

Oxytocin Modulates Amygdala Reactivity to Masked Fearful Eyes

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The amygdala reveals enhanced reactivity to fearful eye whites, even when they are backwardly masked by a neutral face and therefore processed with limited visual awareness. In our fMRI study, we investigated whether this effect is indeed associated with fear detection within the eyes of the neutral face mask, or more generally, with reactivity to any salient increase in eye white area. In addition, we examined whether a single dose of intranasal oxytocin would modulate amygdala responses to masked fearful eye whites via a double-blind, placebo-controlled pharmacological protocol. We found that increased amygdala responses to salient changes within a face's eye region occurred specifically for masked fearful eyes but not for similar increases in white area as induced by nonsocial control stimuli. Administration of oxytocin attenuated amygdala responses to masked fearful eye whites. Our results suggest that the amygdala is particularly tuned to potential threat signals from the eye region. The dampening effects of oxytocin on early amygdala reactivity may reflect reduced vigilance for facial threat cues at a preconscious level. Future studies may investigate whether this early modulation accounts for the beneficial effects of oxytocin on social cognition in anxiety-related disorders, as suggested by previous studies. *Neuropsychopharmacology* (2015) **40**, 2632–2638; doi:10.1038/npp.2015.111; published online 6 May 2015

INTRODUCTION

The eye region on a face conveys information that is crucial for several aspects of social cognition, including emotion discrimination and identity recognition. Evidence from eye movement studies suggests that the eye is the facial feature that is attended to first and longest during face processing (Scheller *et al*, 2012). The neuropeptide oxytocin plays a crucial role in regulating mammalian social cognition and behavior (Heinrichs *et al*, 2009; Meyer-Lindenberg *et al*, 2011) and it seems to particularly influence the processing of information from the eye region on faces. For example, the intranasal administration of oxytocin was found to improve mental state attribution based on subtle cues from the eye region (Domes *et al*, 2007b) and to facilitate attentional shifts following gaze cues in emotional faces (Tollenaar *et al*, 2013). Evidence from eye tracking studies points to a valence-dependent modulation of eye gazing behavior by oxytocin with increased orientation to the eye region on neutral and positive faces (Domes *et al*, 2013b; Gamer *et al*, 2010; Guastella *et al*, 2008), but decreased attentional capture by

threatening eye cues (Domes *et al*, 2013b). Notably, oxytocin's effects on both facial emotion processing and eye gazing behavior seem to be mediated via the amygdala (Gamer *et al*, 2010; for a recent review, see Kanat *et al*, 2014) and to occur very early during stimulus perception (Kanat *et al*, 2015; Schulze *et al*, 2011). In a recent study, we showed that intranasal oxytocin specifically reduces amygdala responses and its functional coupling with visual cortex areas when attending to cues from the eye region signaling social threat even when awareness of these cues is largely restricted (Kanat *et al*, 2015).

The eyes are particularly important in fear recognition (Adolphs *et al*, 2005; Scheller *et al*, 2012). A study using intracerebral electrophysiological recordings demonstrated that the amygdala preferentially responds to the eye region as compared with whole faces, and that this effect is most pronounced in conjunction with fearful eyes (Meletti *et al*, 2012). Evidence from imaging studies further substantiates the amygdala's critical role in processing fear signals conveyed by the eyes (Morris *et al*, 2002) and in attentional orienting to fearful eyes (Gamer and Buchel, 2009). Sections of wide-open, fearful eyes were found to elicit stronger responses in the left amygdala than gaze shifts of neutral eyes, despite a similar increase in eye white area (Hardee *et al*, 2008). Together, these results suggest that the amygdala is specifically tuned to salient eye signals associated with fear.

The amygdala reveals increased responses to fearful faces even when these are immediately masked by another

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stimulus and thereby processed without conscious awareness (Liddell *et al*, 2005; Whalen *et al*, 1998). Results from another study suggest that the amygdala's enhanced reactivity to masked fearful expressions relies largely on the increase in the white scleral field within fearful eyes (Whalen *et al*, 2004). However, amygdala responses to masked fearful expressions have been shown to rely on an interaction between emotional and masking stimuli (Kim *et al*, 2010). Correspondingly, the enhanced amygdala response to fearful eye whites in backward masking paradigms was found to disappear when either the position of the eye stimuli was changed or when the neutral face mask was replaced by another masking stimulus (Straube *et al*, 2010), suggesting that the amygdala mainly responds to salient events within the eye region of the masking stimulus that are potentially associated with fear. Whether this response is indeed associated with fear detection or whether the amygdala reacts more generally to any salient increase in eye white area has not been investigated yet.

We addressed this question with a functional magnetic resonance imaging (fMRI) study that assessed brain responses to masked fearful and happy eye whites. Based on the above-mentioned studies, we assumed that the amygdala responds more strongly to eye whites of masked fearful than to happy expressions. We further predicted that the same effect would not be observed by similar increases in the white area in nonsocial control stimuli. Furthermore, we examined whether a single dose of intranasal oxytocin would modulate responses of the amygdala and associated brain structures to masked fearful eye whites by means of a double-blind, placebo-controlled pharmacological protocol. As previous studies reported dampening oxytocin effects on amygdala reactivity to facial threat in men (Domes *et al*, 2007a; Kanat *et al*, 2015; Kirsch *et al*, 2005; Petrovic *et al*, 2008), we expected decreased amygdala responses to fearful eye whites following oxytocin as compared with placebo administration.

MATERIALS AND METHODS

Participants and Experimental Procedure

A total of 50 healthy male participants were recruited at the University of Freiburg to participate in a study on 'oxytocin and face processing'. All participants were right-handed nonsmokers and had normal or corrected-to-normal vision. They reported no previous or current medical illness or psychiatric disorder, with the latter validated using the *Structured Clinical Interview for DSM-IV*. Individuals were excluded in case of regular medication use or if they fulfilled MR-specific contraindications (eg, cardiac pacemaker, metal in body). Women were excluded from participation because of known sex differences regarding emotional reactivity as well as cycle-dependent hormonal variability. All participants gave their written informed consent and received monetary reimbursement following participation. They were asked to abstain from caffeine, alcohol, and medication use on the day of testing, and were instructed not to eat or drink anything (except water) 2 h before the experiment. The study took place in accordance with the Declaration of Helsinki and was approved by the local ethics commission.

On the testing day, participants filled out questionnaires and received thorough instruction on the testing procedure

and experiment. To become familiar with the task, they completed eight blocks of testing trials on a notebook. For another experimental task that preceded the task reported here, they were equipped with an electrode cap for facial EMG measurements. The electrode cap was not removed for the eye white task in order to save scanning time and to ensure that oxytocin levels remained high enough. Notably, as the first experimental task tested for oxytocin effects on facial mimicry behavior, it did not interfere with the research question being addressed in this study. Following electrode placement, participants were randomly assigned to receive OT (Syntocinon-Spray, Novartis) or placebo (containing all ingredients except the neuropeptide) via a nasal spray in a double-blind manner. Under the experimenter's supervision, they self-administered 3 puffs into each nostril amounting to a total dosage of 24 IU in the oxytocin condition. Administration was completed ~55 min before the experiment started. To control for potential oxytocin effects on mood, wakefulness, and calmness, participants completed a multi-dimensional questionnaire (Steyer *et al*, 1997) before substance administration and before entering the scanner. After the scanning session, participants were asked to describe the experimental stimuli and to report any perceived peculiarity throughout the experimental task. They were then debriefed about the nature of the experiment and shown some of the masked target stimuli. In case of self-reported awareness of these stimuli, subjects were excluded from data analysis.

Experimental Task and Stimuli

Before beginning the experiment, participants were told that they would see faces briefly appearing on the screen and that their task was to identify the gender of the last face within each block by pressing one of two mouse buttons. This cover story was used to maintain a high level of attention throughout the experimental blocks. As oxytocin is known to alter amygdala-mediated eye gazing behavior (Domes *et al*, 2013b; Guastella *et al*, 2008), participants were explicitly instructed to focus on the eye region on faces in order to rule out substance-induced differences in visual attention as a potential confounder. Participants then viewed blocks of masked fearful or happy eyes or nonsocial control stimuli that had been matched for the amount of white area. Control stimuli were included to rule out the possibility that the amygdala reacts to salient changes within the eye region of the masking stimulus irrespective of emotional significance.

All stimuli were based on pictures of seven male and seven female Caucasian faces taken from the NimStim Face Stimulus Set (<http://www.macbrain.org/resources.htm>). For each identity, pictures depicting a neutral, fearful, and happy expression were selected and converted to a black-and-white color scale. To create the neutral masking stimuli, hair and nonfacial parts were removed. To create the emotional stimuli, the eye region on happy and fearful faces was cut-out and spurs of gray shadows removed from the sclera. Control stimuli consisted of a scrambled version of these fearful or happy eyes and were therefore characterized by a similar amount of white area as the eye stimuli. The position of the eye and control stimuli was carefully matched to the neutral face of the masking stimulus. Images were projected on a semiopaque screen (resolution: 1280 × 1024 pixels) made visible via a mirror mounted on the head coil.

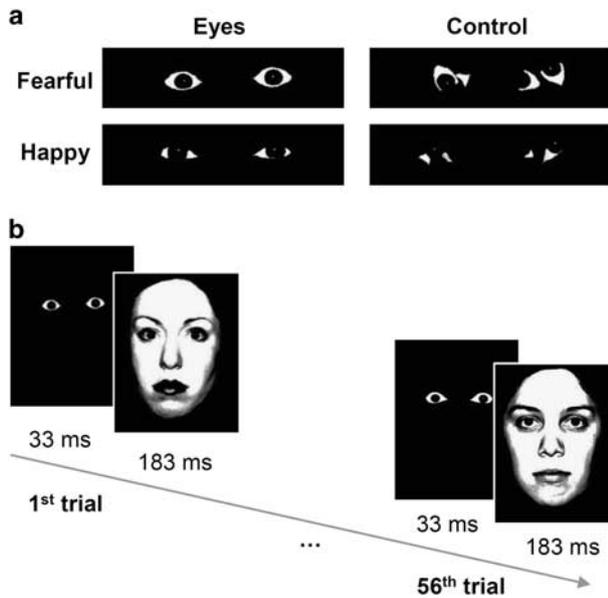


Figure 1 (a) Example stimuli for the four experimental conditions. (b) Block structure and duration of target and masking stimuli as exemplified for the fearful eyes condition.

In total, 12 experimental blocks were shown (three blocks per experimental condition) that alternated with rest blocks in which subjects viewed a red crosshair. Blocks were presented within a single run lasting ~ 14 min. Each experimental block consisted of 56 trials. Both blocks and trials within a block were presented in pseudorandomized order to rule out that the same experimental condition or same facial identity could be presented back to back. Each trial began with the target picture (33 ms) displaying happy or fearful eyes or the corresponding scrambled eye components (see Figure 1). The target picture was immediately masked by a neutral face (183 ms) of the same identity. Between trials, a black screen appeared for 300 ms. Regarding the target stimuli, we decided on a duration longer than that used in previous studies on processing fearful eye whites to allow for more variance in both substance groups. Stimulus presentation was controlled by Presentation 14 (www.neurobs.com).

Imaging Parameters and Data Analysis

Imaging was performed on a Siemens TIM Trio 3T system (Siemens Medical Systems, Erlangen, Germany) with a 12-channel head coil at the University Hospital Freiburg. Head motion was minimized using fasteners and additional foam paddings. A total of 408 functional images were acquired in a single session with a T2*-weighted gradient-echo planar sequence using BOLD contrast (TR = 2.04 s; TE = 28 ms; flip angle = 70°; field of view = 224 mm, voxel size = 3.0 × 3.0 × 3.5, 1 mm gap between slices). Each brain volume comprised 34 oblique axial slices measured in descending order and covering the whole brain except lower parts of the cerebellum. To establish magnetization equilibrium, the first five volumes of each functional time series were discarded from subsequent analyses. In addition to functional scans, an anatomical image was acquired for each participant with a

3D MPRAGE sequence (TR = 2.2 s; TE = 2.15 ms; flip angle = 12°; 1 × 1 × 1 mm isotropic resolution) and later coregistered with the functional data.

Functional images were corrected from motion and distortion artifacts during scanning by means of a point spread function mapping approach (Zaitsev *et al*, 2004). Following visual inspection of artifacts related to fast motion, data were preprocessed and analyzed in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). Images were spatially normalized to MNI space based on segmentation parameters from anatomical scans, and smoothed using a 9 mm FWHM (full width at half maximum) Gaussian kernel. On the single-subject level, experimental runs of each condition were modeled as box-car functions with a canonical hemodynamic response function. To remove residual movement-related variance, movement parameters estimated from raw functional images were included as potential confounds. As we were mainly interested in effects within the amygdala, a structure known to display substantial changes in activation following stimulus repetition (Breiter *et al*, 1996), we additionally modeled exponential decay regressors for each experimental block. Low-frequency noise within the time series was removed by applying a 128-s high-pass filter.

For each individual and experimental condition, regression coefficients were estimated and forwarded to a full-factorial random effects analysis on the group level. Within this analysis, we tested for effects of substance group (oxytocin, placebo), emotion (happy, fearful), and stimulus type (eyes, control) on BOLD activity. As the bilateral amygdalae represented our main regions of interest (ROIs), we applied a small volume correction in these areas via anatomical masks derived from the WFU PickAtlas (Tzourio-Mazoyer *et al*, 2002). To retrace the contribution of distinct amygdala subregions to observed effects, we applied maximum probabilistic anatomical maps in a second step using the anatomy toolbox integrated in SPM (Eickhoff *et al*, 2005). The significance threshold was set to $p < 0.05$, corrected for the number of voxels within the ROI. We also conducted an exploratory whole-brain analysis with a liberal threshold of $p < 0.001$ and minimum cluster size of 10 contiguous voxels.

RESULTS

In the placebo group, we had to exclude four subjects because of subjective awareness of the target stimuli ($n = 1$), anatomical abnormalities ($n = 1$), or severe and uncorrectable motion artifacts ($n = 2$). In the oxytocin group, motion artifacts led to the exclusion of two participants. Our remaining sample therefore comprised 43 subjects (PL: $n = 21$; OT: $n = 22$). Substance groups did not differ in age (mean age \pm SD: PL: 23.9 \pm 2.74, OT: 24.32 \pm 3.43; $T_{41} = -0.485$, $p = 0.630$), potentially relevant personality traits such as anxiety (STAI: PL: 37.19 \pm 8.94, OT: 35.19 \pm 10.83; $T_{40} = 0.653$, $p = 0.518$), or autistic traits (AQ: PL: 16.00 \pm 6.60, OT: 15.95 \pm 5.07; $T_{40} = 0.026$, $p = 0.979$).

Analyses within the Placebo Group

We first conducted separate voxel-wise analyses within the left and right amygdala under placebo conditions. This procedure revealed voxels within both amygdalae that

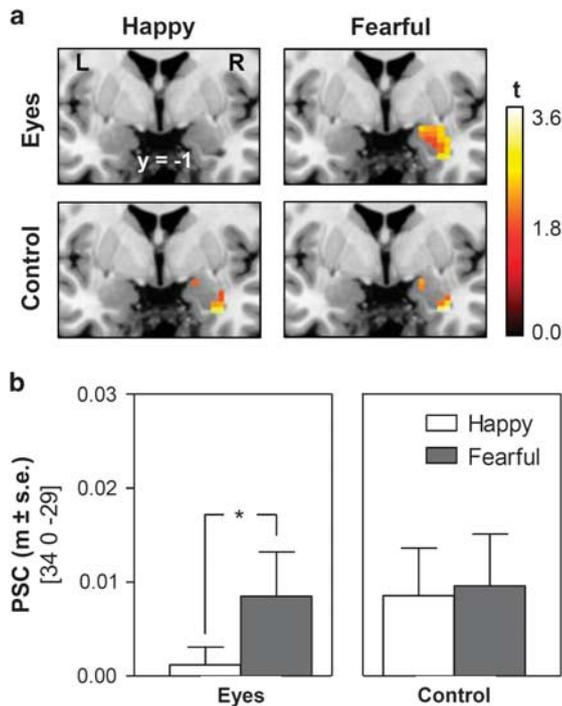


Figure 2 Effects of salient changes in the eye region on the neutral face mask with the right amygdala ROI for both stimulus type conditions. (a) Fearful eyes significantly increased activation within the right amygdala (x, y , and z : 34, 0, -29; $T = 3.31$; $p_{\text{SVC}} = 0.010$), whereas similar effects were absent in the control condition ($p_{\text{SVC}} > 0.05$). For illustration purposes, the SPMs are displayed at an uncorrected threshold of $p < 0.05$. (b) Percent signal change within the right amygdala peak voxel for masked 'fearful' and 'happy' target stimuli in the eyes and control condition.

showed increased responses to fearful as compared with happy target cues irrespective of stimulus type, that is, that were generally activated by salient changes within the eye region on the mask (left: $k = 8$; x, y, z : -19, -7, -17; $T = 2.88$; $p_{\text{SVC}} = 0.029$; right: $k = 17$; x, y, z : 27, -7, -14; $T = 2.84$; $p_{\text{SVC}} = 0.035$). We next tested for differential amygdala reactivity to fearful eye whites as compared with control stimuli using the interaction contrast $\text{Eyes}^{\text{Fear} > \text{Happy}} > \text{Control}^{\text{Fear} > \text{Happy}}$. There were no voxels displaying a significant interaction between the degree of white area and the stimulus type (left: $p_{\text{SVC}} > 0.05$ for all voxels). However, testing for both stimulus types separately revealed significant reactivity to fearful as compared with happy targets only in the eye condition (left: $k = 10$; x, y, z : -22, -7, -14; $T = 2.76$; $p_{\text{SVC}} = 0.039$; right: $k = 41$; x, y, z : 34, 0, -29; $T = 3.31$; $p_{\text{SVC}} = 0.010$), whereas no voxels showed increased responses to fearful targets in the control condition (left and right amygdala: $p_{\text{SVC}} > 0.05$ for all voxels; see Figure 2).

The additional exploratory whole-brain analysis revealed a significant modulation of brain activity by salient changes within the eye region on the neutral face mask beyond the predefined amygdala ROI (see Supplementary Table S1). Several brain areas, including the right pulvinar ($k = 90$; x, y, z : 13, -28, 4; $T = 4.09$; $p_{\text{uncorr}} < 0.001$), left anterior cingulate cortex ($k = 13$; x, y, z : -8, 49, -2; $T = 3.56$; $p_{\text{uncorr}} < 0.001$), and right medial orbitofrontal cortex ($k = 21$; x, y, z : 3, 67, -2; $T = 4.25$; $p_{\text{uncorr}} < 0.001$) responded to fearful targets

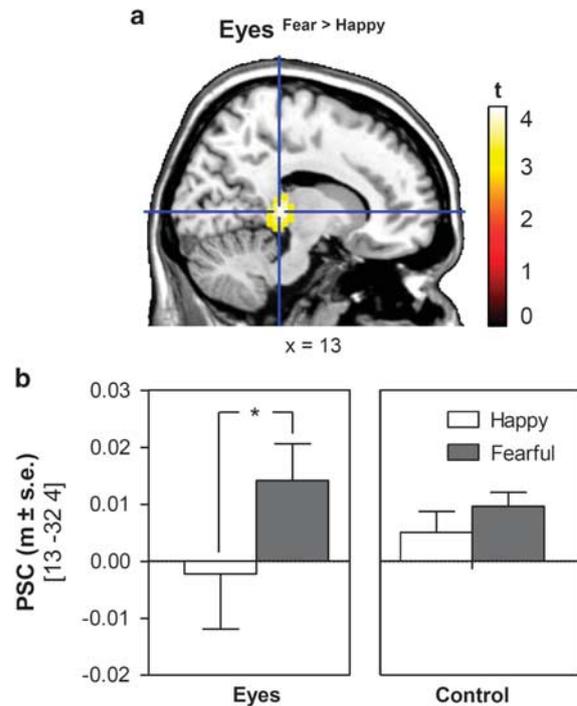


Figure 3 Effects of salient changes in the eye region of the neutral face mask on pulvinar activity for both stimulus type conditions as revealed by whole-brain analysis. (a) Fearful eyes significantly increased activation of the right pulvinar (whole-brain analysis; x, y , and z : 13, -32, 4; $T = 4.31$; $p_{\text{uncorr}} < 0.001$), whereas similar effects were absent in the control condition ($p_{\text{uncorr}} > 0.001$). (b) Percent signal change within the right pulvinar peak voxel for masked 'fearful' and 'happy' target stimuli in the eyes and control condition.

irrespective of stimulus type (Fearful > Happy; Supplementary Table S1). However, within separate analyses of the two stimulus types, the pulvinar was the only region that specifically responded to the eye condition ($k = 135$; x, y, z : 13, -32, 4; $T = 4.31$; $p_{\text{uncorr}} < 0.001$), whereas significant effects on the same statistical threshold were absent in the control condition (see Figure 3 and Supplementary Table S1). Notably, across the whole brain, no voxels displayed a significant interaction between stimulus type and the amount of white area. In sum, analyses within the placebo group revealed significant modulation by salient changes within the eye region on the masking stimulus within the right amygdala and right pulvinar that seemed specific to eye stimuli.

Modulation of Brain Responses by Intranasal Oxytocin

We next tested for brain-activity modulation via intranasal oxytocin with specific focus on oxytocin effects on responses within the bilateral amygdalae and right pulvinar as regions of interest. Within the amygdalae, oxytocin administration had no effect during the processing of fearful as compared with happy control stimuli ($p_{\text{SVC}} > 0.05$ for all voxels). Conversely, oxytocin significantly reduced right amygdala responses to fearful as compared with happy stimuli in the eye condition ($\text{Placebo}^{\text{Eyes: Fear} > \text{Happy}} > \text{Oxytocin}^{\text{Eyes: Fear} > \text{Happy}}$; $k = 35$; x, y, z : 34, 0, -26; $T = 2.77$; $p_{\text{SVC}} = 0.042$; Figure 4). Applying maximum probability maps to the observed

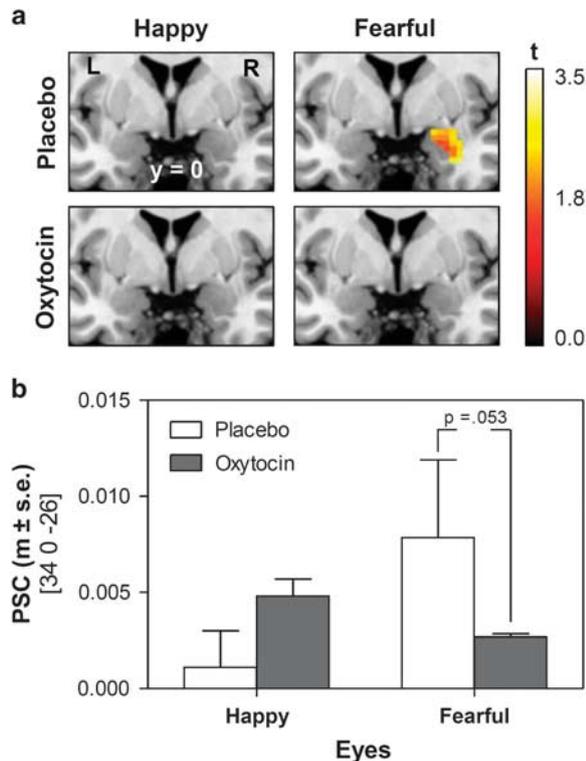


Figure 4 Effects of intranasal oxytocin on reactivity to masked fearful as compared with happy eyes within the right amygdala ROI. (a) Oxytocin significantly reduced right amygdala responses to masked fearful eyes (x, y , and z : 34, 0, -26; $T=2.77$; $p_{SVC}=0.042$). For illustration purposes, the SPMs are displayed at an uncorrected threshold of $p<0.05$. (b) Percent signal change within the right amygdala peak voxel for masked 'fearful' and 'happy' eye stimuli in the placebo and oxytocin condition.

oxytocin effect revealed that the majority of significant voxels including the peak voxel were located within the basolateral amygdala, whereas the remaining voxels of the cluster lay within the superficial complex (see Supplementary Figure S1). Analysis within the right pulvinar revealed no significant oxytocin effects on reactivity to either fearful eye whites or fearful control stimuli ($p_{SVC}>0.05$ for all voxels). However, observed as a trend, oxytocin lowered right pulvinar reactivity to fearful targets irrespective of stimulus type (Placebo^{Fear>Happy}>Oxytocin^{Fear>Happy}: $k=41$; x, y, z : 17, -35, 1; $T=2.62$; $p_{SVC}=0.053$). In contrast, neither the amygdalae nor right pulvinar displayed an increase in responses to fearful targets following oxytocin administration.

Results from the subsequent exploratory whole-brain analysis within the oxytocin group are reported in Supplementary Table S2. In addition, we applied differential contrasts that tested for significant effects of oxytocin *versus* placebo administration (see Supplementary Table S3). These analyses revealed dampening oxytocin effects on brain responses to fearful as compared with happy stimuli across stimulus type conditions within the left anterior cingulate cortex ($k=13$; x, y, z : -8, 49, -2; $T=3.53$; $p_{uncorr}<0.001$) and left midtemporal gyrus ($k=18$; x, y, z : -54, -7, -14; $T=3.42$; $p_{uncorr}<0.001$). Both regions displayed enhanced reactivity to salient increases in white area within the eye region on the neutral face mask under placebo, whereas this effect disappeared following oxytocin administration (additional clusters are reported in Supplementary Table S3).

We observed no significant voxels displaying increased reactivity to salient, that is, 'fearful', stimuli under oxytocin as compared with placebo ($p_{uncorr}>0.001$).

To control for differential changes within subjective state measures following substance administration, we ran a repeated-measures ANOVA on the MBDF subscales. This analysis revealed that oxytocin administration had no differential effect on changes in self-reported wakefulness or mood across the experimental session (*substance* × *time interaction*: all $F_{1,38} \leq 2.7$, all $p \geq 0.11$; Supplementary Table S4). Regarding self-perceived calmness, the oxytocin group demonstrated higher values than the placebo group despite randomized assignment to substance groups (*main effect of substance group*: $F_{1,38}=7.19$, $p=0.011$). Entering each participant's baseline value as a covariate into our group analysis, however, did not change our results' significance.

DISCUSSION

This study examined whether the increased amygdala response to masked fearful eye whites as observed in previous studies is emotion specific or whether it is solely driven by salient changes within the eye region on the neutral face mask irrespective of emotional meaning. Furthermore, we investigated whether a single dose of intranasal oxytocin would alter neural reactivity to masked fearful eye whites within the amygdala and associated areas. Under placebo conditions, we noted enhanced amygdala reactivity to fearful as compared with happy eye whites masked with a neutral face, thereby replicating previous studies' results (Straube *et al*, 2010; Whalen *et al*, 2004). In addition, we observed the same effect within the pulvinar that is known to be extensively interconnected with the amygdala both anatomically (Tamietto *et al*, 2012) and functionally (Morris *et al*, 1999; Troiani *et al*, 2014). These heightened neural responses occurred despite subjective unawareness of the presented stimuli. Furthermore, they seemed specific to fearful eye whites and not driven solely by increases in luminance as control stimuli (scrambled eye whites) evoked no significant differential responses. Our findings therefore suggest that the amygdala does not generally respond to an increase in white area within the eye region on a face mask. Rather, both the amygdala and pulvinar seem to display a preference for fear-related eye cues before conscious stimulus processing. This underlines the involvement of both structures in preconscious fear processing (Liddell *et al*, 2005; Morris *et al*, 2002).

The administration of intranasal oxytocin decreased amygdala responses to masked fearful eye whites. This finding concurs with a recent study's data showing that oxytocin attenuates amygdala responses to threat cues from the eye region at very early stages of emotion perception (Kanat *et al*, 2015). In addition, oxytocin reduced the reactivity of the pulvinar, anterior cingulate cortex, and parts of the ventral stream to salient changes within the eye region on the neutral face mask irrespective of emotional meaning. Although all of these structures have previously been implicated in the processing of masked fearful faces (Liddell *et al*, 2005), our results suggest that a subtle increase in eye white suffices to activate this 'alarm network'. Within this system, the pulvinar is thought to amplify the processing of salient and emotionally significant stimuli via its

widespread connections with visual cortex areas and with the structures involved in salience processing such as the amygdala and anterior cingulate cortex (Pessoa and Adolphs, 2010). Beyond this context, the oxytocin effects we observed may reflect an impairment in the early processing of fear-related signals from the eye region by modulatory influences on an emotional salience network (cf. Koch et al, 2014).

Such early oxytocin modulation may underlie its known effects on social attention. For example, there is evidence that oxytocin facilitates attentional disengagement from negative facial expressions (Domes et al, 2013b; Ellenbogen et al, 2012) and enhances the allocation of attentional resources toward positive but not negative social cues (Domes et al, 2013a; Prehn et al, 2013). In addition, decreased neural reactivity to threat cues from the eyes following oxytocin administration may contribute to its prosocial effects when evaluating negative stimuli. For instance, intranasal oxytocin reduces subjective experiences of threat from aversively conditioned facial expressions (Petrovic et al, 2008), increases approach motivation to socially threatening stimuli (Radke et al, 2013), and attenuates affective reactions to social betrayal (Baumgartner et al, 2008).

An early modulation of facial threat perception by oxytocin may be particularly relevant in disorders characterized by hypersensitivity to social threat. For example, social anxiety is associated with increased orientation to facial threat (Mogg et al, 2007; Mogg and Bradley, 2002), enhanced attentional cuing by fearful eye gazes (Fox et al, 2007), and aversion to direct eye gaze (for a recent review, see Schulze et al, 2013). On the neural level, anxious individuals reveal increased amygdala responses to fearful faces (Labuschagne et al, 2010) as well as decreased connectivity between the amygdala and prefrontal cortex regions (Dodhia et al, 2014; Kim et al, 2011). The amygdala's basolateral complex is known to promote reactivity to fear signals through interaction with the noradrenergic system (Hurlemann et al, 2010). Notably, individual anxiety levels are known to correlate with basolateral amygdala responsiveness to backwardly masked fearful faces (Etkin et al, 2004), and damage to this structure is assumed to induce hypervigilance for threat cues (Terburg et al, 2012).

In our study, increased amygdala responses to masked fearful eye whites were located within the basolateral amygdala, whereas this effect tended to vanish following oxytocin administration, suggesting anxiolytic effects. This result is consistent with the normalizing effects of intranasal oxytocin on both heightened amygdala responses to fearful faces (Labuschagne et al, 2010) and hypoconnectivity between the amygdala and medial prefrontal cortex in social anxiety disorder (Dodhia et al, 2014). Moreover, it bolsters recent evidence from an eye tracking study suggesting that oxytocin may reduce hypervigilance in particular to threat cues from the eye region and associated amygdala reactivity (Bertsch et al, 2013). Our findings suggest that oxytocin decreases reactivity to subtle fear cues from the eye region via inhibitory influences on the basolateral amygdala and, potentially, its coupling with the noradrenergic system. This may serve as a key mechanism by which oxytocin could help to reduce hypervigilance for social threat in anxiety-related disorders.

Taken together, our results support the idea that a network comprising the amygdala, pulvinar, anterior cingulate, and visual cortex regions automatically detects salient changes within the eye region on faces and classifies their emotional relevance before conscious stimulus evaluation. This network's modulations observed via oxytocin administration may reflect a decrease in the preconscious ascriptions of biological significance to potential threat cues from the eyes. Future studies may investigate whether these modulations account for oxytocin's positive effects on social attention processes in social anxiety.

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