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Enhanced orienting of attention in response to emotional gaze cues after oxytocin administration in healthy young men

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Summary
Background: Oxytocin is known to enhance recognition of emotional expressions and may increase attention to the eye region. Therefore, we investigated whether oxytocin administration would lead to increased orienting of attention in response to gaze cues of emotional faces.
Methods: In a randomized placebo-controlled double-blind crossover study 20 healthy males received 24 IU of oxytocin or placebo. Thirty-five minutes after administration they performed a gaze cueing task with happy, fearful and neutral faces. Stress levels were measured throughout the study.
Results: Oxytocin did not affect stress levels during the study, but significantly increased gaze cueing scores for happy and fearful expressions compared to placebo. No effects were found for neutral expressions. Trait anxiety or depression did not moderate the effect.
Conclusions: Oxytocin increases orienting of attention in response to emotional gaze cues, both for happy and fearful expressions. Replication is needed in female and clinical populations. Effects of oxytocin on early, automatic processing levels should be studied in relation to previously found pro-social and behavioral effects of oxytocin.

1. Introduction

Oxytocin affects many social and emotion-related behaviors including trust, attachment behavior, responding to stress, social memory, and the ability to recognize and discern

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emotions (for reviews see Heinrichs et al., 2009; Striepens et al., 2011; Bos et al., 2012). Oxytocin is thought to increase socially oriented or approach-related behaviors via increased positive emotions, but facilitation of negative emotions has repeatedly been found as well (for an overview see Kemp and Guastella, 2011). Emotional information from faces, and especially the eye region, is generally recognized better after oxytocin administration (e.g. Domes et al., 2007; Marsh et al., 2010; Schulze et al., 2011; for a review see van Ijzendoorn and Bakermans-Kranenburg, 2012). This might be induced by increases in attention towards the eye region (e.g. Guastella et al., 2008a,b; Gamer et al., 2010; Domes et al., 2012a), although several studies found no effects of oxytocin on gaze behavior (Domes et al., 2010; Lischke et al., 2012b), or even showed that emotion recognition can be affected without changes in gaze behavior (Lischke et al., 2012a). Modulation of amygdala activity by oxytocin may be responsible for the changes in attentional processes, emotion recognition and behavior (Meyer-Lindenberg et al., 2011; Bos et al., 2012; Striepens et al., 2012).

Most behavioral effects of oxytocin are found on more conceptual and elaborate processing levels, but recent evidence shows that even early automatic attentional or recognition processes may be affected by oxytocin (Guastella et al., 2009; Schulze et al., 2011; Domes et al., 2012a; Ellenbogen et al., 2012a,b). As recognition of emotional expressions in faces, and attention to the eye region seem enhanced by oxytocin, we sought to investigate whether oxytocin administration would lead to increased orienting of attention in response to eye gazes of emotional faces. This might indicate amplified information processing during socially salient encounters, as emotional gazes may indicate safety or threat in a specific location. Changes in such early attentional processing due to oxytocin may underlie changes in cognitive and emotional processing at more elaborate and behavioral levels.

In the current study we examined performance on an emotional gaze cueing task after oxytocin compared to placebo. When a face that gazes toward the periphery is presented in the centre of a computer screen, spatial attention in the observer is quickly and automatically oriented toward the gazed at side of the screen. This will speed up responding when a target is presented at the gazed location (valid cue) and slow down responding when a target is presented on the other side (invalid cue), leading to a cueing effect (i.e. a positive difference between reaction times to invalid minus valid cues). We hypothesized that intranasal oxytocin administration would enhance orientation of spatial attention in response to moving eye gazes when these are expressed in emotional versus neutral faces. With regard to the pro-social theory on oxytocin, we might expect this enhancement specifically on cueing scores for positive (happy) faces, but social salience theory would predict enhanced cueing scores for both positive and negative (fearful) faces. We hope to shed more light on this distinction. Because stress reducing effects of OXT have been found before (Bos et al., 2012), we also investigated whether changes in physiological or psychological stress levels would mediate the effects of oxytocin.

2. Methods

2.1. Participants

Twenty healthy young men aged 18–27 years (M = 21, SD = 3) from Leiden University participated. For the purpose of homogeneity only males were included, as gender differences in oxytocin effects have been found before (Domes et al., 2010; Lischke et al., 2012b). All men were medication and drug free, reported no (history of) major physical, neurological or psychiatric illness. Participants were instructed to use no alcohol or caffeine on the day of the experiment, and not to eat or drink 2 h in advance, except water. Participants gave written informed consent and the study was approved by the local review board. One participant dropped-out after the first session due to illness, and was hence not included in the analyses.

2.2. Procedure

A placebo-controlled double-blind randomized crossover design was employed. Test sessions were separated by 5–7 days and started between 8:30 am and 6:00 pm. The two sessions started around the same time per participant, to control for circadian rhythms in cortisol. Each participant once received 24 international units (IU) of oxytocin via a nasal spray (3 puffs per nostril with 4 IUs[1] of Syntocinon, Sigma Tau), and once 6 puffs from an identical looking placebo nasal spray containing all ingredients except oxytocin. No undesired side effects were observed. Trait anxiety (STAI; Spielberger et al., 1983, max score 80) and depression (BDI-II; Beck et al., 1996, max score 63) measures were collected on the first session. The emotional gaze cue task was performed 35 min after treatment. To control for non-specific mood and anxiety effects, STAI-*state* was measured at 3 moments during the experiment; before treatment and 30 and 60 min after treatment. Also, blood pressure and heart rate measures, as well as saliva samples to measure cortisol levels were taken at these times as physiological measures for stress.

2.3. Emotional gaze cueing task

The emotional gaze cueing task used eight different oval gray-scaled cut-outs from photos of facial expressions (four males and four females) from Ekman and Friesen's Pictures of Facial Affect (Ekman and Friesen, 1976), and directly gazing faces from the Karolinska Directed Emotional Faces (Lundqvist et al., 1998). After presentation of a fixation cross for 750 ms, directly gazing happy, neutral, or fearful faces were presented for 100 ms with the fixation cross superimposed on it. These static faces appeared for another 200 ms, depicting the same person with the same expression, with eyes looking toward the left or right side. Participants were instructed to

[1] Recent analyses of the nasal sprays that were used for this experiment (Blockland DRUM03211) by the academic pharmacy revealed that there is inter- and intra-individual variance in the amount of IU that is delivered per puff, with an average of 2.5 IU per puff (i.e. 15 IUs in total).

fixate on the cross and ignore the face, as this would not predict target occurrence. Then a triangle-shaped target appeared 9° to the left or right side of the fixation cross and the participants had to indicate as fast as possible whether the triangle pointed up or downwards with their dominant index finger on a keyboard. Response times (RT) were recorded after onset of the target. Upon recording of RT or after 1500 ms, the screen would go blank for 2—3 s before a next trial began. After 6 practice trials, 96 trials with equal numbers of neutral, happy and fearful trials, valid and invalid cueing trials, and left and right target presentations were presented, fully counterbalanced and randomized. The EGCT lasted approximately 7 min.

3. Data reduction and analyses

To measure the effects of oxytocin on stress levels, we performed a Multivariate Repeated Measures (RM-) ANOVA with time (before, 30 min and 60 min after treatment) and treatment (oxytocin versus placebo) as within-subject variables and cortisol levels, heart rate, systolic blood pressure and STAI-*state* anxiety scores as dependent variables.

Before analyses of the EGCT, error trials were removed, after which RTs below 200 ms were removed as premature response, and RTs of 3 SDs above the mean were removed as slow outliers (first session 1: 750 ms; second session: 692 ms). One participant had 23% of scores removed during his placebo session due to errors or outliers. He was hence removed from further analyses, leaving 18 participants for analyses. There were no differences between the oxytocin and placebo session in errors (mean oxytocin = 2.2 (2.1), mean placebo = 2.1 (1.8), $F(1,17) = .147$, $p = .71$, $\eta_p^2 = .009$ premature responses (mean oxytocin = 0 (0), mean placebo = 0.05 (.24), $F(1,17) = 1.0$, $p = .33$, $\eta_p^2 = .056$) or slow outliers (mean oxytocin = 1.3 (1.7), mean placebo = 2.4 (3.1), $F(1,17) = 2.1$, $p = .16$, $\eta_p^2 = .11$).

Cueing scores were then calculated by subtracting mean RTs to valid cueing trials from mean RTs to invalid cueing trials, separately for neutral, happy and fearful gaze cue conditions. Higher cueing scores indicate stronger attentional cueing for that face type. A RM-ANOVA was performed with emotion (neutral, happy, fearful) and treatment (oxytocin, placebo) as within-subject variables, and treatment order as between-subject variable. Post hoc ANOVAs per emotion were performed. Subsequently, trait anxiety and depression scores were added to the RM-ANOVA as covariates.

All analyses were performed in SPSS 19, alpha was set at 0.05 (two-tailed), and as estimates of effect size we report partial eta-squared (η_p^2).

4. Results

STAI-*trait* anxiety scores ranged between 30 and 51 ($M = 35.8$, $SD = 5.4$) and BDI depression scores ranged between 0 and 17 ($M = 6.8$, $SD = 5.2$). Cortisol levels (nmol/L), heart rate, systolic blood pressure and STAI-*state* anxiety scores were entered in a Multivariate RM-ANOVA to test whether oxytocin reduced stress levels at 30 and 60 min after administration. While stress levels decreased over time ($F(8,52) = 7.9$, $p < .001$, $\eta_p^2 = .55$), no interaction between treatment and time was found ($F(8,52) = 1.6$, $p = .15$, $\eta_p^2 = .20$), see Table 1. When average starting time was included as a covariate to account for circadian rhythms, the effect of oxytocin did not differ (treatment by time interaction: $F(8,48) = 0.67$, $p = .72$, $\eta_p^2 = .10$). No stress reducing effects of oxytocin were shown, and stress level was hence not included as a mediator in subsequent analyses.

Cueing scores (RT invalid minus RT valid) per emotion and treatment are shown in Fig. 1. A RM-ANOVA with emotion (neutral, happy, fearful) and treatment (oxytocin, placebo) as within-subject variables and treatment order as between-subject variable showed that there was no main effect of emotion on cueing scores ($F(2,32) = 1.93$, $p = .16$, $\eta_p^2 = .11$). Also within the placebo session, no main effect of emotion was found ($F(2,32) = 2.39$, $p = .11$, $\eta_p^2 = .13$). There was a main effect of treatment ($F(1,16) = 5.37$, $p = .034$, $\eta_p^2 = .25$), and the crucial emotion by treatment interaction was also significant ($F(2,32) = 3.35$, $p = .048$, $\eta_p^2 = .17$). Post hoc ANOVAs showed that cueing scores were higher after oxytocin treatment versus placebo for the happy and fearful faces (resp. ($F(1,16) = 6.63$, $p = .020$, $\eta_p^2 = .29$) and ($F(1,16) = 5.07$, $p = .039$, $\eta_p^2 = .24$)), but not for the neutral faces ($F(1,16) = .52$, $p = .48$, $\eta_p^2 = .032$), indicating increased gaze cued orienting of attention for emotional faces after oxytocin administration compared to placebo.

No effects of treatment order were found in any of the analyses (all p's $> .13$). There were furthermore no significant interactions between treatment, emotion and STAI-*trait* anxiety (all p's $> .068$) or BDI depression scores (all p's $> .65$) when these were entered as covariates.

Table 1 Means (SD) for all four stress measures over time in the placebo and oxytocin condition.

Stress measures	Treatment	Before treatment	30 min after treatment	60 min after treatment
Cortisol (nmol/L)	Placebo	14.5 (1.8)	11.0 (1.7)	8.3 (1.1)
	Oxytocin	14.4 (2.7)	11.3 (1.9)	9.2 (1.6)
Heart rate (bpm)	Placebo	65.9 (3.5)	60.4 (2.2)	56.7 (2.2)
	Oxytocin	60.8 (2.9)	57.7 (2.5)	55.2 (2.3)
Systolic blood pressure (mmHg)	Placebo	128 (3.1)	118 (2.4)	116 (2.6)
	Oxytocin	126 (2.5)	121 (2.3)	122 (2.5)
STAI-state	Placebo	30.1 (1.3)	28.6 (1.8)	29.8 (1.6)
	Oxytocin	30.0 (1.2)	27.6 (1.3)	27.9 (1.0)

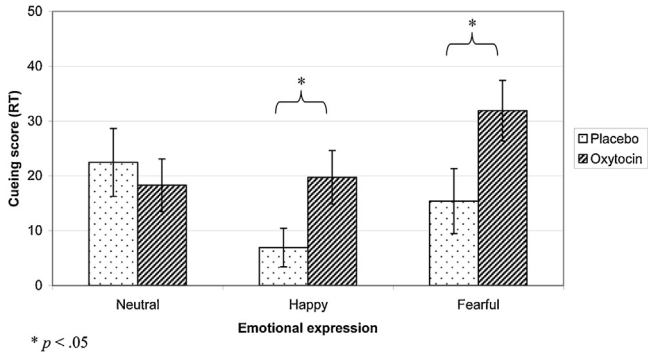

Figure 1 Gaze cueing scores (*M*, SEM) per emotion and treatment ($N = 18$).

5. Discussion

In the current study we show that oxytocin administration in healthy young men leads to an increase in the orienting of attention to gaze cues when these are presented in happy and fearful faces but not in neutral faces. These results are in line with the views that oxytocin increases social salience (for discussions see Bartz et al., 2011; Kemp and Guastella, 2011), and that it enhances the processing of (emotional) information already at an early stage (see also Schulze et al., 2011; Domes et al., 2012a; Ellenbogen et al., 2012a,b).

Oxytocin thus seems to induce automatic responding to perception of socially relevant information from the eye region, either by increased perception of emotional gaze cues or by stronger automatic orienting in response to this information. This may be useful in detecting safety and threat signals, as to avert potential stress from these signals or to decide to approach or avoid an object or location. This finding suggests a relation between oxytocin and an important cognitive-emotional process that is of great importance in social conduct and theory of mind (Emery, 2000).

While we studied early automatic orienting of attention to information from the eyes, increased attention to the human eye region after oxytocin administration has been shown before, although with mixed results. That is, Guastella et al. (2008a,b) found increased gaze behavior to neutral faces and Gamer et al. (2010) to neutral, happy and fearful expressions. However, while Domes et al. (2012b) also found increased gaze behavior to neutral and happy expressions, they found a decrease in eye gaze to angry expressions, and Domes et al. (2010), Lischke et al. (2012b) and Lischke et al. (2012a) found no effects of oxytocin on gaze behavior at all. In another study though, Domes et al. (2012a) found an increase in covert attention to happy expressions, but not to overt gaze behavior, indicating that early automatic attentional orienting is a different process than the (reflexive) shifting of eye gazes towards a location. In the current study, we now show that oxytocin guides spatial attention by cues from the eyes, but only for emotional facial expressions. How these findings relate to changes in more overt gaze behavior and e.g. emotion recognition due to oxytocin should to topic of future research.

We thus found both enhanced orienting of attention to gaze cues from positive (happy) and negative (fearful) faces, indicating a general emotional facilitation of spatial attention irrespective of valence. This contradicts views of prosocial or fear reducing effects of oxytocin, which are found at more elaborate processing levels, and recently on early attentional processes as well (Domes et al., 2012a; Ellenbogen et al., 2012b). That is, Domes et al. (2012a) only found enhanced attentional bias for positive (happy) faces but not to negative (angry) faces, and Ellenbogen et al. (2012b) showed a reduced attentional bias for negative (sad/angry) faces after oxytocin compared to placebo. Both of those findings are more in line with pro-social effects of oxytocin. Several reasons may account for these seemingly contradictory findings to our results. While both of those studies used exogenous cueing tasks, we studied automatic attentional orienting to centrally presented cues, indicating a possible differential processing of centrally presented emotional cues after oxytocin administration than peripherally presented cues. In a later study by Ellenbogen et al. (2012a), in which they studied the inhibition of centrally presented emotional faces, they found a reduced inhibition of sad facial expressions (although only in a group with depressive symptoms, and not for happy and angry expressions). This reduced inhibition is more analogous to the reduced ability to suppress automatic responding to centrally presented emotional gaze cues in the current study. Furthermore, the current study used averting gazes instead of directly gazing faces, which may change the perception of the emotional content of the expression (Adams et al., 2003). Moreover, these previous studies used sad and/or angry facial expressions, while we used fear as a negative emotion, and contrasted this with happy faces. While fearful and happy expressions may indicate signals for safety (approach) and danger (avoid), angry faces may elicit either approach or avoidance behavior (Putman et al., 2004), while sad faces may elicit empathic responses. As different types of negative expressions may induce different action tendencies, oxytocin can have expression-specific effects. In conclusion, the early attentional processing of emotional faces after oxytocin administration may be expression-specific, and the (spatial) context and presentation of facial and eye cues can significantly affect outcomes. Future research should carefully compare the diverse attentional processes and emotions that are either suppressed or enhanced by oxytocin, both at very early automatic, and relatively later, more elaborate processing levels.

We found no moderation of the effect by trait anxiety or depressed mood, suggesting the effect may be independent of potential existing emotional biases. However, we tested a relatively small and non-anxious group that showed no emotional bias in the cueing scores to start with. Previously, enhanced attentional orienting to fearful compared to happy

faces in healthy subjects under placebo condition has been shown with a comparable gaze cue paradigm (Putman et al., 2010). The fact that we found no emotional bias under placebo may be due to strict exclusion criteria for psychological problems, reflecting a healthy population without any emotional biases. However, as oxytocin may differentially affect early attentional processes dependent on pre-existing biases (Ellenbogen et al., 2012b), it would be important to test whether oxytocin also specifically enhances emotional biases in the orientation of attention in groups with (sub)-clinical levels of anxiety or depression as well, which are known to have heightened attentional biases to negative information (Frewen et al., 2008).

In sum, we add new findings to the recently established early attentional effects of oxytocin, in specific an enhancement of orienting in response to emotional gaze cues. These effects are found in a healthy male population, and should be replicated in (sub)clinical populations and in females, as gender difference in the response to oxytocin have been found before (Domes et al., 2010; Lischke et al., 2012b). Because the effects of oxytocin on early attentional processing in this and in earlier studies are relatively small, replication is needed, and the significance of these findings for higher level functioning, e.g. emotion recognition, approach behavior and social memory, should be topic of future research.

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Conflict of interest

None of the authors has any conflict of interest to declare.

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