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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