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Oxytocin increases amygdala reactivity to threatening scenes in females

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Summary The neuropeptide oxytocin (OT) is well known for its profound effects on social behavior, which appear to be mediated by an OT-dependent modulation of amygdala activity in the context of social stimuli. In humans, OT decreases amygdala reactivity to threatening faces in males, but enhances amygdala reactivity to similar faces in females, suggesting sex-specific differences in OT-dependent threat-processing. To further explore whether OT generally enhances amygdala-dependent threat-processing in females, we used functional magnetic resonance imaging (fMRI) in a randomized within-subject crossover design to measure amygdala activity in response to threatening and non-threatening scenes in 14 females following intranasal administration of OT or placebo. Participants' eye movements were recorded to investigate whether an OT-dependent modulation of amygdala activity is accompanied by enhanced exploration of salient scene features. Although OT had no effect on participants' gazing behavior, it increased amygdala reactivity to scenes depicting social and non-social threat. In females, OT may, thus, enhance the detection of threatening stimuli in the environment, potentially by interacting with gonadal steroids, such as progesterone and estrogen.
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1. Introduction

The neuropeptide oxytocin (OT) is crucially involved in the regulation of reproductive and social behavior in non-human mammals (Lee et al., 2009), including parturition, lactation, parental care, play, bonding and mating. OT also appears to be a potent modulator of human social behavior (Meyer-Lindenberg et al., 2011). In humans, OT attenuates anxiety and stress (Ditzen et al., 2009; Heinrichs et al., 2003), promotes trust (Kosfeld et al., 2005) and facilitates the encoding (Guastella et al., 2008; Rimmele et al., 2009) and recognition of facial expressions (Di Simplicio et al., 2009; Domes et al., 2007b; Fischer-Shofty et al., 2010; Lischke et al., 2011; Marsh et al., 2010; Schulze et al., 2011).

With regard to the neurobiological mechanism mediating the behavioral effects of OT, the amygdala with its cortical and subcortical projections appears to be a key region (Pittman and Spencer, 2005). OT is released within the rat amygdala (Bosch et al., 2005; Ebner et al., 2005), where it acts on specific receptors (Huber et al., 2005; Terenzi and Ingram, 2005) to modulate fear (McCarthy et al., 1996) and aggression (Bosch et al., 2005). Recent evidence suggests that OT modulates neuronal activity in the human amygdala in a similar way, especially in response to threatening stimuli (Baumgartner et al., 2008; Domes et al., 2007a, 2010a; Gamer et al., 2010; Kirsch et al., 2005; Petrovic et al., 2008; Singer et al., 2008). Interestingly, OT decreases amygdala reactivity to aversive, threat-related scenes (Kirsch et al., 2005) and fearful, threat-related faces (Domes et al., 2007a; Gamer et al., 2010; Kirsch et al., 2005; Petrovic et al., 2008) in males, but increases amygdala reactivity to similar faces in females (Domes et al., 2010a). Although sex differences in neuropeptidergic functioning are well known in non-human mammals (Carter et al., 2009), they have rarely been studied in humans. In fact, our initial finding of enhanced amygdala reactivity to fearful faces in females receiving OT has not been replicated yet (Domes et al., 2010a). In addition, it remains unresolved whether the observed OT effects are specific to facial stimuli or generalize to other stimulus classes such as more complex emotional scenes.

In consideration of this, the current study examined how OT modulates amygdala reactivity to negative, positive and neutral scenes in females. We also measured how OT affects visual exploration of these scenes because it has been shown that OT alters visual processing of emotional stimuli in males (Gamer et al., 2010). Based on our previous findings (Domes et al., 2010a), we hypothesized that OT specifically enhances amygdala activity to negative scenes, potentially by increasing exploration of salient scene features.

2. Methods

2.1. Participants

Fourteen female adults (age: $M = 23.79$ years, $SD = 2.32$ years) participated voluntarily in this study. Exclusion criteria were medical or mental illness, use of medication, substance abuse, smoking, pregnancy, and lactation. Exclusion was determined based on a brief clinical interview and several self-report questionnaires (see Supplementary Methods). All participants provided written, informed consent and were paid for participation. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Rostock.

2.2. Experimental procedure

In a double-blind, placebo-controlled and counter-balanced within-subject design, participants were tested twice during the mid-luteal phase of their menstrual cycle within an interval of approximately four weeks. The mid-luteal phase was determined by participants' self-reports and validated by blood samples drawn on the testing days (see Supplementary Methods). In addition, pregnancy tests were carried out to confirm that none of the participants was pregnant at the time of testing. Following a standardized protocol (Domes et al., 2010a), participants self-administered a nasal spray either containing 24 international units (IU) of OT (Syntocinon Spray; Novartis, Basel, Switzerland) or placebo (PL; containing all ingredients except for the neuropeptide) 45 min before the beginning of the functional magnetic resonance imaging (fMRI). Substance-induced changes in mood, arousal and wakefulness were tracked by administering a multidimensional mood questionnaire (MDBF, Steyer et al., 1997) before and after substance application. Blood samples were also drawn before and after substance application to control for differences in OT assimilation (see Supplementary Methods).

2.3. Experimental paradigm

During fMRI scanning, participants performed an emotional arousal rating task while viewing positive, negative and neutral scenes selected from the International Affective Picture System (IAPS, Lang et al., 2005; see Supplementary Methods) via a set of fiber optic goggles (VisuaStim, Resonance Technology, Los Angeles, CA, USA). All scenes of a particular valence were randomly presented in blocks that consisted of an 18.6 s viewing and 3 s rating phase. In the viewing phase, six scenes of the same valence were presented for 3 s each, with an interstimulus interval of 100 ms. In the subsequent rating phase, the previously presented scenes had to be collectively rated on a four-point scale for emotional arousal (0 = *low arousal* and 3 = *high arousal*) by pressing a corresponding button within 3 s. For each valence category, four blocks of scenes were presented, resulting in a total of 12 blocks, whose order was randomly determined. The interblock interval amounted to 13—15.75 s. Scene presentation and response registration were controlled using Presentation 12.1 (Neurobehavioral Systems, Albany, CA, USA).

2.4. Eye-tracking

During fMRI scanning, participants' eye movements were recorded with an MRI compliant infra-red eye-tracker (VisuaStim, Resonance Technology, Los Angeles, CA, USA) to control for substance-induced differences in visual attention. Raw data were collected at a 60 Hz sampling rate with a spatial resolution of approximately 0.15° for tracking resolution and 0.25—1.0° for gaze position accuracy. After filtering

of the raw data, fixations were coded when gaze remained for at least 100 ms within a 14-pixel diameter region. Matlab 7.7 (MathWorks Inc., Natick, MA, USA) was then used to determine the mean number and duration of fixations for an entire scene as well as for predefined regions of interests (see Supplementary Methods). Finally, the relative number and duration of fixations for these regions compared to the entire scene was calculated and used for statistical analyses.

Eye tracking and behavioral data were analyzed using a series of 2×3 repeated measures ANOVAs (Condition $\times$ Valence). The Greenhouse–Geisser correction was applied to correct for potential violations of the sphericity assumption whenever appropriate. Partial η^2 is reported as an effect size estimate.

2.5. Magnetic-resonance imaging

2.5.1. Data acquisition

Magnetic-resonance imaging was performed on a 1.5-T whole-body MR-scanner (Magnetom Avanto, Siemens, Erlangen, Germany) equipped with a standard head coil. Using a T2*-sensitive gradient echo-planar imaging sequence (repetition time, 2670 ms; echo time, 40 ms; flip angel, 90°; field of view, 205 mm $\times$ 205 mm; matrix, 64×64; in-plane resolution, 3.2 mm $\times$ 3.2 mm), 36 axial slices (slice thickness, 3.5 mm; no gap) were acquired covering the whole brain. Additionally, isotropic high-resolution ($1 \times 1 \times 1$ mm^3) structural images were recorded using a T1-weighted coronal oriented magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time, 1500 ms; echo time, 3.9 ms; flip angle, 15°; field of view, 256 $\times$ 256; matrix, 256 mm $\times$ 256 mm) with 160 sagittal slices (slice thickness, 1 mm).

2.5.2. Data analysis

Image preprocessing and statistical data analysis were performed with the Statistical Parametric Mapping software SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Prior to image preprocessing, the first four images of each functional series were discarded due to T1 equilibration effects. The remaining images were then realigned to the first image in the series and unwarped to account for movement-related artifacts (Andersson et al., 2001). Thereafter, the functional images of both runs (OT and PL) were co-registered to the T1 image of each participant. The T1 image was then segmented to determine normalization parameters which were subsequently used to spatially normalize all functional images to the standard anatomical Montreal Neurological Institute (MNI) space. Finally, functional images were smoothed with an isotropic Gaussian kernel (FWHM: 10 mm) and temporally filtered with an autoregressive AR model (Ashburner, 2007) and a 128 s high-pass filter to account for serial correlations in the functional series.

For the first-level fixed-effects analysis, scene presentation was modeled as separate boxcar regressors for each experimental condition (negative, positive and neutral valence) and convolved with the hemodynamic response function (hrf). Subsequently, simple contrasts were calculated to investigate brain activation in response to positive, negative and neutral scenes, respectively. The resulting contrast maps were used to construct a 2×3 design matrix (repeated measures ANOVA) as a second-level random-effects analysis. Within this model, we compared brain activation between negative and neutral as well as positive and neutral scenes in the PL and OT condition and we calculated interaction contrasts to test whether these differential activations differed between the PL and OT condition.

Since we were primarily interested in amygdala activation, we performed a small volume correction with a threshold of $p < .05$ in predefined anatomical amygdala regions of interest (Tzourio-Mazoyer et al., 2002). In addition to this hypothesis-driven region of interest analysis, we performed an exploratory whole brain analysis with a threshold of $p < .001$ (uncorrected) and a cluster threshold of $k \geq 20$ voxels. For illustration purposes, statistical parametric maps were thresholded at $p < .01$ (uncorrected) and overlaid on a representative structural image using MRIcron (http://www.cabiatl.com/mricro/mricro/index.html).

3. Results

3.1. Hormones and mental state

Participants' progesterone and estrogen levels on the testing days were in the range typically displayed during the mid-luteal phase of the menstrual cycle (Nelson, 2005). Paired t-tests with Bonferroni correction revealed no significant differences in participants' hormone levels between the OT and PL condition, although estrogen levels tended to be higher in the OT than in the PL condition (see Table 1). A 2×2 repeated measures ANOVA (Condition $\times$ Time) indicated that participants' OT levels before substance application were not significantly different in the PL and OT condition, whereas their OT levels after substance application were significantly higher in the OT than in the PL condition (see Table 1; main effect condition: $F[1,13] = 6.30$, $p = .03$; main effect time: $F[1,13] = 39.46$, $p < .001$, $\eta^2 = 0.75$; interaction Condition $\times$ Time: $F[1,13] = 26.29$, $p < .001$, $\eta^2 = 0.67$). However, a series of 2×2 repeated measures ANOVAs (Condition $\times$ Time) showed that OT application had no effect on participants' mood, arousal or wakefulness (all Fs < 1.27, all ps $> .28$ for all substance related effects, see Table 1).

3.2. Experimental paradigm

3.2.1. Behavioral data

A 2×3 repeated measures ANOVA (Condition $\times$ Valence) on the arousal ratings revealed no significant differences between the OT and PL condition (see Table 1; main effect condition: $F[1,13] = 0.04$, $p = .84$, $\eta^2 = 0.00$; main effect valence: $F[2,26] = 182.41$, $\varepsilon = 0.86$, $p < .001$, $\eta^2 = 0.93$; interaction Condition $\times$ Valence: $F[2,26] = 1.12$, $\varepsilon = 0.81$, $p = .33$, $\eta^2 = 0.08$). In both conditions, participants rated emotional scenes as more arousing than non-emotional ones (positive vs. neutral scenes: $p < .001$; negative vs. neutral scenes: $p < .001$). Among emotional scenes, negative scenes yielded higher arousal ratings than positive ones ($p < .001$).

3.2.2. Eye tracking data

A series of 2×3 repeated measures ANOVA (Condition $\times$ Valence) showed no significant differences between the PL and OT condition with regard to the number of fixations (see Table 1; main effect condition: $F[1,11] = 0.11$,

Table 1 Group differences in hormone levels, mental state, arousal ratings and visual attention.

	Placebo		Oxytocin		Test statistic	
	M	*SD*	*M*	*SD*	*t*(df)	*p*
Hormone levels						
Progesterone (ng/ml)[a] [pre]	7.93	5.73	6.70	5.33	$t(11) = 0.60$	.56
Estrogen (pg/ml)[b] [pre]	129.10	53.88	177.57	90.31	$t(10) = 2.05$	.07
Oxytocin (pg/ml) [pre]	9.98	25.52	21.20	68.15	$t(13) = 0.98$	.35
Oxytocin (pg/ml) [post]	14.29	34.05	61.09	76.37	$t(13) = 3.70$	$<.01$ **
Mental state						
Mood [post-pre]	−0.11	0.21	−0.13	0.19	$t(13) = 0.19$	.85
Arousal [post-pre]	−0.04	0.58	0.04	0.61	$t(13) = 0.30$	.77
Wakefulness [post-pre]	−0.07	0.44	−0.07	0.39	$t(13) = 0.00$	1.00
Arousal rating						
Positive scenes	2.71	0.63	2.86	0.67	$t(13) = 0.66$	.52
Negative scenes	3.66	0.47	3.50	0.53	$t(13) = 1.03$	.32
Neutral scenes	1.30	0.41	1.39	0.46	$t(13) = 0.73$	.48
Visual attention[a] – relative number and duration of fixations						
Positive scenes [number]	.65	.07	.63	.06	$t(11) = 0.23$	.82
Positive scenes [duration]	.67	.07	.67	.06	$t(11) = 0.15$	.99
Negative scenes [number]	.62	.09	.65	.06	$t(11) = 1.47$	.17
Negative scenes [duration]	.67	.10	.69	.07	$t(11) = 1.04$	.32
Neutral scenes [number]	.68	.07	.66	.09	$t(11) = 0.59$	.57
Neutral scenes [duration]	.71	.08	.69	.10	$t(11) = 0.60$	.56

Note. Pre: pre-application; post: post-application.
[a] $n = 12$.
[b] $n = 11$.
** $p < .01$, two-tailed.

$p = .75$, $\eta^2 = 0.10$; main effect valence: $F[2,22] = 1.97$, $\varepsilon = 0.99$, $p = .16$, $\eta^2 = 0.15$; interaction Condition × Valence: $F[2,22] = 1.26$, $\varepsilon = 0.89$, $p = .30$, $\eta^2 = 0.10$) or duration of fixations in the predefined ROIs (see Table 1; main effect condition: $F[1,11] = 0.06$, $p = .81$, $\eta^2 = 0.00$; main effect valence: $F[2,22] = 1.10$, $\varepsilon = 0.83$, $p = .34$, $\eta^2 = 0.09$; interaction Condition × Valence: $F[2,22] = 0.77$, $\varepsilon = 0.80$, $p = .45$, $\eta^2 = 0.07$).

3.2.3. Imaging data

After PL administration, negative scenes activated the right amygdala significantly more than neutral ones ($Z = 2.92$, $p = .031$, see Table 2). A similar, albeit non-significant, effect was found in the left amygdala ($Z = 2.49$, $p = .077$, see Table 2). This effect was significant in both amygdalae after OT administration (left amygdala: $Z = 4.46$, $p < .001$; right amygdala: $Z = 5.70$, $p < .001$, see Table 2). Positive relative to neutral scenes, on the contrary, had no effect on amygdala activity after PL administration and only on right amygdala activity after OT administration ($Z = 3.58$, $p = .004$, see Table 2). An interaction analysis directly contrasting the OT with the PL condition revealed more right-lateralized amygdala activity to negative relative to neutral scenes after OT than after PL administration ($Z = 3.01$, $p = .024$; see Fig. 1 and Table 2). A similar, albeit marginally significant effect was found in the left amygdala ($Z = 2.50$, $p = .075$, see Fig. 1 and Table 2). Contrasting the PL with the OT condition, on the contrary, revealed no evidence for significant differences in amygdala activity. The results of this imaging analysis are summarized in Table 2. The exploratory whole brain analysis

Table 2 Amygdala activations for negative and positive as compared to neutral scenes in the PL and OT condition.

	Left amygdala							Right amygdala						
	x	*y*	*z*	*k*	*Z*	p_{FWE}	$p_{uncorr.}$	*x*	*y*	*z*	*k*	*Z*	p_{FWE}	$p_{uncorr.}$
PL														
Negative-neutral	−30	2	−18	3	2.49	.077	.006	26	2	−22	69	2.92	.031	.002
OT														
Positive-neutral								24	6	−16	51	3.58	.004	<.001
Negative-neutral	−24	−6	−16	217	4.46	<.001	<.001	26	6	−18	228	5.70	<.001	<.001
OT > PL														
Negative-neutral	−22	−8	−14	3	2.50	.075	.006	24	6	−16	24	3.01	.024	.001

Note. Activations are reported when $p_{FWE} < .10$ (small volume correction for anatomical amygdala regions of interest). PL = placebo. OT = oxytocin. *k* = cluster size in voxels (voxel size after preprocessing was $2 \times 2 \times 2$ mm^3). Peak coordinates of each cluster are reported in MNI space.

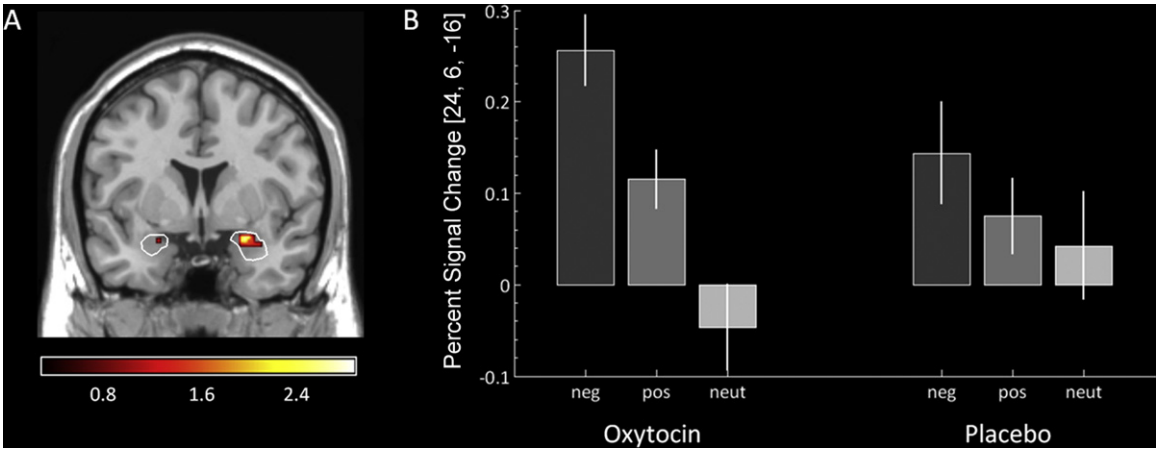

Figure 1 Region-of-interest analysis for the amygdala. Oxytocin increased amygdala activity to negative as compared to neutral scenes. (A) Statistical parametric map (coronal plane, $y = 4$) revealing a statistically significant effect in the right amygdala (peak voxel: $x = 24$, $y = 6$, $z = -16$; $Z = 3.01$; $p = .024$, FWE-corrected) and a marginally significant effect in the left amygdala (peak voxel: $x = -22$, $y = -8$, $z = -14$; $Z = 2.50$; $p = .075$, FWE-corrected) for the contrast $OT^{neg\text{-}neut} > PL^{neg\text{-}neut}$. The anatomical amygdala region of interest is visualized with a white outline. (B) Percent signal change as a function of condition and picture valence in the right amygdala (peak voxel: $x = 24$, $y = 6$, $z = -16$). Error bars depict standard errors of the mean. *Note*. For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.

only revealed few brain regions showing a modulatory effect of OT (see Table S2, Supplementary Results). Although *p*-values were not corrected for multiple comparisons in this analysis, a comparably large cluster in the left anterior temporal lobe seemed to show a similar activation pattern as the amygdala.

In order to test whether the marginally significant difference in estrogen levels between the OT and the PL condition accounted for the observed OT effect on amygdala activity, we performed a correlation analysis between estrogen levels and activity changes in the amygdala. However, correlating the difference between estrogen levels in the OT and PL condition with the percentage signal change of the observed interaction effect ($OT^{neg\text{-}neut} > PL^{neg\text{-}neut}$) in the corresponding peak voxels (left amygdala: $x = -22$, $y = -8$, $z = -14$; right amygdala: $x = 24$, $y = 6$, $z = -16$), revealed no substantial correlation, neither for the left ($r = .31$, $t[9] = 0.99$, $p = .35$), nor for the right ($r = -.16$, $t[9] = 0.49$, $p = .64$) amygdala.

4. Discussion

The aim of the present study was to investigate how OT modulates amygdala activity during the processing of emotional scenes in females. We found that OT selectively increased amygdala reactivity to threatening scenes, which is consistent with a recent report of enhanced amygdala reactivity to threat-related faces in females receiving OT (Domes et al., 2010a). Moreover, an exploratory whole brain analysis revealed a similar response in the left anterior temporal lobe, a structure that has also been implicated in social and emotional processing (Olson et al., 2007). These effects could not be explained by differences in the exploration of salient scene features and they were not evident in subjective arousal ratings. It has to be mentioned, however, that arousal ratings were only given on a roughly graded four-point scale for a series of scenes. Therefore, it seems possible that these ratings were too insensitive to detect subtle changes in arousal during scene presentation. Future studies should, thus, use more sensitive measures (e.g., skin conductance measures) to investigate whether the reported changes in amygdala activity are accompanied by behavioral changes. The currently observed effect of enhanced amygdala reactivity to threatening scenes following OT treatment in females sharply contrasts with the observation of attenuated amygdala activity in response to threat-related scenes (Kirsch et al., 2005) and faces (Domes et al., 2007a; Gamer et al., 2010; Kirsch et al., 2005; Petrovic et al., 2008) in males. Taken together, these findings suggest that OT differentially affects the neural processing of threatening stimuli in males and females.

The amygdala is crucially implicated in the processing of potentially threatening stimuli in the environment (Bishop, 2008). The basal and lateral nuclei of the amygdala receive highly processed sensory information, which enable the detection of threat-related stimuli. The central nucleus subsequently initiates fear responses via projections to the brain stem, allowing the organism to behave appropriately in a hostile environment. The OT-dependent increase in amygdala reactivity to threatening scenes may thus reflect an effect of the neuropeptide on female threat-avoidance and safety seeking behavior. In the present study, the threatening scenes depicted social and non-social sources of threat (e.g., snarling dogs, injured children or exploding cars), which may lead to the speculation that OT generally enhances threat-processing in females. In males, on the contrary, the processing of threat-related stimuli appears to be attenuated by OT as indicated by a decrease in amygdala reactivity to threatening stimuli following OT administration (Domes et al., 2007a; Gamer et al., 2010; Kirsch et al., 2005; Petrovic et al., 2008). As discussed previously (Kirsch et al., 2005), this reduction in amygdala activity appeared to be more pronounced in the context of social as compared to non-social threat, suggesting that OT may selectively attenuate

social-threat sensitivity in males. Although these findings suggest a possible sexual-dimorphism in the processing of social and non-social threat, they should be interpreted very cautiously as none of the above mentioned studies was explicitly designed to investigate this issue. For example, the use of a block design in the present study precluded the possibility to investigate whether OT differentially affected the processing of social and non-social scenes. Future studies should, therefore, employ more sophisticated designs to investigate the neural effects of OT on social and non-social threat-processing in males and females.

Sex-specific differences in amygdala reactivity to threat-related scenes have previously been reported (Domes et al., 2010b; Mackiewicz et al., 2006), indicating that threat-processing is generally enhanced in females. Gonadal steroids presumably contribute to these differences because amygdala responsiveness to threatening scenes seems to be modulated by progesterone and estrogen (Andreano and Cahill, 2010; Goldstein et al., 2005, 2010). Progesterone and estrogen are also implicated in sex-specific alterations of the OT-system (de Vries, 2008). Estrogen, in particular, stimulates OT release from hypothalamic neurons (Akaishi and Sakuma, 1985) and promotes OT receptor gene expression (Bale et al., 1995; Quinones-Jenab et al., 1997) as well as OT receptor binding in the amygdala (Young et al., 1998). Considering that estrogen levels, which are generally elevated during the mid-luteal phase (Nelson, 2005), tended to be higher in the OT compared to the PL condition, suggests that estrogen may have contributed to the observed changes in threat-related amygdala activity after OT administration. However, the present results do not provide convincing evidence for this notion, which may be due to the limitations of the present study design. For example, all participants were investigated during the mid-luteal phase which may have reduced the variance in estrogen levels that would have been necessary for the respective correlation analysis. Future studies should, therefore, investigate the impact of estrogen on OT induced-changes in amygdala-dependent threat-processing during different cycle phases.

From an evolutionary viewpoint, enhanced processing of potentially threatening stimuli may be highly adaptive for females during pregnancy, nursing, and infant care as these situations render them vulnerable to a broad array of threats. Accordingly, females may be exceptionally threat-sensitive during times of increased gonadal steroid concentrations, such as during times of fertility and pregnancy as suggested by estrogen and progesterone modulated changes in amygdala-dependent threat-processing (Andreano and Cahill, 2010; Goldstein et al., 2005, 2010). Gonadal steroids are elevated during pregnancy as well as during the mid-luteal phase (Nelson, 2005), suggesting that OT may have further enhanced females' propensity to detect threatening stimuli in the environment.

OT-dependent alterations in female threat-detection and safety-seeking behavior have also been found in non-human mammals (Bosch, 2011), suggesting that the observed OT-effects may indeed reflect an evolutionary adaptation to hostile environments. In female rats, local OT-levels within the amygdala increase during an intruder—encounter and are associated with the degree of aggression displayed toward the intruder (Bosch et al., 2005). Most relevant here, OT increases aggression toward the intruder but not toward the offspring, indicating a role for OT in the protection of the offspring. Interestingly, the observed OT-effects appear to be mediated by the rats' innate level of anxiety, suggesting that anxious rats perceive the encounter as more threatening than non-anxious ones and consequently display more maternal aggression (Bosch et al., 2005). Besides OT, gonadal steroids, in particular estrogen, are implicated in rats' maternal aggression (Lonstein and Gammie, 2002), which further supports the notion that the observed OT-effects, which appear to be mediated by estrogen, reflect an evolutionary shaped threat—response.

5. Conclusion

Taken together, the findings of the present study, which are consistent with previous ones (Domes et al., 2010a), suggest that OT promotes female threat-detection by increasing amygdala-dependent processing of threat-related stimuli. In males, on the contrary, OT appears to attenuate threat-sensitivity by decreasing amygdala reactivity to threat-related stimuli, particularly to those depicting social threat (Domes et al., 2007a; Gamer et al., 2010; Kirsch et al., 2005; Petrovic et al., 2008). However, these conclusions should be drawn with caution, considering that we only investigated a relatively small number of females during the mid-luteal phase. Besides this, we were unable to test whether social and non-social scenes differentially affected amygdala-dependent threat-processing. Moreover, we only focused on the processing of threat-related stimuli and did not consider the processing of other aversive stimuli, which may also be affected by OT (Riem et al., 2011). We suggest that future studies should be explicitly designed to investigate amygdala-dependent emotion processing in males and females after OT administration, preferably by explicitly considering cyclic variations in gonadal steroid levels. It, thus, remains an interesting question for future research to determine whether sex-specific differences in neuropeptidergic functioning during the processing of emotional, especially threatening, stimuli are indeed mediated by gonadal steroids (Carter et al., 2009).

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.psyneuen.2012.01.011.

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