, statistical parametric maps are displayed on slices of a normalized high-resolution T1 image (Holmes et al., 1998). Percent signal change (PSC) was calculated by averaging the signal from 8 mm spheres centered on the group peak voxel of the respective contrast (Glascher, 2009). Coordinates of statistical maxima ("peak voxels") are reported according to the Montreal Neurological Institute (MNI) standard brain provided with SPM5.

In addition, a region-of-interest analysis was performed for amygdala activity. Data extraction for the ROI analyses was performed using the rfxplot toolbox (Glascher, 2009) implemented in SPM5. For the bilateral amygdala the mean signal from the anatomical templates provided by the AAL toolbox (Tzourio-Mazoyer et al., 2002) was extracted. The individual mean PSC values were then subject to separate analyses of variance (ANOVA) for repeated measures to test for main effects of OXT as well as the OXT-by-facial valence interactions on the group level. For statistical analyses of the ROI data we used SPSS (Statistical Package for the Social Sciences, Version 13 for Windows).

## 3. Results

### 3.1. Confounding variables

In a first step, we analyzed differences between the two drug treatment conditions in order to rule out the influence of possible confounding variables, including basal peripheral steroid and OXT levels, changes in calmness, alertness, mood, arousal induced by the facial expressions, and fixation pattern (see Table 1).

The mean levels of peripheral progesterone and estradiol were in the range typically displayed during the luteal phase of the menstrual cycle (Derntl et al., 2008). Paired *t*-tests with Bonferroni correction for the endocrine data revealed that basal estradiol and progesterone levels in the OXT and in the PLA condition did not differ significantly, although estradiol level tended to be higher in the OXT condition. Furthermore, basal OXT levels did not differ between the OXT and PLA condition, but as expected, there was a marked increase in plasma OXT after nasal spray administration in the OXT condition, as indicated by a two-way repeated measures ANOVA (main effect of drug: $F[1,15] = 13.80$, $p = 0.002$; main effect of time: $F[1,15] = 24.18$, $p < 0.001$; drug $\times$ time interaction: $F[1,15] = 28.80$, $p < 0.001$).

Paired *t*-tests indicated no significant differences between the OXT and PLA condition for the MDBF scales of calmness, alertness and mood before and after nasal spray administration. Furthermore, the two-way repeated measures ANOVA revealed that there were no significant differences between participants' emotional arousal ratings for the presented faces in the OXT and PLA condition (main effect of drug: $F[1,15] = 0.126$, $p = 0.728$; drug $\times$ valence interaction: $F[3,45] = 0.998$, $p = 0.403$) and that emotional faces significantly elicited more emotional arousal than neutral faces (main effect of facial emotion: $F[3,45] = 33.463$, $p < 0.001$).

The duration and number of fixations towards the whole face relatively to the whole picture did not differ significantly between the OXT and PLA condition. The same held true for the duration and number of fixations towards the eye region relatively to the whole face. In addition, no effect of OXT on the fixation pattern for a particular facial emotion was found, as indicated by non-significant interactions in the corresponding 2-way ANOVAs.

### 3.2. Functional imaging—whole brain analysis

Whole brain analyses began by testing for the main effects of facial valence on brain activity calculating the contrasts for a specific emotion (fearful, angry, happy) with the neutral expression condition collapsed over PLA and OXT condition. For the contrast *fearful* > *neutral* faces, we found enhanced activation in the left inferior occipital gyrus (IOG; $p_{corr} < 0.001$), left medial temporal lobe (MTL; $p_{corr} = 0.002$), left amygdala ($p_{corr} = 0.003$), right IOG ($p_{corr} = 0.016$), right superior temporal gyrus (STG), right cerebellum, left precentral gyrus (PCG), and the brainstem. For the contrast *angry* > *neutral* faces we found significant clusters in the left MTL ($p_{corr} = 0.013$), left cerebellum ($p_{corr} = 0.014$), right STG ($p_{corr} = 0.037$), right cerebellum, left IOG, and left posterior insula. For the contrast *happy* > *neutral* faces, the whole brain analysis revealed a significant cluster in the right cerebellum (Table 2).

The calculation of the simple main effect of the *fearful* -> *neutral* contrast for the OXT condition (Table 3a) revealed significant clusters in the left MTL, left amygdala, left parahippocampal gyrus, right hippocampus, right lateral fusiform gyrus (FG), left IOG, and the brainstem. In the PLA condition

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016

**Table 1** Comparison of oxytocin (pre administration vs. post administration), basal estradiol, progesterone, changes in calmness, alertness, and mood for the placebo and oxytocin sessions.

| | Placebo | | Oxytocin | | *t* | *p* |
|---|---|---|---|---|---|---|
| | *m* | sd | *m* | sd | | |
| *Endocrine variables* | | | | | | |
| Oxytocin (pg/ml)—pre | 5.70 | 8.10 | 3.43 | 2.40 | −1.10 | ns |
| Oxytocin (pg/ml)—post | 5.52 | 5.01 | 37.65 | 26.10 | 4.61 | <0.001 |
| Progesterone[a] (ng/ml) | 7.14 | 5.25 | 5.91 | 5.65 | 0.88 | ns |
| Estradiol[a] (pg/ml) | 100.55 | 64.30 | 160.13 | 92.75 | 2.64 | 0.080 |
| *Mental state*[b] | | | | | | |
| Calmness (post−pre) | 0.06 | 0.43 | 0.10 | 0.43 | 0.53 | ns |
| Alertness (post−pre) | −0.03 | 0.58 | −0.05 | 0.45 | −0.15 | ns |
| Mood (post−pre) | −0.09 | 0.29 | 0.10 | 0.26 | 1.57 | ns |
| *Arousal ratings* | | | | | | |
| Neutral faces | 0.41 | 0.61 | 0.56 | 0.60 | 0.86 | ns |
| Happy faces | 2.03 | 0.43 | 1.89 | 0.44 | −0.82 | ns |
| Fearful faces | 1.94 | 0.83 | 2.02 | 0.76 | 0.50 | ns |
| Angry faces | 1.77 | 0.79 | 1.83 | 0.82 | 0.72 | ns |
| *Fixation pattern*[c] | | | | | | |
| Duration—face/whole display | 0.95 | 0.05 | 0.94 | 0.04 | −1.00 | ns |
| Duration—eye region/face | 0.67 | 0.18 | 0.66 | 0.16 | −0.36 | ns |
| Number—face/whole display | 0.95 | 0.05 | 0.94 | 0.04 | −0.85 | ns |
| Number—eye region/face | 0.66 | 0.17 | 0.65 | 0.15 | −0.38 | ns |

Differences were tested using paired *t*-tests with Bonferroni-correction for multiple comparisons.
[a] $n = 14$.
[b] Pre−post administration difference; $n = 15$.
[c] Proportion; $n = 14$.

we only found activity in the right STG, and in the left IOG. For the simple main effects of *angry* > *neutral* faces (Table 3b) there were no significant clusters in the PLA condition, but significant clusters in the left MTL, right STG, right ventro-lateral PFC and the bilateral cerebellum in the OXT condition. Finally, the simple main effect of *happy* > *neutral* faces (Table 3c) in the OXT condition revealed significant activations in the bilateral MTL and

**Table 2** Main effects of face valence collapsed over oxytocin and placebo condition.

| | Coord. | *Z* | *p* |
|---|---|---|---|
| a. *Fearful* > *neutral* | | | |
| L IOG | −27, −78, −6 | 5.75 | <0.001[a] |
| L MTL | −33, 0, −24 | 5.34 | 0.002[a] |
| L amygdala | −24, −6, 21 | 5.25 | 0.003[a] |
| R IOG | 30, −81, −6 | 4.90 | 0.016[a] |
| R STG | 51, −36, −6 | 4.36 | <0.001 |
| R cerebellum | 24, −51, −27 | 4.48 | <0.001 |
| L PCG | −51, −18, 57 | 4.18 | <0.001 |
| Brainstem | 3, −30, −36 | 4.01 | <0.001 |
| b. *Angry* > *neutral* | | | |
| L MTL | −39, 0, −30 | 4.94 | 0.013[a] |
| L cerebellum | −21, −66, −30 | 4.92 | 0.014[a] |
| R STG | 51, −36, 0 | 4.70 | 0.037[a] |
| R cerebellum | 21, −45, −30 | 4.25 | <0.001 |
| L IOG | −24, −84, 0 | 4.24 | <0.001 |
| L insula | −42, −18, 12 | 3.50 | <0.001 |
| c. *Happy* > *neutral* | | | |
| R cerebellum | 24, −45, −30 | 4.48 | <0.001 |

IOG, inferior occipital gyrus; MTL, medial temporal lobe; STG, superior temporal gyrus; PCG, precentral gyrus.
[a] FWE-corrected for the whole brain.

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016

**Table 3** Simple main effects of emotional vs. neutral facial expressions in the oxytocin and placebo condition and the interaction effects.

| | Oxytocin | | | Placebo | | | Oxytocin > Placebo | | | Placebo > Oxytocin | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Coord. | *Z* | *p* | Coord. | *Z* | *p* | Coord. | *Z* | *p* | Coord. | *Z* | *p* |
| a. *Fearful* > *neutral* | | | | | | | | | | | | |
| L MTL | −33, 0, −24 | 5.54 | 0.001* | | | | −39, 0, −36 | 3.61 | <0.001 | | | |
| L amygdala | −21, −3, −21 | 4.89 | 0.016* | | | | −30, 3, −18 | 3.24 | <0.002 | | | |
| R hippocampus | 27, −27, −9 | 3.96 | <0.001 | | | | | | | | | |
| L parahippoc. g. | −36, −45, −9 | 4.31 | <0.001 | | | | | | | | | |
| L fusiform gyrus | | | | | | | −21, −33, −18 | 3.54 | <0.001 | | | |
| R fusiform gyrus | 30, −42, −12 | 3.86 | <0.001 | | | | 27, −36, −12 | 3.11 | <0.002 | | | |
| L STG | | | | | | | −51, −9, −3 | 3.36 | <0.001 | | | |
| R STG | | | | 51, −36, 3 | 3.61 | <0.001 | | | | | | |
| R dlPFC | | | | | | | | | | 18, 66, 12 | 3.84 | <0.001 |
| L insula | | | | | | | −39, 0, 18 | 3.99 | <0.001 | | | |
| L IOG | −30, −75, −6 | 4.95 | 0.013[a] | −24, −87, −3 | 4.18 | <0.001 | | | | | | |
| R cerebellum | | | | | | | 15, −63, −36 | 3.28 | <0.002 | | | |
| Brainstem | 12, −18, −18 | 4.45 | <0.001 | | | | 12, −18, −15 | 3.51 | <0.001 | | | |
| b. *Angry* > *neutral* | | | | | | | | | | | | |
| L MTL | 39, 0, −30 | 4.95 | 0.012* | | | | | | | | | |
| R STG | 57, −33, 6 | 4.03 | <0.001 | | | | | | | | | |
| L rolandic oper. | | | | | | | −48, −3, 12 | 3.79 | <0.001 | | | |
| R rolandic oper. | | | | | | | 54, −3, 12 | 3.80 | <0.001 | | | |
| R dlPFC | | | | | | | 24, 30, 54 | 3.86 | <0.001 | | | |
| L vlPFC | | | | | | | −27, 36, 9 | 3.93 | <0.001 | | | |
| R vlPFC | 36, 36, 0 | 4.45 | <0.001 | | | | 36, 36, −3 | 4.25 | <0.001 | | | |
| L cerebellum | 3, −30, 24 | 3.90 | <0.001 | | | | | | | | | |
| R cerebellum | 21, −51, −30 | 4.15 | <0.001 | | | | | | | | | |
| c. *Happy* > *neutral* | | | | | | | | | | | | |
| L MTL | −36, 3, −30 | 4.50 | <0.001 | | | | −39, 3, −39 | 3.20 | <0.002 | | | |
| R MTL | 24, −3, −27 | 3.77 | <0.001 | | | | | | | | | |
| R hippocampus | | | | | | | 30, −6, −33 | 3.88 | <0.001 | | | |
| L STG | | | | | | | −60, −18, 9 | 3.26 | <0.002 | | | |
| L fusiform gyrus | | | | | | | −21, −33, −18 | 4.25 | <0.001 | | | |
| L insula | | | | | | | −59, −3, 15 | 4.34 | <0.001 | | | |
| R rolandic oper. | | | | | | | 57, 3, 9 | 3.34 | <0.001 | | | |
| R dlPFC | | | | | | | | | | 21, 66, 9 | 4.17 | <0.001 |
| L cerebellum | −18, −36, −18 | 4.95 | 0.013* | | | | | | | | | |
| R cerebellum | 21, −48, −30 | 5.00 | 0.010* | | | | 12, −57, −27 | 4.03 | <0.001 | | | |

MTL, medial temporal lobe; STG, superior temporal gyrus; dlPFC, dorso-lateral prefrontal cortex; IOG, inferior occipital gyrus; vlPFC, ventro-lateral prefrontal cortex.
[a] FWE-corrected for the whole brain.

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016

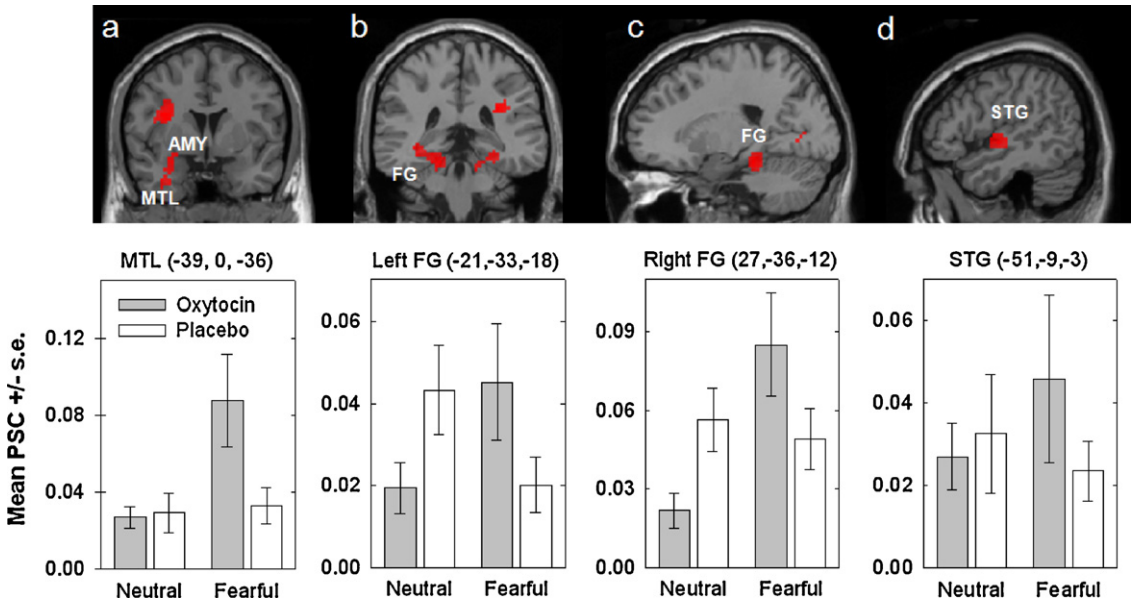


**Figure 1** Effects of OXT on brain activity in response to *fearful faces*. Significant clusters ($p < 0.005$, uncorrected) for the contrast $OXT^{fearful>neutral} > PLA^{fearful>neutral}$ were found in the (a) left MTL, (b) left and (c) right FG and (d) left STG. Barcharts of PSC (mean ± s.e.) illustrate the observed differential effect of OXT on the processing of fearful vs. neutral faces.

the bilateral cerebellum. No above threshold voxels were found in the PLA condition.

In order to test for differential effects of OXT and PLA on the brain areas associated with the processing of facial emotions, we calculated the interaction contrasts of drug treatment and facial valence. For the interaction contrast $OXT^{fearful>neutral} > PLA^{fearful>neutral}$ (Table 3a) we found significant clusters in the left MTL (Fig. 1a), the left amygdala (Fig. 1a; $p_{uncorr} < 0.002$), left insula, left FG and right FG (Fig. 1b and c; $p_{uncorr} < 0.002$), left superior temporal gyrus (Fig. 1d), right cerebellum ($p_{uncorr} < 0.002$) and the brainstem. Inspecting the mean PSC of these interactions, the effects appeared to be mainly driven by enhanced activity to fearful faces in the OXT condition. The reverse contrast revealed a single small cluster in the right prefrontal cortex. Employing the same statistical threshold for the contrast $OXT^{anger>neutral} > PLA^{anger>neutral}$ (Table 3b) we found significant clusters in the rolandic opercula of the bilateral inferior

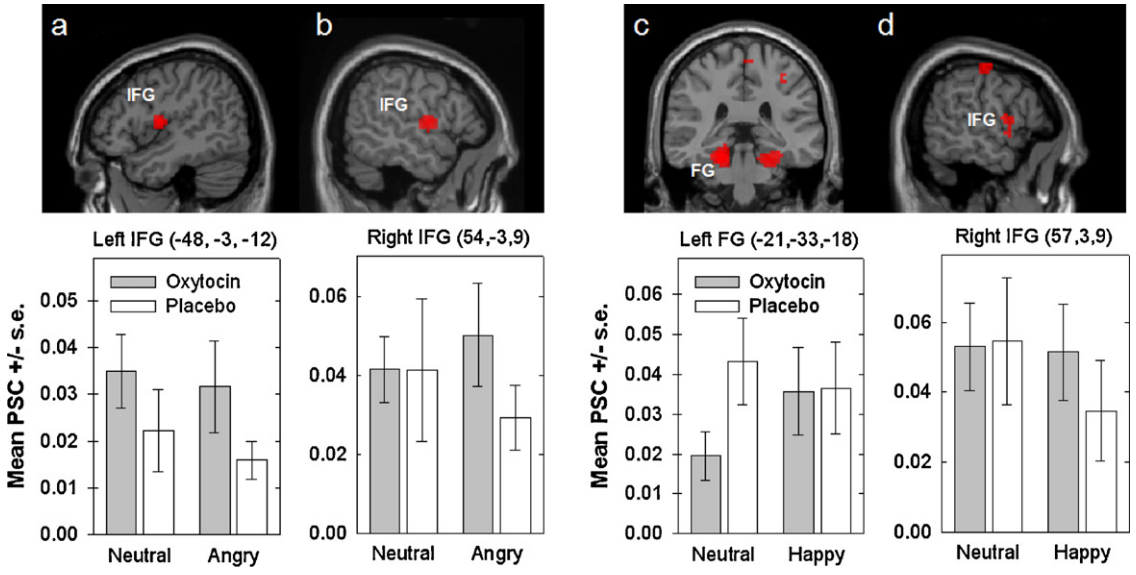


**Figure 2** Effects of OXT on brain activity in response to (a and b) *angry faces* and to (c and d) *happy faces* as compared to neutral faces. Significant clusters ($p < 0.005$, uncorrected) for the contrast $OXT^{angry>neutral} > PLA^{angry>neutral}$ were found in the (a) left and (b) the right inferior frontal gyrus (IFG), and for the contrast $OXT^{happy>neutral} > PLA^{happy>neutral}$ in the (c) left fusiform gyrus (FG) and (d) the right IFG. Barcharts of percent signal change (PSC; mean ± s.e.) illustrate the observed differential effect of OXT on the processing of emotional vs. neutral faces.

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016

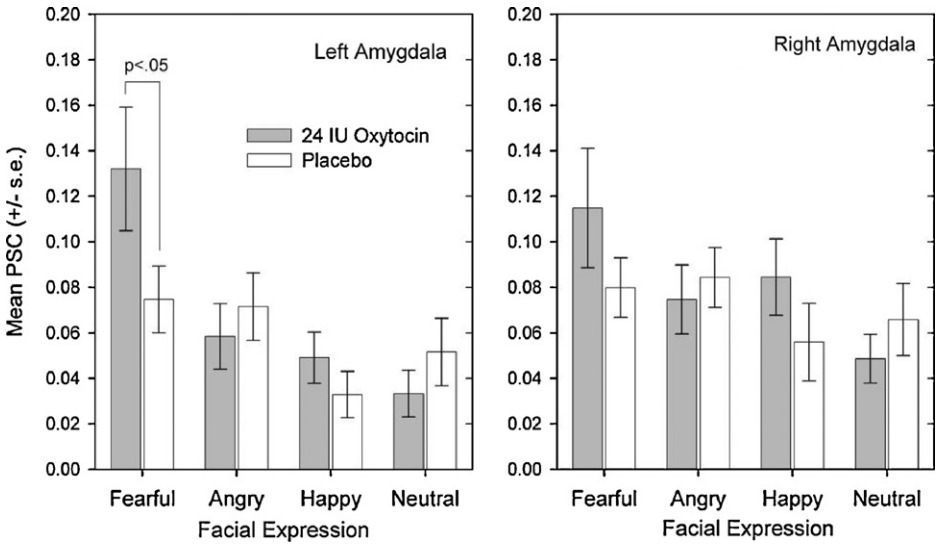


**Figure 3** Effects of oxytocin on the neural activity in left and right amygdala as revealed by the ROI analysis. The graphs depict mean percent signal change (PSC; mean ± s.e.) extracted from anatomical templates of the bilateral amygdala as a function of stimulus valence and drug treatment. Oxytocin increased left amygdala activity in response to fearful faces in the sample of healthy women [$t(15) = 2.15$; $p = 0.048$, two-sided].

PFC (Fig. 3a and b), in the bilateral ventro-lateral PFC, and in the right dorso-lateral PFC. The PSC values show that OXT enhanced activity to angry faces in all of the depicted regions as compared to placebo. There was no significant cluster for the reverse contrast. Finally, we found significant activation for the contrast $OXT^{happy>neutral} > PLA^{happy>neutral}$ (Table 3c) in the left MTL ($p_{uncorr} < 0.002$), the left FG (Fig. 2c), the insula, bilateral rolandic operculum (Fig. 2d for the left operculum), left STG ($p_{uncorr} < 0.002$), right hippocampus, and the right cerebellum. For the reverse contrast there was again a small significant cluster in the left dorso-lateral PFC. All reported effects were significant at a threshold of $p < 0.001$ (uncorrected) unless otherwise stated in brackets.

### 3.3. Region of interest analysis—amygdala

As expected, ROI analyses of amygdala activity (see Fig. 3) revealed a significant main effect of facial valence for the left amygdala ($F[3,45] = 7.177$; $p < 0.001$) and for the right amygdala ($F[3,45] = 2.92$; $p = 0.044$).The main effects of OXT were not significant (left amygdala: $F[1,15] = 0.87$; $p = 0.365$; right amygdala: $F[1,15] = 0.53$; $p = 0.480$). In contrast, the interaction of drug treatment and facial valence was significant for the left amygdala ($F[3,45] = 3.05$; $p = 0.038$), but not for the right amygdala ($F[3,45] = 1.12$; $p = 0.352$). Post hoc paired $t$-tests revealed that OXT enhanced left amygdala activity in response to fearful faces [$t(15) = 2.15$; $p = 0.048$, two-sided], while no other difference reached statistical significance.

### 3.4. Influence of plasma estradiol and progesterone

In order to explore possible modulations of the observed effects of exogenous OXT on brain activity by gonadal steroid, we calculated correlations between the individual levels of estradiol and progesterone and the percent signal change in the amygdala, MTL, FG, and STG for the contrasts employed in the whole brain analysis. None of these correlations reached statistical significance (all $r < 0.30$; all $p > 0.05$, two-sided).

## 4. Discussion

This is the first study to investigate the modulation of neural activity to social emotional stimuli by intranasal OXT in women. In sum, we found that intranasal OXT enhanced the activity in brain structures involved in face processing while processing emotional compared to neutral faces. In particular, after OXT treatment women showed enhanced activity (a) in the medial and superior temporal cortex, in the bilateral fusiform gyrus while processing fearful facial expressions, (b) in the inferior frontal gyrus and ventro-lateral prefrontal regions in response to angry facial expressions, and (c) in the inferior frontal gyrus and the fusiform gyrus to happy faces. In contrast to the previously reported attenuating effect of OXT on amygdala activity in men (Baumgartner et al., 2008; Domes et al., 2007a; Kirsch et al., 2005; Petrovic et al., 2008; Singer et al., 2008), the results of the present study suggest that in women, OXT selectively enhances amygdala reactivity to fearful faces in the luteal phase of the menstrual cycle. Since there were no basal differences in peripheral progesterone and OXT between the placebo and the OXT session, it seems unlikely that session differences in these variables account for the observed effect. However, there was a trend towards a difference in peripheral estradiol between the OXT and placebo condition, but no correlation between these endocrine variables and the activation in the regions of interest. Furthermore, there was no effect of OXT on fixation pattern, which would have been a major confound, since effects of OXT on eye gaze have been previously reported in men

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016

(Guastella et al., 2008a). In the following we will discuss the effects of OXT on blood-oxygen-level-dependent (BOLD) signal in the areas previously considered parts of the network underlying the processing of facial emotions, i.e. the amygdala, the fusiform gyrus and the superior temporal gyrus (Adolphs, 2002) and in the inferior frontal gyrus (Gallese et al., 2004).

Although there is no evidence for stress- or anxiety-reducing effects of intranasal OXT in women to date, the present results of enhanced amygdala responding following OXT administration seem to be in contrast to the stress-reducing effects on the reactivity of the hypothalamo-pituitary-adrenal (HPA) axis suggested for endogenous OXT release in breast-feeding women (Heinrichs et al., 2001; Heinrichs et al., 2002) and the inhibitory effect of intra-cerebral OXT on the stress-induced HPA-axis activity in female rats (Neumann et al., 2000). Similarly, intranasal OXT has been found to reduce the behavioral and endocrine responses to psychosocial stress in healthy men (Heinrichs et al., 2003), a finding that concurs with the reported attenuating effect of oxytocin on amygdala reactivity in men (Heinrichs and Domes, 2008).

Amygdala activity has been associated with the salience or the motivational significance of stimuli (Davis and Whalen, 2001). Humans mainly rely on the visual input rather than other sensory modalities to evaluate their social environment, and thus reliable activations of the amygdala in response to emotional facial expressions have been described in numerous studies (for a review: Phan et al., 2002). Furthermore, the fusiform gyrus has been associated with the visual processing of faces (Kanwisher and Yovel, 2006), and has therefore been regarded a key structure of the face processing network within the ventral visual stream (Adolphs, 2002). Other studies have reported fusiform gyrus activations during the processing of visual emotional stimuli, in particular for emotional facial expressions (Phan et al., 2002). Structural as well as functional connections between the fusiform gyrus and the amygdala have been previously established (Amaral and Price, 1984; Morris et al., 1996; Sprengelmeyer et al., 1998). Our finding of enhanced activity in the fusiform gyrus in response to fearful and happy faces, and also in the amygdala in response to fearful faces after OXT administration is in line with these findings, and further suggests that OXT enhanced the sensitivity to salient social stimuli in the present study.

The other regions that were differentially modulated by OXT in the present study were the superior temporal gyrus and parts of the inferior frontal gyrus. The superior temporal gyrus has been attributed to the representation of changeable features of faces and thereby seem to be especially involved in the encoding of facial expressions and eye gaze (Haxby et al., 2000). Other studies have shown that the posterior parts of the inferior frontal gyrus are activated during the imitation and the observation of body movements including facial expressions and have thus been considered a central part of the so-called "mirror-neuron-system" that is supposed to subserve social cognitive functioning (Gallese et al., 2004; Rizzolatti and Fabbri-Destro, 2008). In the present study, OXT might have enhanced activity in these areas in response to emotional as compared to neutral facial expressions reflecting enhanced processing of social cues of the emotional state of others. Although initial studies in men support the notion that OXT promotes emotion recognition (Domes et al., 2007b; Hollander et al., 2007), further studies are needed to explicitly investigate the relationship between OXT-induced modulation of brain activity and social cognitive functioning in women and men.

From an evolutionary viewpoint, it has been argued that the emotional response to threat-related stimuli is essential for individual's survival, since it triggers adaptive behaviors to avoid threats to physical safety (Calder et al., 2001). Recent studies have shown that in women the perception of threatening stimuli is affected by the menstrual cycle (Conway et al., 2007; Pearson and Lewis, 2005). These studies suggest that the influence of the menstrual cycle on threat perception is most likely mediated by gonadal steroid hormones. Pearson and Lewis (2005) pointed out that high levels of estradiol are associated with an enhanced recognition of fearful faces. Similarly, Conway et al. (2007) demonstrated that women's enhanced sensitivity to fearful and disgusted faces is associated with high levels of progesterone. Since high levels of progesterone and to a lower extent estradiol are typically found in the mid-luteal phase of the menstrual cycle at the possible time of conception and during pregnancy (Hawkins and Matzuk, 2008), we speculate that these steroids enhance the perception of threat-related stimuli and trigger behavior that protects the fetal development. In addition to this, we speculate that the administration of OXT further enhances the vigilance to signals of potential threat, which in the present study is reflected by increased amygdala activity to fearful faces. OXT-induced enhancement of vigilance to threat signals during pregnancy and post-parturition might be especially adaptive as it might reduce the likelihood of physical injury to the mother and the child.

Another possible explanation for the different effects of OXT in men and women might be differences in OXT receptor affinity. Steroid hormones, such as estradiol and progesterone have been found to modulate the OXT receptor, in particular estradiol enhances OXT receptor affinity while progesterone has been shown to decrease receptor binding (Choleris et al., 2008; Gimpl et al., 2002). Women essentially differ from men in the luteal phase with regard to gonadal steroid hormones (Hawkins and Matzuk, 2008), thus differences in the sensitivity of the OXT system to exogenous OXT which could be due to modulations by gonadal steroids might be an explanation for the inconsistent finding between men and women. Future studies could explicitly investigate the modulatory role of gonadal steroids, for example by examining women in different cycle phases in comparison to men. Another promising approach to study the modulatory effects of receptor affinity could be the investigation of OXT action in the brains of lactating women, as OXT receptor affinity is comparably high during lactation.

Some limitations of the present study should be mentioned. The effects induced by intranasally administered OXT in humans might have different effects as compared to the direct manipulation of the OXT system by selective antagonist, the direct administration of the peptide to the brain or by genetic manipulations in rodents. Therefore, caution should be exercised when using animal data to support the interpretation of the present results. Furthermore, the effects of endogenous OXT secretion, triggered by breastfeeding for example (Heinrichs et al., 2001), might

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016

significantly differ from those induced by exogenous administration. Finally, future studies will need to directly compare women and men within the same experiment to further elucidate the sexual dimorphism of the OXT system in humans.

The present study provides first evidence of modulatory effects of OXT on neural activity to facial emotional expressions in healthy women. In contrast to previously published results in healthy men, OXT increased amygdala reactivity to social signals of threat, i.e. to fearful facial expression. Furthermore, fusiform gyrus activity was increased after OXT treatment in response to both positive and negative facial expressions. The present results suggest significant sex differences in the OXT responsiveness of brain areas which are relevant for the processing of emotional and social information. Future studies are needed to further elucidate the functional role of OXT in the modulation of emotional and social information processing in women, sex differences and the possible interactions with female gonadal steroids.

## Conflict of interest

The authors report no conflict of interest.

## Acknowledgements

Gregor Domes and Alexander Lischke contributed equally to the study. We are grateful to our colleagues at the Max Planck Institute for Human Development for providing the facial stimuli and to Gisela Irmisch for assistance with the collection of the data. Funding for this study was provided by grants from the German Research Foundation (DFG Do1312/1-1 to G.D.), the Federal Ministry of Education and Research (BMBF 01GW0784 to S.H.) and by grants from the Swiss National Science Foundation (SNSF PP001-114788) and the Research Priority Program "Foundations of Human Social Behavior" at the University of Zurich (to M.H.). DFG, BMBF and SNSF had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

## References

Adolphs, R., 2002. Recognizing emotion from facial expressions: psychological and neurological mechanisms. Behav. Cogn. Neurosci. Rev. 1, 21–62.

Amaral, D.G., Price, J.L., 1984. Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). J. Comp. Neurol. 230, 465–496.

Bales, K.L., Carter, C.S., 2003. Sex differences and developmental effects of oxytocin on aggression and social behavior in prairie voles (*Microtus ochrogaster*). Horm. Behav. 44, 178–184.

Bales, K.L., Pfeifer, L.A., Carter, C.S., 2004. Sex differences and developmental effects of manipulations of oxytocin on alloparenting and anxiety in prairie voles. Dev. Psychobiol. 44, 123–131.

Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., Fehr, E., 2008. Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron 58, 639–650.

Blume, A., Bosch, O.J., Miklos, S., Torner, L., Wales, L., Waldherr, M., et al., 2008. Oxytocin reduces anxiety via ERK1/2 activation: local effect within the rat hypothalamic paraventricular nucleus. Eur. J. Neurosci. 27, 1947–1956.

Born, J., Lange, T., Kern, W., McGregor, G.P., Bickel, U., Fehm, H.L., 2002. Sniffing neuropeptides: a transnasal approach to the human brain. Nat. Neurosci. 5, 514–516.

Calder, A.J., Lawrence, A.D., Young, A.W., 2001. Neuropsychology of fear and loathing. Nat. Rev. Neurosci. 2, 352–363.

Carter, C.S., 2007. Sex differences in oxytocin and vasopressin: implications for autism spectrum disorders? Behav. Brain Res. 176, 170–186.

Choleris, E., Devidze, N., Kavaliers, M., Pfaff, D.W., 2008. Steroidal/neuropeptide interactions in hypothalamus and amygdala related to social anxiety. Prog. Brain Res. 170, 291–303.

Conway, C.A., Jones, B.C., DeBruine, L.M., Welling, L.L., Law Smith, M.J., Perrett, D.I., et al., 2007. Salience of emotional displays of danger and contagion in faces is enhanced when progesterone levels are raised. Horm. Behav. 51, 202–206.

Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. Mol. Psychiatry 6, 13–34.

Derntl, B., Windischberger, C., Robinson, S., Lamplmayr, E., Kryspin-Exner, I., Gur, R.C., et al., 2008. Facial emotion recognition and amygdala activation are associated with menstrual cycle phase. Psychoneuroendocrinology 33, 1031–1040.

Domes, G., Heinrichs, M., Glascher, J., Buchel, C., Braus, D.F., Herpertz, S.C., 2007a. Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biol. Psychiatry 62, 1187–1190.

Domes, G., Heinrichs, M., Michel, A., Berger, C., Herpertz, S.C., 2007b. Oxytocin improves "mind-reading" in humans. Biol. Psychiatry 61, 731–733.

Donaldson, Z.R., Young, L.J., 2008. Oxytocin, vasopressin, and the neurogenetics of sociality. Science 322, 900–904.

Gallese, V., Keysers, C., Rizzolatti, G., 2004. A unifying view of the basis of social cognition. Trends Cogn. Sci. 8, 396–403.

Gimpl, G., Fahrenholz, F., 2001. The oxytocin receptor system: structure, function, and regulation. Physiol. Rev. 81, 629–683.

Gimpl, G., Wiegand, V., Burger, K., Fahrenholz, F., 2002. Cholesterol and steroid hormones: modulators of oxytocin receptor function. Prog. Brain Res. 139, 43–55.

Glascher, J., 2009. Visualization of group inference data in functional neuroimaging. Neuroinformatics 7, 73–82.

Guastella, A.J., Howard, A.L., Dadds, M.R., Mitchell, P., Carson, D.S., 2009. A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. Psychoneuroendocrinology 34, 917–923.

Guastella, A.J., Mitchell, P.B., Dadds, M.R., 2008a. Oxytocin increases gaze to the eye region of human faces. Biol. Psychiatry 63, 3–5.

Guastella, A.J., Mitchell, P.B., Mathews, F., 2008b. Oxytocin enhances the encoding of positive social memories in humans. Biol. Psychiatry 64, 256–258.

Hawkins, S.M., Matzuk, M.M., 2008. The menstrual cycle: basic biology. Ann. N.Y. Acad. Sci. 1135, 10–18.

Haxby, J.V., Hoffman, E.A., Gobbini, M.I., 2000. The distributed human neural system for face perception. Trends Cogn. Sci. 4, 223–233.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., Ehlert, U., 2003. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol. Psychiatry 54, 1389–1398.

Heinrichs, M., Domes, G., 2008. Neuropeptides and social behavior: effects of oxytocin and vasopressin in humans. Prog. Brain Res. 170, 337–350.

Heinrichs, M., Meinlschmidt, G., Neumann, I., Wagner, S., Kirschbaum, C., Ehlert, U., et al., 2001. Effects of suckling on hypothalamic-pituitary-adrenal axis responses to psychosocial stress in postpartum lactating women. J. Clin. Endocrinol. Metab. 86, 4798–4804.

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016

Heinrichs, M., Neumann, I., Ehlert, U., 2002. Lactation and stress: protective effects of breast-feeding in humans. Stress 5, 195–203.

Heinrichs, M., von Dawans, B., Domes, G., 2009. Oxytocin, vasopressin, and human social behavior. Front. Neuroendocrinol. doi:10.1016/j.yfrne.2009.05.005.

Hollander, E., Bartz, J., Chaplin, W., Phillips, A., Sumner, J., Soorya, L., et al., 2007. Oxytocin increases retention of social cognition in autism. Biol. Psychiatry 61, 498–503.

Holmes, C.J., Hoge, R., Collins, L., Woods, R., Toga, A.W., Evans, A.C., 1998. Enhancement of MR images using registration for signal averaging. J. Comput. Assist. Tomogr. 22, 324–333.

Huber, D., Veinante, P., Stoop, R., 2005. Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. Science 308, 245–248.

Insel, T.R., Young, L., Wang, Z., 1997. Central oxytocin and reproductive behaviours. Rev. Reprod. 2, 28–37.

Insel, T.R., Young, L.J., 2001. The neurobiology of attachment. Nat. Rev. Neurosci. 2, 129–136.

Kanwisher, N., Yovel, G., 2006. The fusiform face area: a cortical region specialized for the perception of faces. Philos. Trans. R. Soc. Lond. B Biol. Sci. 361, 2109–2128.

Kimura, T., Tanizawa, O., Mori, K., Brownstein, M.J., Okayama, H., 1992. Structure and expression of a human oxytocin receptor. Nature 356, 526–529.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., et al., 2005. Oxytocin modulates neural circuitry for social cognition and fear in humans. J. Neurosci. 25, 11489–11493.

Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., Fehr, E., 2005. Oxytocin increases trust in humans. Nature 435, 673–676.

Kramer, K.M., Cushing, B.S., Carter, C.S., Wu, J., Ottinger, M.A., 2004. Sex and species differences in plasma oxytocin using an enzyme immunoassay. Can. J. Zool. 82, 1194–1200.

Landgraf, R., 1981. Simultaneous measurement of arginine vasopressin and oxytocin in plasma and neurohypophyses by radioimmunoassay. Endokrinologie 78, 191–204.

Landgraf, R., Neumann, I.D., 2004. Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. Front. Neuroendocrinol. 25, 150–176.

Mikl, M., Marecek, R., Hlustik, P., Pavlicova, M., Drastich, A., Chlebus, P., et al., 2008. Effects of spatial smoothing on fMRI group inferences. Magn. Reson. Imag. 26, 490–503.

Morris, J.S., Frith, C.D., Perrett, D.I., Rowland, D., Young, A.W., Calder, A.J., et al., 1996. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 383, 812–815.

Neumann, I.D., Wigger, A., Torner, L., Holsboer, F., Landgraf, R., 2000. Brain oxytocin inhibits basal and stress-induced activity of the hypothalamo-pituitary-adrenal axis in male and female rats: partial action within the paraventricular nucleus. J. Neuroendocrinol. 12, 235–243.

Pearson, R., Lewis, M.B., 2005. Fear recognition across the menstrual cycle. Horm. Behav. 47, 267–271.

Petrovic, P., Kalisch, R., Singer, T., Dolan, R.J., 2008. Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. J. Neurosci. 28, 6607–6615.

Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. NeuroImage 16, 331–348.

Rimmele, U., Hediger, K., Heinrichs, M., Klaver, P., 2009. Oxytocin makes a face in memory familiar. J. Neurosci. 29, 38–42.

Rizzolatti, G., Fabbri-Destro, M., 2008. The mirror system and its role in social cognition. Curr. Opin. Neurobiol. 18, 179–184.

Singer, T., Snozzi, R., Bird, G., Petrovic, P., Silani, G., Heinrichs, M., et al., 2008. Effects of oxytocin and prosocial behavior on brain responses to direct and vicariously experienced pain. Emotion 8, 781–791.

Smeltzer, M.D., Curtis, J.T., Aragona, B.J., Wang, Z., 2006. Dopamine, oxytocin, and vasopressin receptor binding in the medial prefrontal cortex of monogamous and promiscuous voles. Neurosci. Lett. 394, 146–151.

Sprengelmeyer, R., Rausch, M., Eysel, U.T., Przuntek, H., 1998. Neural structures associated with recognition of facial expressions of basic emotions. Proc. R. Soc. Lond. B Biol. Sci. 265, 1931–1971.

Steyer, R., Schwenkmezger, P., Notz, P., Eid, M., 1997. Der Mehrdimensionale Befindlichkeitsfragebogen MDBF [Multidimensional mood questionnaire]. Hogrefe, Göttingen.

Tomizawa, K., Iga, N., Lu, Y.F., Moriwaki, A., Matsushita, M., Li, S.T., et al., 2003. Oxytocin improves long-lasting spatial memory during motherhood through MAP kinase cascade. Nat. Neurosci. 6, 384–390.

Tribollet, E., Dubois-Dauphin, M., Dreifuss, J.J., Barberis, C., Jard, S., 1992. Oxytocin receptors in the central nervous system. Distribution, development, and species differences. Ann. N.Y. Acad. Sci. 652, 29–38.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15, 273–289.

Uhl-Bronner, S., Waltisperger, E., Martinez-Lorenzana, G., Condes Lara, M., Freund-Mercier, M.J., 2005. Sexually dimorphic expression of oxytocin binding sites in forebrain and spinal cord of the rat. Neuroscience 135, 147–154.

Young, L.J., Wang, Z., 2004. The neurobiology of pair bonding. Nat. Neurosci. 7, 1048–1054.

Please cite this article in press as: Domes, G., et al., Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology (2009), doi:10.1016/j.psyneuen.2009.06.016