NeuroImage 162 (2017) 127–137

Contents lists available at ScienceDirect

NeuroImage

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

Sex-dependent neural effect of oxytocin during subliminal processing of negative emotion faces

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ARTICLE INFO

Keywords:
Oxytocin
Face emotion
Sex difference
Cingulate cortex
Inferior frontal gyrus
Anxiety

ABSTRACT

In line with animal models indicating sexually dimorphic effects of oxytocin (OXT) on social-emotional processing, a growing number of OXT-administration studies in humans have also reported sex-dependent effects during social information processing. To explore whether sex-dependent effects already occur during early, subliminal, processing stages the present pharmacological fMRI-study combined the intranasal-application of either OXT or placebo (n = 86–43 males) with a backward-masking emotional face paradigm. Results showed that while OXT suppressed inferior frontal gyrus, dorsal anterior cingulate and anterior insula responses to threatening face stimuli in men it increased them in women. In women increased anterior cingulate reactivity during subliminal threat processing was also positively associated with trait anxiety. On the network level, sex-dependent effects were observed on amygdala, anterior cingulate and inferior frontal gyrus functional connectivity that were mainly driven by reduced coupling in women following OXT. Our findings demonstrate that OXT produces sex-dependent effects even at the early stages of social-emotional processing, and suggest that while it attenuates neural responses to threatening social stimuli in men it increases them in women. Thus in a therapeutic context OXT may potentially produce different effects on anxiety disorders in men and women.

1. Introduction

The hypothalamic neuropeptide oxytocin (OXT) plays a key role in the regulation of complex social cognition and behavior. Initially well known for its modulating effects on social attachment and affiliation in rodents and sheep (Bethlehem et al., 2013; Bosch, 2011; Insel, 2010; Young et al., 2001), subsequent studies have revealed modulatory effects on a broad range of social functions, including promoting social behavior and interactions (Lukas et al., 2011), facilitating social evaluation (Lambert et al., 2014; Leknes et al., 2013) and decreasing social anxiety (Bale et al., 2001; Parker et al., 2005). In humans intranasal OXT has also been reported to influence a wide range of social and emotional behaviors (Kanat et al., 2014; Kendrick et al., 2001; Striepens et al., 2011). It has been hypothesized that OXT may play a key role in influencing emotion perception domains, particularly in relation to the perception of cues that are important for interpersonal interactions, such as emotional facial expressions (Shamay-Tsoory and Abu-Akel, 2016). In line with this hypothesis, recent meta-analyses have consistently concluded that a single dose of intranasal OXT can enhance facial emotion recognition, particularly of fearful and happy expressions (Shahrestani et al., 2013; Van IJzendoorn and Bakermans-Kranenburg, 2012), although not all studies have found consistent effects across emotions (Domes et al., 2013; Lischke et al., 2012a) and factors such as valence and presentation time may influence the outcome (see (Shahrestani et al., 2013)). There is also some evidence that OXT can improve recognition of angry, and particularly happy faces even under conditions of subliminal presentation (Schulze et al., 2011).

Intranasal OXT administration studies in humans have until recently primarily used male subjects, with a few early reports failing to find evidence for sex differences in the domains of social memory (Savaskan et al., 2008) and evaluation of facial trustworthiness (Theodoridou et al., 2009). However, a growing body of more recent studies involving larger numbers of subjects have revealed that intranasal OXT may often produce opposite effects in men and women. For example, behavioral studies

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http://dx.doi.org/10.1016/j.neuroimage.2017.08.079
Received 15 October 2016; Accepted 30 August 2017
Available online 4 September 2017

have reported opposite effects of intranasal OXT on the perception of social relationships (Fischer-Shofty et al., 2013), social judgments of facial stimuli (Hoge et al., 2014), and self-reported distress during social stress (Kubzansky et al., 2012). The neural correlates of these sex-differences remain largely unknown, although initial studies have reported that opposite effects of OXT in men and women during social information processing are accompanied by parallel differential effects on striatal activity as well as amygdala activity and connectivity (Chen et al., 2016; Feng et al., 2015; Gao et al., 2016). These previous studies targeted higher order social processing domains and despite some initial evidence from separate OXT-administration studies in men and women suggesting the possibility that there may also be sex differences in its effects on basic emotion processing domains, including emotional perception (Kanat et al., 2014; Wigton et al., 2015), no study has directly examined this in both sexes.

In contrast, sex-differences in basic emotion processing domains have been widely studied, although there is some inconsistency in relation to the magnitude of such differences, and in general behavioral effects on negative valence are more established than those for positive valence (Bradley et al., 2001). At the neural level, meta-analytic data suggests that men show generally greater responsivity in limbic, particularly amygdala and hippocampal regions, and in medial prefrontal regions during facial emotion processing (Fusar-Poli et al., 2009). A more recent meta-analysis covering neuroimaging studies using emotional scenes as well as faces reported generally greater responsivity in men in the insula and inferior frontal gyrus and additionally emphasized the important role of stimulus valence in this context, with women exhibiting stronger amygdala reactivity to negative stimuli while men exhibited stronger reactivity to positive ones (Stevens and Hamann, 2012).

Findings from studies using single intranasal application of OXT in healthy men have consistently reported modulatory effects on core nodes of the emotional face processing networks (Fusar-Poli et al., 2009), particularly the amygdala, but also hippocampus, insula and prefrontal regions (Kanat et al., 2014; Wigton et al., 2015). Although there has been some inconsistency in relation to reported effects of valence, most studies in men have found decreased limbic, particularly amygdala, responses to negatively valenced faces (Domes et al., 2007; Gamer et al., 2010; Kirsch et al., 2005).

On the other hand, several OXT-administration experiments in women have reported that OXT enhances rather than reduces amygdala responses to fearful faces and scenes (Domes et al., 2010; Lischke et al., 2012b), as well as activity in a more extensive network including anterior cingulate, insula, hippocampal and inferior frontal regions during evaluation of explicit emotional face stimuli (Domes et al., 2010; Pincus et al., 2010).

Against this background, the present study administered either a single dose of intranasal OXT or placebo (PLC) 86 participants (n = 43 males) to evaluate whether OXT modulates basic emotional processing differentially in men and women. To specifically address early emotional processes and to control for potential confounding effects on higher-order social evaluation, a backward-masking procedure was used to subliminally present emotional faces during fMRI acquisition. To increase the statistical power to determine sex-differential neural effects of OXT the analysis focused on key brain regions of the face processing networks that have previously been reported to show both sex differences (Fusar-Poli et al., 2009; Stevens and Hamann, 2012) and intranasal OXT effects (Kanat et al., 2014; Wigton et al., 2015): amygdala, hippocampus, anterior cingulate cortex, insula, inferior frontal gyrus, fusiform gyrus and medial temporal gyrus. Based on previous OXT administration studies, we hypothesized valence and sex-dependent effects of intranasal OXT, with neural responses being reduced in men but increased in women during the subliminal processing of negatively valenced emotional faces.

2. Materials and methods

2.1. Participants and treatment

A total of 86 healthy, young right-handed Chinese (Han) students (43 males; age range = 18–29 years; M±SD = 22.41 ± 2.054 years) from the University of Electronic Science and Technology of China (UESTC) participated in the study after providing written informed consent. All volunteers were free of current or past medical, neurological, or psychiatric disorders. Exclusion criteria included: MRI contraindications, history of head injury, pregnancy, uterine cavity operations conducted within one year, rhinitis and regular drug, cigarette or alcohol use. All female participants were nulliparous and not taking oral contraceptives. 33 out of 43 females reported being in the luteal phase of their menstrual cycle. There were no significant differences between OXT and PLC groups in terms of menstrual cycle phase ($p = 0.14$).

Male and female participants were randomly assigned to either 24 IU intranasal administration of OXT (Oxytocin Spray – Sichuan Meike Pharmacy Co., Ltd, Sichuan, China) (n = 44, 22 males) or placebo (PLC identical Spray without OXT, provided by the same supplier) (n = 42, 21 males) using a standardized intranasal administration protocol (Guastella et al., 2013). In line with previous studies that applied intranasal OXT (Scheele et al., 2013; Striepens et al., 2012) the fMRI experiment started 45 min after treatment administration. Subjects were randomly allocation to treatment groups and a double-blind experimental protocol was used.

To evaluate the potential therapeutic relevance of intranasal OXT's effect on sub-liminal social-emotional processing, depression and anxiety symptom levels were assessed using validated Chinese versions of self-report scales: Beck Depression Inventory, BDI-II (Beck et al., 1996; Wang et al., 2011); and State-Trait Anxiety Inventory, STAI (Li and Qian, 1995; Speilberger et al., 1983).

The study was approved by the local Ethical Committee at UESTC, in compliance with the latest revision of the Declaration of Helsinki and registered at ClinicalTrials.gov (Identifier: NCT02183948; https://clinicaltrials.gov/show/NCT02183948). The data was acquired between June and December 2014. It should be noted that the completion date originally specified in the clinical trial registration was revised from July 2014 to December 2014 and that no detailed analysis plan was provided.

2.2. Face stimuli

Stimuli were selected from two standardized facial expression databases: Chinese Facial Affective Picture System (Gong et al., 2011) and Taiwanese Facial Expression Image Database (TFEID) (Chen and Yen, 2007). Individual characteristics (e.g. hair) were covered using an oval frame with the same color as the background (*see* Fig. 1). Emotional faces (happy, angry, fearful, sad, disgust, 36 stimuli per condition, balanced for gender, 18 males and 18 females) were backward masked with neutral faces from the same individual. In addition, another 36 neutral faces masking their mirror-reversed versions were incorporated as control stimuli. An additional 120 novel neutral faces (60 males, 60 females) were included in the post scan behavioral assessment.

2.3. fMRI backward masking paradigm

Stimuli were presented in an event-related design and distributed over 4 subsequent runs (balanced for emotion and gender) with 54 trials per run (duration per run: 354s; *see* Fig. 1*a*). In line with previous studies (Milders et al., 2008), each trial displayed a 20 ms emotional or neutral face (masked face) immediately followed by a 120 ms masking neutral face of the same individual. A total of 6 stimulus conditions were presented: happy-neutral (HN), angry-neutral (AN), fearful-neutral (FN), sad-neutral (SN), disgusted-neutral (DN) and mirror-reversed neutral-neutral (NN). Between the trials a jittered fixation-cross serving as