Oxytocin, the peptide that bonds the sexes also divides them

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Facilitation of social attraction and bonding by the evolutionarily conserved neuropeptide oxytocin is well-established in female mammals. However, accumulating behavioral evidence suggests that oxytocin may have evolved sex-specific functional roles in the domain of human social cognition. A critical question is how oxytocin differentially modulates neural processing of social information in men and women, leading to divergent behavioral responses. Here we show that intranasal oxytocin treatment produces sex- and valence-dependent increases in amygdala activation when women view individuals identified as praising others but in men those who criticize them. Women subsequently show increased liking for the faces of these individuals, whereas in men it is reduced. Thus, oxytocin may act differentially via the amygdala to enhance the salience of positive social attributes in women but negative ones in men. We hypothesize that oxytocin may have evolved different but complementary roles to help ensure successful reproduction by encouraging mothers to promote a prosocial rearing environment for offspring and fathers to protect against antisocial influences.

oxytocin | sex differences | amygdala | functional imaging | social cognition

The hypothalamic neuropeptide oxytocin (OXT) plays a key role in promoting maternal behavior and mother–infant bonding in mammals (1) as well as pair bonds with males in monogamous species (2). Recent studies in both monkeys and humans have suggested that it has not only evolved a more extensive role in social cognition in female primates but also become progressively used by males in this domain (3). Although OXT appears to facilitate both salience and motivational aspects of social cues in both sexes (3, 4), there is increasing evidence that it may often produce opposite effects in these domains in men and women (5–7), raising the intriguing possibility that it has evolved some sex-specific functions at both neural and behavioral levels. In particular, behavioral studies have reported that whereas OXT tends to facilitate positive social judgments (7), social approach (8), kinship recognition (5), and altruism (9) in women, in men it can facilitate negative social judgments (7), social avoidance (10), competitor recognition (5), and selfishness (9). Similarly, in response to couple conflict, OXT decreased sympathetic activity and arousal in women but increased them in men (6). The neural basis of these opposing sex-dependent behavioral effects of OXT has not, however, been established.

Previous research has shown that the amygdala has different responses to positive and negative valence social information in men and women (11) and also may be a critical target for sex-specific functional effects of OXT. The amygdala has a sexually dimorphic distribution and expression of OXT receptors in nonprimate mammals (12, 13), and separate OXT-application studies in humans have indicated that there may be differential amygdala reactivity to fearful faces and fearful/threatening scenes in men (14, 15) and women (16, 17). Importantly, this region plays a key role in processing social salience (18) and controlling approach and avoidance behaviors (10),

which OXT has been shown to modulate (3, 4, 6, 19). Here we have used behavioral pharmacology combined with functional magnetic resonance imaging (fMRI) to establish whether OXT can produce opposite effects on male and female behaviors and amygdala responses by using a social judgment, "first-impression" paradigm known to involve this region (20).

During social interactions, we make rapid judgments about new people that determine whether to approach or avoid and shape our future interactions with them (21). Individuals paired with positive valence characteristics are rated as more likeable and approachable but the opposite for those with negative information (22). In our paradigm (Fig. 1), we therefore manipulated the valence context during impression formation by associating neutral faces of different individuals with verbal statements assigning them positive (praising others or objects), negative (criticizing others or objects), or mixed (both) valence characteristics. We first observed whether amygdala responses to the faces combined with different valenced information were differentially influenced by OXT in male and female subjects, and then whether this resulted in different likeability judgments when the faces were subsequently presented alone. We hypothesized that OXT would sex-specifically modulate amygdala responses and its functional interactions with other regions in the social salience network, such that in women it would enhance the salience of positive social attributes (i.e., praising) but in men that of negative ones (i.e., criticizing). To evaluate our hypothesis, male and female subjects self-administered either OXT

Significance

To interpret and respond appropriately to social cues is a fundamental aspect of human nature that becomes impaired in many mental disorders. The past decade has witnessed unprecedented excitement across neuroscience, psychology, and psychiatry regarding the role of oxytocin in human social cognition and its potential therapeutic use. There is also a considerable long-established public interest in behavioral sex differences and the molecular and brain mechanisms responsible. The current findings provide the first mechanistic explanation, to our knowledge, for how this key social molecule has evolved sex-dependent actions on amygdala function to influence the salience and attractiveness of positive social attributes in women but negative ones in men.
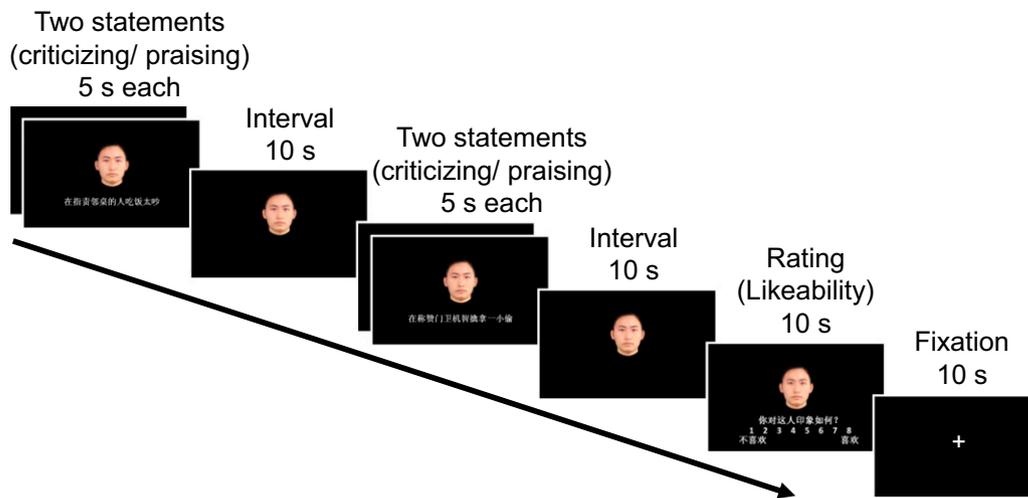

Fig. 1. Example of a trial in the first-impression task.

(24 IU) or placebo (PLC) intranasally in a double-blind design and, after 45 min, underwent the first-impression task during fMRI.

Results

Based on our hypothesis, a whole-brain fMRI mixed-effect analysis of variance (ANOVA) aimed to identify brain regions showing treatment × sex interactions associated with people-directed statement valence (criticism vs. praise). This yielded a significant treatment × sex interaction in the left amygdala for social criticism vs. praise ($k = 262$, familywise error (FWE) corrected $P_{FWE} = 0.001$) (Fig. 2A). Probabilistic mapping indicated that the effect was mainly localized in the laterobasal subregion of the amygdala (for details, see *SI Text*). Extraction of parameter estimates from this cluster revealed that OXT enhanced in males ($t_{35} = 3.1$, $P = 0.004$, Cohen's $d = 1.02$) but attenuated in females ($t_{35} = -3.18$, $P = 0.003$, Cohen's $d = 1.09$) left amygdala responses to criticizing vs. praising other people (Fig. 2B), with greater reactivity in men to those who criticized others ($t_{35} = 3.22$, $P = 0.003$, Cohen's $d = 1.04$) but in women to those who praised them ($t_{35} = 2.45$, $P = 0.019$, Cohen's $d = 0.82$) (Fig. 2C). Importantly, no such effect was found in the parallel object-directed condition, indicating the observed OXT effect was restricted to the social domain.

Given current conceptualizations of OXT as a regulator of social salience (4), we further explored whether OXT produced sex-different effects on the interplay of the left amygdala with core regions of the salience network, including the insula, anterior cingulate cortex, and inferior frontal gyrus. A functional connectivity analysis revealed a treatment × sex interaction for left amygdala coupling with the right insula ($t_{70} = 4.19$, $P_{FWE} = 0.009$) (Fig. 3A). Extracted parameter estimates further demonstrated that OXT increased coupling strength in males ($t_{35} = 3.59$, $P = 0.001$, Cohen's $d = 1.18$) but reduced it in females ($t_{35} = -2.29$, $P = 0.03$, Cohen's $d = 0.76$) for criticizing vs. praising others (Fig. 3B), with connectivity being weaker in females ($t_{35} = -2.74$, $P = 0.01$, Cohen's $d = 0.9$) but stronger in males ($t_{35} = 2.49$, $P = 0.02$, Cohen's $d = 0.81$) for criticizers, and for praisers, in contrast, stronger in females ($t_{35} = 2.03$, $P = 0.05$, Cohen's $d = 0.68$) but weaker in males ($t_{35} = -2.15$, $P = 0.04$, Cohen's $d = 0.71$) (Fig. 3C). Moreover, following OXT, but not PLC, left amygdala–right insula connectivity for criticizing people in males (OXT, $r = 0.62$, $P = 0.02$; PLC, $r = -0.14$, $P = 0.63$; Fisher's $z = 2.41$, $P = 0.008$) and praising people in females (OXT, $r = 0.5$, $P = 0.04$; PLC, $r = -0.35$; $P = 0.26$; Fisher's $z = 2.51$, $P = 0.006$) was significantly associated with
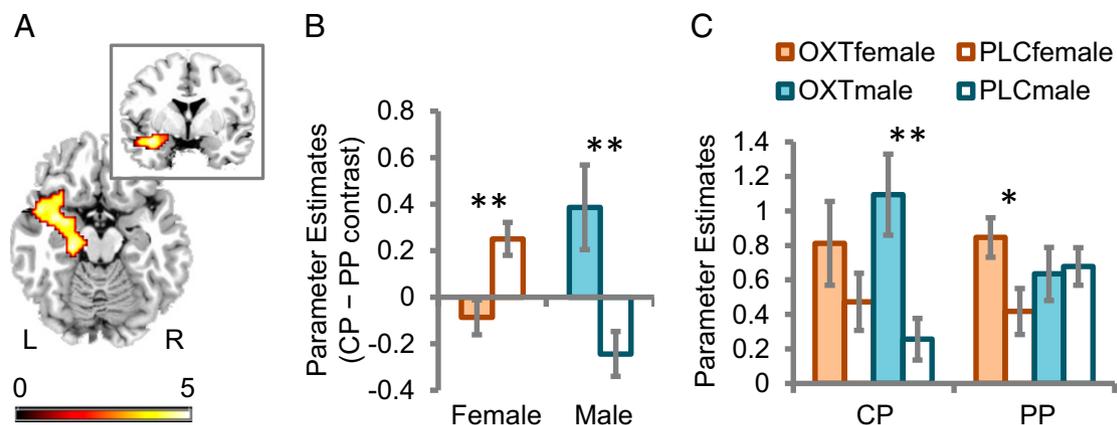
Fig. 2. Interaction effect of OXT with subject sex on the left amygdala activation difference between the criticizing people (CP) and praising people (PP) conditions ($n = 74$). (A) The t map of the interaction effect ($k = 262$, $t = 3.21$, $P_{FWE} = 0.001$) showed an activated cluster peaking at the left amygdala ($x = -30$, $y = -3$, $z = -21$; $t_{70} = 4.6$). Parameter estimates were extracted using a 6-mm-radius sphere centered at the peak MNI coordinates. L, left; R, right. (B) Extraction based on the CP > PP contrast revealed that OXT increased in males but reduced in females the response difference between CP and PP. (C) Separate extraction for CP and PP showed greater response of men to CP but of women to PP. *$P < 0.05$, **$P < 0.01$, two-tailed t test. Bars indicate $M \pm$ SE.
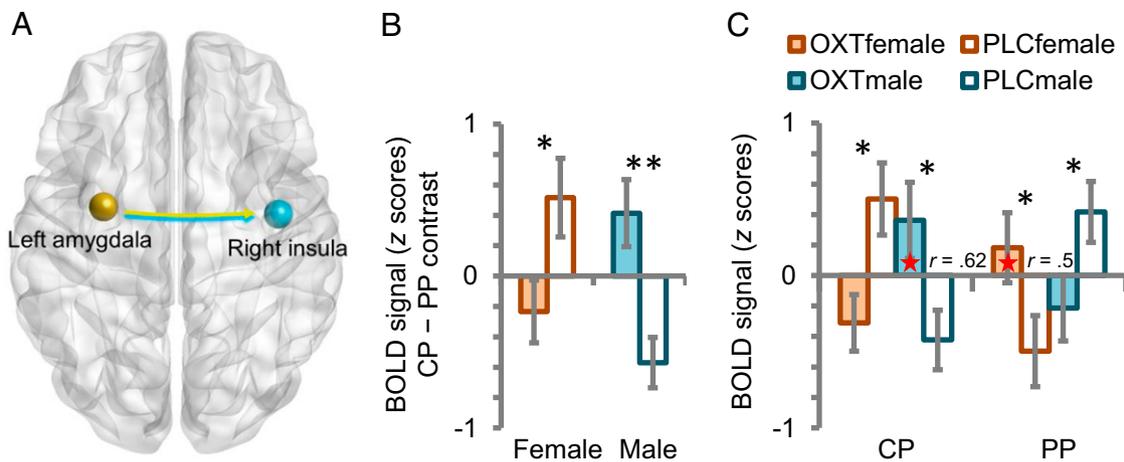
Fig. 3. Functional connectivity analysis of treatment × sex interaction effects for the difference between responses to the criticizing people and praising people conditions (n = 74). (A) The treatment × sex interaction altered left amygdala coupling with the right insula (x = 42, y = −6, z = −9). (B and C) Bar graphs illustrate the extraction of parameter estimates from left amygdala connectivity with the right insula (M ± SE). (B) Extraction based on the CP > PP contrast. (C) Extraction for CP and PP. Red stars indicate significant partial correlations (Ps < 0.05) with likeability ratings (controlling for anxiety and mood). *P < 0.05, **P < 0.01, two-tailed t test.

their likeability ratings after controlling for anxiety and mood (*Materials and Methods*).

Subsequent effects on likeability ratings for the faces presented alone were assessed by a repeated-measures ANOVA with "treatment" and "subject sex" as between-subject variables and "statement valence" (praise, criticism, or both) and "target" (social or nonsocial) as within-subject variables. Results showed significant main effects of valence ($F_{2, 140} = 213.51$, $P < 0.001$, $\eta^2 P = 0.75$) and target ($F_{1, 70} = 35.83$, $P < 0.001$, $\eta^2 P = 0.34$). The likeability of faces paired with criticism was rated lowest [mean (M) ± SE, 3.83 ± 0.1] and those paired with praise was rated highest (6 ± 0.09). Individuals targeting nonsocial objects (5.1 ± 0.07) were rated more likeable than those targeting other people (4.76 ± 0.07).

In line with the fMRI findings, a significant treatment × sex interaction was found ($F_{1, 70} = 7.08$, $P = 0.01$, $\eta^2 P = 0.09$), revealing that whereas OXT relative to PLC increased females' overall likeability ratings ($F_{1, 70} = 4.25$, $P = 0.04$, $\eta^2 P = 0.06$), in males it tended to decrease them ($F_{1, 70} = 2.89$, $P = 0.09$, $\eta^2 P = 0.04$) (Fig. 4). Moreover, male ratings were generally lower than female ones following OXT ($F_{1, 70} = 6.83$, $P = 0.01$, $\eta^2 P = 0.09$) but not PLC. No further main or interaction effects involving OXT were observed.

Discussion

In summary, our findings demonstrate that whereas OXT enhances the salience of positive social attributes in women, it makes men focus more on negative ones. Importantly, our neuroimaging results provide the first evidence, to our knowledge, that OXT exerts markedly different neural effects in men and women, with greater left amygdala response in women to individuals exhibiting socially but not nonsocially directed praise although in men to those who criticize others. These social-specific effects of OXT are in line with many previous studies (23) (but see ref. 24). The absence of simple main effects of OXT, sex, or valence in the amygdala indicates that the effect is likely to be driven by a sex-specific, valence-dependent action of the peptide (Table S1). Additionally, the lack of OXT modulation in a face-alone control condition argues against confounding effects of OXT on face perception per se (25) or face sex (Tables S2 and S3).

The sex-dependent salience effect of OXT we have observed on amygdala responses was mainly localized to the laterobasal region known to play an important role in sensory processing of social cues and salience (26). This link with altered social salience processing is underpinned by our finding that OXT evoked parallel

changes in the functional connectivity of the amygdala with other core nodes of the salience network, notably the insula. Indeed, other studies have also reported that OXT effects on amygdala responses often occur with concurrent changes in its connections with, and activation of, the insula (27–29).

Previous studies on amygdala responses to fearful faces and fearful/threatening scenes (14–17, 30) and social risk (31) have also indicated that OXT may induce sex-dependent changes in amygdala activation to emotional stimuli. However, these changes are in terms of responses in opposite directions (i.e., decreased in men and increased in women) to stimuli of the same valence rather than the increased activation to differently valenced stimuli (i.e., individuals who praise or criticize others) we have observed here in the context of making social judgments. Another study on male and female subjects following trauma found no sex difference in amygdala responses to fear-expression faces, suggesting that sex-dependent salience effects of OXT may be influenced by emotional experience as well as contextual factors (32).
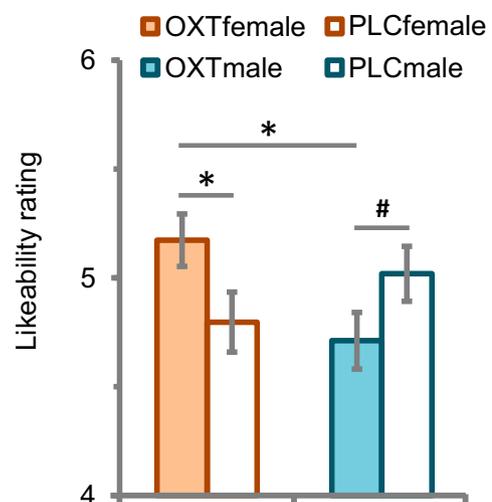
Fig. 4. Treatment × sex interaction in likeability ratings independent of statement valence and target (n = 74). *P < 0.05, #P = 0.09. Bars depict M ± SE.

Overall, the present findings support our hypothesis that OXT's fundamental functional role in modulating social preferences and subsequent social interactions via the amygdala may have evolved to subserve different purposes in men and women. Our observations correspond to OXT enhancing the salience of positive social cues to facilitate "tend-and-befriend" (33) and approach behavior in females toward individuals with prosocial attributes (8). This could help women to raise children more successfully by promoting formation of beneficial alliances within a social group and bonding with male partners who have good social and parenting qualities. For males, on the other hand, OXT may enhance the salience of negative social cues to help reduce antisocial influences by facilitating aggression toward or avoidance of (i.e., "fight or flight") individuals in their environment with negative social attributes (3, 4, 34), and perhaps also by reducing partner conflict (6). For both sexes, OXT release would thereby serve the common purpose of helping foster an optimal social environment for successfully raising children.

Materials and Methods

Participants. Subjects were recruited by local advertisement and provided written informed consent before study enrollment. Eighty healthy right-handed volunteers (age range, 19–27 y; $M \pm SD$, 22.8 ± 1.7 y) participated in the experiment. Data from six subjects were lost due to technical failures during data acquisition. Consequently, data from 37 females (OXT, $n = 21$) and 37 males (OXT, $n = 18$) were included in the final analyses. All subjects were free of current and past physical, neurological, or psychiatric disorders and had not taken any medication in the 4 wk before the experiment. None of the female subjects was pregnant or using oral contraceptives. Fisher's exact test showed that between the two treatment groups there were no differences in proportion of female subjects in follicular and luteal phases ($P = 0.19$, two-sided). Subjects were asked to maintain their regular sleep pattern and to abstain from caffeine and alcohol intake the day before and on the day of the experiment. Tobacco smokers and subjects with MRI contraindications were excluded from participation.

To control for potential confounding effects of OXT on anxiety and mood, all subjects completed two questionnaires (Chinese versions), the State-Trait Anxiety Inventory (STAI) (35) and the Positive and Negative Affect Schedule (PANAS) (36), immediately before the fMRI experiment. Analysis of these variables showed no significant differences between the OXT- and PLC-treated males and females (all Ps > 0.1; Table S4), indicating that the observed OXT effects could not be attributed to basic effects of OXT on anxiety or mood.

The present study had full ethical approval from the local ethics committee at the University of Electronic Science and Technology of China and was in accordance with the latest version of the Declaration of Helsinki.

Stimuli. All 36 facial pictures (18 males) used in the first-impression paradigm were evaluated in a pretest incorporating an independent sample ($n = 36$; 18 males). Subjects rated the faces as emotionally neutral ($M \pm SD$, 4.98 ± 0.15) and average in attractiveness (4.37 ± 0.35) and trustworthiness (4.87 ± 0.32) using 9-point Likert scales. Statements of four categories (criticizing people/praising people/criticizing objects/praising objects) were also evaluated in a pretest involving an independent sample ($n = 30$; 15 males). In terms of valence, a 2 (criticizing vs. praising) × 2 (people vs. objects) repeated-measures ANOVA yielded a significant difference between statements describing criticizing behavior and those describing praising behavior ($F_{1, 29} = 144.11$, $P < 0.001$, $\eta^2 P = 0.83$); no other effects were found. Importantly, there were no significant differences between the four statement categories in terms of arousal, likelihood, and comprehension ratings (all Ps > 0.1; Table S5).

The First-Impression Task. Four statements were sequentially assigned to one face to form a first impression. One-third of the faces were paired with statements all describing criticizing behavior and one-third all describing praising behavior, and the remaining were paired with descriptions of both criticizing and praising behavior (first two criticism, next two praise, or vice versa). All descriptive statements paired with one face remained constant in terms of target (either other people or nonsocial objects). Facial stimuli and descriptive statements were paired and presented according to one of three pseudorandom orders and counterbalanced across subject groups. Each face–statement combination was shown for 5 s. In a person profile, two face–statement combinations were followed by a 10-s face-alone interval, which served as a control for simple effects of OXT on facial processing in the later

analysis, followed by two face–statement combinations. After the presentation of the entire person profile, subjects were shown a rating scale for 10 s during which they were required to rate the likeability of the person on an 8-point scale (1 = I don't like the person; 8 = I like the person). Between different person profiles a fixation cross was displayed that served as a low-level baseline during the analyses.

Procedure. The study used a placebo-controlled, double-blind, between-subject design; that is, subjects were randomly assigned to intranasal administration of either OXT (24 IU; Oxytocin spray; Sichuan Meike Pharmacy; three puffs per nostril, each with 4 IU OXT) or PLC (provided in the identical type of dispenser bottle by the same pharmaceutical company, containing all of the same ingredients as the OXT nasal spray except the neuropeptide, i.e., glycerin and sodium chloride; also three puffs per nostril). Forty-five minutes after the treatment, subjects performed the first-impression paradigm during fMRI acquisition, which lasted ~40 min. In postexperiment interviews, subjects showed no differences between OXT and PLC groups in identifying whether they had received OXT or PLC ($\chi^2 = 0.7$, $P = 0.4$).

Acquisition and Analysis of fMRI Data. fMRI using blood oxygenation level-dependent (BOLD) contrast was conducted in a whole-body 3.0-T MRI scanner (Siemens Trio) with a 12-channel head coil as signal receiver. Echo-planar images were acquired with a gradient echo-planar imaging sequence (TR, 2,000 ms; TE, 30 ms; slices, 32; thickness, 4 mm; gap, 0 mm; field of view, 240 × 240 mm²; flip angle, 90°; matrix size, 64 × 64; voxel size, 3.8 × 3.8 × 4 mm³). High-resolution whole-brain structural T1-weighted images were also obtained using a magnetization-prepared gradient echo sequence (TR, 1,900 ms; TE, 2.26 ms; thickness, 1 mm; sagittal field of view, 256 × 256 mm²; flip angle, 9°; matrix, 256 × 256 × 176; voxel size, 1 × 1 × 1 mm³) to control for any anatomic abnormalities and increase normalization accuracy during fMRI data preprocessing.

fMRI data were preprocessed using DPARSF version 2.3 (Data Processing Assistant for Resting-State fMRI software; www.restfmri.net/forum/DPARSF) and analyzed using SPM8 software (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging; www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7 (MathWorks). The first five volumes of each functional time series were discarded to allow for T1 equilibration. Images were corrected for head movement between scans by an affine registration. A two-pass procedure was used by which images were initially realigned to the first image of the time series and subsequently realigned to the mean of all images. For spatial normalization, the mean T1 image of each subject was normalized to the current Montreal Neurological Institute (MNI) template using DARTEL (37). All functional images were hereby transformed into standard MNI space and resampled at 3 × 3 × 3-mm³ voxel size. The normalized images were spatially smoothed using an 8-mm FWHM Gaussian kernel.

On the first level, six conditions, "criticizing people," "praising people," "criticizing objects," "praising objects," "face alone," and "rating," were modeled by a stick function convolved with the hemodynamic response function (38). Fixation periods served as a low-level baseline. Head-movement parameters were included in the design matrix to control for movement-related artifacts. Based on the main aim of the present study, the second-level analysis focused on the interaction between treatment, sex, and valence using a mixed-effect ANOVA with the between-subject factors treatment (OXT vs. PLC) and sex (males vs. females) and the within-subject factor valence (criticizing vs. praising people). To examine whether OXT specifically modulated processing in the social domain, a corresponding repeated-measures ANOVA was performed on the object condition (criticizing vs. praising objects). Corresponding main effects of treatment, sex, and valence were assessed to evaluate their confounding effects on the three-way interaction. To control for basal effects of OXT on face processing, the face-alone condition was examined in a full factorial ANOVA with the factors treatment (OXT vs. PLC) and sex (males vs. females) using the "face alone > baseline" contrast. To further disentangle the interaction effects, individual parameter estimates were extracted from 6-mm spheres centered at the coordinates of the maximum t value of the corresponding neural effect. All analyses used a whole-brain approach with a significance threshold of $P < 0.05$ corrected for multiple comparisons at cluster level based on FWE.

To further examine the effect of the interaction of OXT with sex on the interplay between brain regions, a functional connectivity (generalized form of context-dependent psychophysiological interactions; gPPI) analysis (39) was performed. Compared with the standard PPI implementation in SPM, the gPPI analysis allows modeling more than two task conditions in the same model by spanning the entire experimental space to improve model fit, specificity to true negative findings, and sensitivity to true positive findings

(39). Functional connectivity of the left amygdala, the key target of the treatment × sex interaction, identified by the whole-brain analysis, was examined. Based on an a priori hypothesis for the modulation of the salience network by OXT and previous studies reporting altered coupling of the amygdala with core regions of the salience network after intranasal OXT (27–29), the analysis focused on the insula, anterior cingulate cortex, and inferior frontal gyrus using structural regions of interest (ROIs) from Wake Forest University PickAtlas (version 3.0), which provides a method for generating ROI masks using the Anatomical Automatic Labeling (AAL) atlas (38, 40, 41). This analysis used a peak-level FWE-corrected significance threshold of $P < 0.05$, adapted to the size of the structural masks using a small-volume correction. Subregional mapping was conducted using probabilistic maps as implemented in the Anatomy toolbox (42–44). All coordinates are reported in MNI space.

Statistics. Behavioral data and parameter estimates extracted from imaging data were analyzed using SPSS 15.0. Behavioral data were examined by means of repeated-measures ANOVAs. Partial eta-squared was calculated as a measure of effect size. The assumption of sphericity was assessed with Mauchly's test, the Greenhouse–Geisser correction for nonsphericity was applied as required, and Bonferroni correction was used when pairwise comparisons were applicable. Group differences in parameter estimates extracted from significant interaction clusters in SPM were further evaluated using direct comparisons via two-sample t tests. Cohen's d was calculated as a measure of effect size. The partial correlation between likeability and extraction of OXT-altered functional connectivity was computed controlling for STAI and PANAS scores because OXT might modulate anxiety and mood (45, 46). All reported P values were two-tailed, and $P < 0.05$ was considered significant.

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