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Original article

Neural substrates underlying the effects of oxytocin: a quantitative meta-analysis of pharmaco-imaging studies

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Abstract

The hypothalamic peptide oxytocin (OT) is crucial in social adaptation and used to treat emotional and social deficits. Here, we conducted a systematic, quantitative meta-analysis of functional-MRI studies intranasally administering OT (IN-OT) to uncover neural substrates underlying the IN-OT effects and to elucidate differential IN-OT effects between healthy and clinical populations. Meta-analyses were conducted on 66 IN-OT fMRI studies, stratified by psychopathology, valence and sex. IN-OT increased bilateral amygdala, caudate head, and superior temporal activity in healthy individuals and increased dorsal anterior cingulate activity in patients. Moreover, IN-OT decreased amygdala activity in both patients and healthy individuals but did so to a greater degree in patients than healthy individuals. The OT-increased amygdala activity was only found on the negative social and affective processes, whereas the OT-decreased amygdala activity was mainly contributed by contrasts on negative-valenced processes. IN-OT increased parahippocampal activity and decreased amygdala activity during negative socio-affective processing. During positive socio-affective processes, IN-OT increased caudate head activity. This study indicates convergent neural substrates and the underlying neuropsychological mechanisms for IN-OT effects on social and affective processes. The common and different effects of IN-OT on patients and healthy individuals and the modulation of OT effects by valence have critical implications.

Key words: oxytocin; social adaptation; fMRI; amygdala; meta-analysis

Introduction

The neuropeptide oxytocin (OT), an evolutionarily ancient neuropeptide and neuromodulator, is an important molecular substrate for social adaptation due to its effects on social and emotional functioning. Moreover, OT is emerging as a pharmacological target for the treatment of mental disorders characterized by social or emotional deficits (Heinrichs *et al.*, 2009; Meyer-Lindenberg *et al.*, 2011; Bakermans-Kranenburg and van Ijzendoorn, 2013; Stavropoulos and Carver, 2013; Ma *et al.*, 2016a). Previous studies have shown consistent effects of OT on various social and emotional processes (such as emotion recognition and in-group cooperation), as well as controversial OT effects on some other processes (e.g. minding-reading and trust). Discrepant effects of intranasal administration of OT (IN-OT) have been reported in some social cognitive and affective processes. For example, whereas several studies have shown that

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IN-OT increases trust (Kosfeld *et al.*, 2005; Baumgartner *et al.*, 2008; Mikolajczak *et al.*, 2010; Klackl *et al.*, 2013), other studies have shown that IN-OT does not influence or even decreases trust (Barraza, 2010; Ebert *et al.*, 2013; Yao *et al.*, 2014). The discrepant or even opposing effects of IN-OT have been proposed to result from contextual factors and personal characteristics (Bartz *et al.*, 2011; Ma *et al.*, 2016a), such as the cooperative-competitive context and personality traits. However, convergent IN-OT effects on some social and affective processes have been observed in previous empirical studies and confirmed by several meta-analyses. IN-OT has been reliably shown to improve facial emotional recognition (e.g. Guastella *et al.*, 2008; Marsh *et al.*, 2010; Domes *et al.*, 2014) and to promote in-group cooperation (e.g. De Dreu *et al.*, 2010, 2011; De Dreu, 2012; Ma *et al.*, 2015a). Moreover, several recent meta-analyses on the behavioral effects of IN-OT have confirmed convergent effects of IN-OT on facial emotional recognition, in-group cooperation, and stress responses (van IJzendoorn and Bakermans-Kranenburg, 2012; Shahrestani *et al.*, 2013; Cardoso *et al.*, 2014).

The effects of OT are due to its role as a neuromodulator in the brain (Neumann, 2007; Bartz and Hollander, 2008); hence, numerous functional MRI studies have examined the effects of IN-OT on social cognitive and affective processes. However, the issues regarding the discrepant effects of IN-OT, the modulations of OT effects by personal milieu and context, and the potential differences in OT effects between healthy and patient groups have challenged the enthusiasm toward the translational potentials of OT (Bartz *et al.*, 2011; Meyer-Lindenberg *et al.*, 2011). The current meta-analysis first applied the activation likelihood estimation (ALE) technique for quantitative coordinate-based meta-analyses of pharmacological neuroimaging studies that have compared IN-OT *vs* placebo (PL) to reveal convergent neural substrates underlying the effects of IN-OT. IN-OT has been shown to either increase or decrease brain responses during social and affective processing (Zink and Meyer-Lindenberg, 2012; Bethlehem *et al.*, 2013). Therefore, a meta-analytic perspective on IN-OT fMRI findings is critically needed in the field to determine whether there are convergent neural substrates underlying the IN-OT effects. There have been two meta-analyses of OT fMRI studies (Rocchetti *et al.*, 2014; Wigton *et al.*, 2015), both including only 11 OT fMRI studies (published before February 2013). The limited number of OT fMRI studies at that time constrained the analyses and findings. Due to the multifaceted positive effects of IN-OT and its potential in clinical trials, a rapidly increasing number of pharmaco-fMRI studies have examined the effects of IN-OT since 2013. The current meta-analysis of 66 pharmaco-fMRI studies (published before March 2017) sought to reveal convergent activity mediating IN-OT effects on social and affective processes.

Second, we sought to elucidate unspecified neuropsychological mechanisms underlying IN-OT effect. Different mechanisms have been proposed (Bartz *et al.*, 2011; Weisman and Feldman, 2013) to explain the OT effects. Recently, in the social adaptation model, OT has been proposed to promote social functioning through different neuropsychological mechanisms, including reduction of negative affect, promotion of rewarding experiences from positive social interaction, and heightened social salience (Ma *et al.*, 2016a). Thus, we applied separate ALE meta-analyses to examine the IN-OT effects on positive and negative social and affective processing, serving as a quantitative examination of these mechanisms.

Third, we sought to examine the IN-OT effects on clinical and healthy populations separately. Most previous OT fMRI studies have examined neural substrates mediating OT effects in the healthy population. The effects of IN-OT have been shown to be modulated by cognitive style (Ma *et al.*, 2015a), attachment style (Bartz *et al.*, 2010), personality traits (Scheele *et al.*, 2014; Perry *et al.*, 2015; Ma *et al.*, 2016b), social support (Winslow and Insel, 2004), and early life experiences (Meinlschmidt and Heim, 2007; Riem *et al.*, 2014). These factors may differ between clinical and healthy populations (MacDonald and Feifel, 2013). Therefore, a key issue for OT translation is to reveal the common and differential IN-OT effects between patients and healthy volunteers (MacDonald and Feifel, 2013). Therefore, separate meta-analyses were conducted on studies involving patients and healthy volunteers to reveal common and different effects of IN-OT.

Finally, we explored factors moderating the IN-OT effects on brain activity, such as the valence of social interactions/processes and sex. Some previous studies have shown sex differences in the IN-OT effects on brain activity. For example, IN-OT has been found to decrease amygdala activity in response to emotional faces in males (Domes *et al.*, 2007) but to increase amygdala activation in females (Domes *et al.*, 2010). Rilling *et al.* (2014) have directly compared the IN-OT effects in males and females within the same paradigm and have found that IN-OT increases activity in the striatum, insula, amygdala, and hippocampus in males but has no effect in females. However, some other studies have not detected sex-dependent IN-OT effects, including recognition of facial expression (Marsh *et al.*, 2010), desire for social engagement (Alvares *et al.*, 2010) and envy (Shamay-Tsoory *et al.*, 2009). We thus used meta-analytic technique to uncover whether convergent common and/or differential IN-OT effects existed between males and females.

Methods

Literature search and study selection

Studies examining IN-OT effects on the human brain published before March 2017, were selected through a standard search in PubMed, Embase and ScienceDirect, with keywords ['oxytocin'] AND ['fMRI' OR 'magnetic resonance imaging']. Additional studies were collected by reviewing the reference lists of relevant papers in the first step and the reference lists of several review articles. The first-level literature search yielded 414 publications, 66 of which met inclusion criteria (Figure 1 for Flow Diagram of the Literature Search; Supplementary Table S1 for details of all eligible studies). All eligible articles were individually screened for the presence of Montreal Neurological Institute (MNI) or Talairach space and OT effects. All coordinates were entered by authors Y. Ma and D. Wang and double-checked by X. Yan.

All relevant studies (414 included) were screened for the following inclusion/exclusion criteria: (1) we included papers reporting empirical studies with humans (188 studies were included) and excluded review articles, meta-analyses, commentaries, conferences and animal studies (226 studies were excluded); (2) we included papers written in English (184 studies were included) and excluded studies not written in English (4 studies were excluded); (3) we included papers using functional MRI (120 studies were included) and excluded papers using Electroencephalogram (EEG), Magnetoencephalography (MEG), Single-Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), Magnetic Resonance Spectroscopy (MRS) or structural analysis only (64 were excluded); (4) we included studies involving IN-OT (83 studies

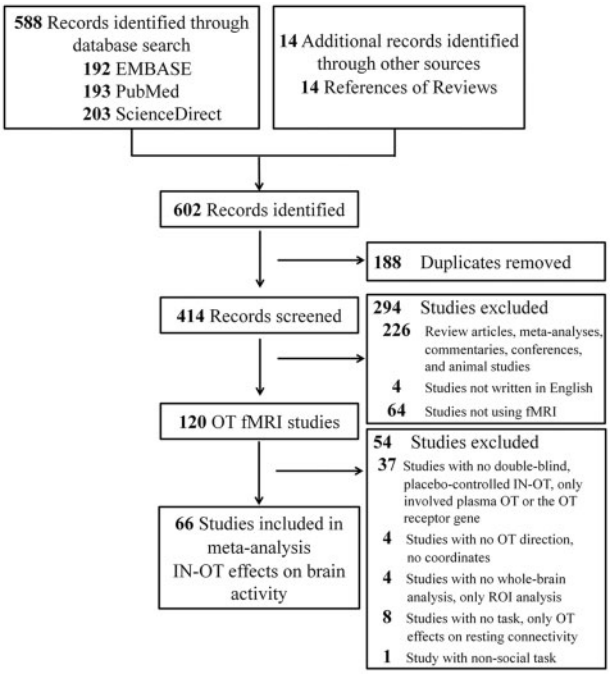

Fig. 1. Flow diagram of the literature search.

were included) and excluded studies that did not use a double-blind, placebo-controlled procedure or involved only plasma OT or the OT receptor gene (37 studies were excluded); (5) we included studies examining the contrast 'OT > PL' or 'OT < PL' (79 studies were included) and excluded studies that did not mention the direction of IN-OT effects or did not report coordinates (4 studies were excluded); (6) we included studies presenting the results of the whole-brain analysis (75 studies were included) and excluded studies reporting only region of interest (ROI) analysis (4 studies were excluded); (7) we included studies with specific tasks (67 studies were included) and excluded studies only examining the OT effect on resting connectivity without any task (8 were excluded). In addition, we focused on the effects of IN-OT on brain activity related to social and affective responses, given that previous human OT studies have primarily examined the IN-OT effects in social cognition and affective responses (66 studies were included) and have excluded studies using non-social tasks (1 study was excluded). Social processes, as defined in social cognitive neuroscience (Lieberman, 2005; 2007; Moskowitz, 2005), refer to the processes related to oneself and other people and the processes that occur at the interface of the self and others. Thus, the IN-OT effects on social cognition included studies examining the IN-OT effects on processes of oneself, others and social interactions, such as mind-reading, friend or foe judgment, theory of mind, eye gaze, interpersonal trust, and cooperation. To investigate the effects of IN-OT on affective processes, similarly to our previous study (Ma, 2015), we included studies examining the IN-OT effects on the implicit or explicit experience of positive/negative affect. Specifically, positive affect was induced by passive viewing or active responses to happy faces, cooperation, pleasant/positive pictures, faces of partner/children, erotic/rewarding pictures or infant laughter. Negative affect was induced by passive viewing or active judgments on fearful, angry, sad, painful or disgusted faces, defection, unpleasant/negative pictures, punishment, stress or infant cry.

ALE analysis

Meta-analyses of eligible studies were based on the ALE method (Laird *et al.*, 2005) and used the revised ALE algorithm (Turkeltaub *et al.*, 2012) in GingerALE 2.3.6 (https://www.brainmap.org/ale/). GingerALE is a quantitative coordinate-based meta-analysis method used to identify voxel-wise spatial convergence of activation coordinates across published studies. Given the within-experiment coherence of coordinates, multiple contrasts from the same population were nested to prevent magnification of the impact of a specific study (Turkeltaub *et al.*, 2012). GingerALE switched ALE methods from fixed effects to random effects, incorporated variable uncertainty on the basis of the sample size of each study (Eickhoff *et al.*, 2009), and added thresholding methods (Laird *et al.*, 2005). GingerALE automatically computed the ALE values for every voxel in the brain by using an automatically determined full-width half-maximum (FWHM) value (Eickhoff *et al.*, 2009), which is calculated by the number of subjects in each experiment. The size of the FWHM of the Gaussian kernel was adjusted for the expected between-subject and between-template variability to model spatial uncertainty (Eickhoff *et al.*, 2009; Turkeltaub *et al.*, 2011).

The procedure involved modeling of all reported coordinates of the selected contrasts as the peaks of 3D Gaussian probability distributions (coordinates originally reported in MNI were converted to Talairach space; Lancaster *et al.*, 2007; Laird *et al.*, 2011), and all coordinates reported in this study were in the Talairach space). The 3D Gaussian distributions were summed to produce a statistical map that estimated the likelihood of activation for each voxel as determined by all studies in the analysis. For the correction of multiple comparisons, we applied stringent threshold algorithms of family-wise error rate (FWE) $P < 0.05$ (1000 permutations, cluster size > 15mm^3) to reveal the robust IN-OT effects (Eickhoff *et al.*, 2012).

GingerALE also allowed for statistical comparisons between two ALE maps. The subtraction and conjunction analyses uncovered statistically significant differences and similarities in OT effects between healthy volunteers and patients; and between studies recruited male and female participants. Given that GingerALE has not developed the threshold algorithm of FWE for statistical comparisons, a threshold of FDR $pN < 0.01$ (1000 permutations), cluster size > 100 mm^3 was applied to the subtraction and conjunction analyses.

Data analysis plan

The ALE meta-analysis focused on IN-OT induced brain activity changes. Neural effects of IN-OT were identified in contrasts between: OT and PL sessions in within-subject studies; and OT and PL groups in between-subjects studies. The contrasts of 'OT > PL' and 'PL > OT' separately identified neural activity increased or decreased by IN-OT. Sixty-six IN-OT-fMRI studies (including 99 contrasts, involving 3286 subjects) were included in the current meta-analyses. Sixty studies (78 contrasts, 2677 healthy participants) examined neural effects of IN-OT in healthy population. Sixteen studies (21 contrasts, 370 patients *vs* 239 healthy controls) examined neural effects of IN-OT in clinical population, including patients with autism spectrum disorder (ASD, 8 studies, 160 patients), social anxiety disorder (SAD, 3 studies, 52 patients), post-traumatic stress disorder (PTSD, 3 studies, 109 patients), major depressive disorder (1 study, 8 patients), and borderline personality disorder (1 study, 41 patients).

First, we summarized IN-OT-fMRI studies to show the convergent general effects of IN-OT on brain activity. Thus ALE meta-

analysis on all eligible studies, collapsing across subject groups (patients and healthy volunteers; males and females) and processing valence, was conducted to reveal brain regions generally affected by IN-OT during social interaction and affective processes. More specifically, separate ALE analyses were conducted on all the 'OT > PL' and 'PL > OT' contrasts to uncover general brain activity increased or decreased by IN-OT. It should be noticed that only positive coordinates were extracted from the OT minus PL contrasts and entered the meta-analysis of 'OT > PL' condition, vice versa. Second, we examined the common and different neural effects of IN-OT in healthy and clinical populations. Separate ALE meta-analyses were conducted on studies involving patients and healthy volunteers to uncover the OT-induced increases ('OT > PL' contrasts) and decreases ('PL > OT' contrasts) in patients and healthy volunteers. Third, we further examined statistically significant difference and similarity in IN-OT effects between healthy volunteers and patients by conducting the conjunction and subtraction analyses on the two sets of activation coordinates showing IN-OT effects in patients and healthy volunteers. Forth, we aimed to elucidate the neuropsychological mechanisms underlying the effects of IN-OT by performing separate ALE meta-analyses on OT-fMRI studies stratified by the treatment directionality (OT-induced increase/decrease) and processing valence (positive/negative). Finally, we aimed to uncover whether the neural effects of IN-OT were modulated by sex by conducting conjunction and subtraction analyses on two sets of activation coordinates from studies recruiting males and females. Given the limited number of pharmaco-fMRI OT studies on patients, the valence analysis and sex-modulation were only performed on healthy volunteers.

Results

General OT-induced brain activity changes

ALE meta-analysis was first conducted on all the reported activation in the eligible studies to uncover the general effect of IN-OT on brain activity. Analysis of 56 'OT > PL' contrasts (368 activation coordinates reported in the eligible studies) revealed convergent OT-induced activity increases in the bilateral amygdala and left caudate (FWE $P < 0.05$; Figure 2A; Supplementary Table S2). IN-OT decreased activity in bilateral amygdala (extending to globus pallidus, GP; FWE $P < 0.05$; 43 'OT < PL' contrasts; 260 activation coordinates; Figure 2B; Supplementary Table S2).

OT effects on healthy and clinical populations

We next conducted separate ALE analyses to reveal IN-OT induced brain activity changes in healthy volunteers and patients. Seventy-seven contrasts examined the effects of IN-OT on brain activity in healthy volunteers. ALE analysis on healthy volunteers revealed that IN-OT increased neural activity in bilateral amygdala, left caudate, and superior temporal gyrus (STG) (FWE $P < 0.05$; 41 'OT > PL' contrasts, 250 activation coordinates; Table 1) and decreased neural activity in right amygdala (FWE $P < 0.05$; 36 'OT < PL' contrasts, 228 activation coordinates; Table 1). Twenty-one contrasts examined the effects of IN-OT in clinical population. ALE analysis from FWE correction revealed that IN-OT increased neural activity in the dorsal anterior cingulate cortex (dACC) (FWE $P < 0.05$; 14 'OT > PL' contrasts, 114 activation coordinates; Table 1) and decreased the left amygdala activity (FWE $P < 0.05$; 7 'OT > PL' contrasts, 33 activation coordinates; Table 1).

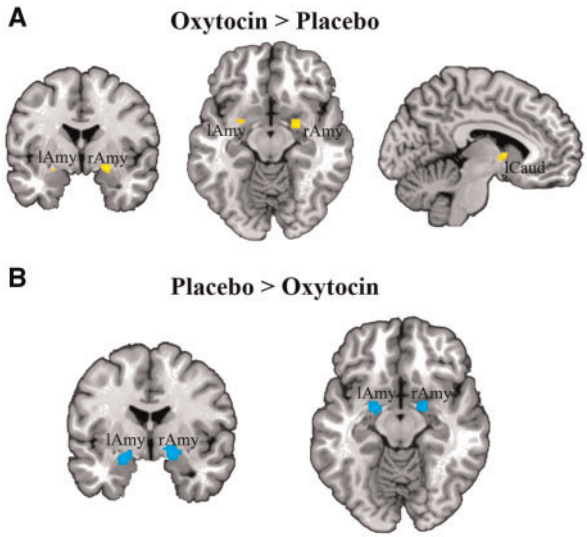

Fig. 2. General neural effects of intranasal administration of oxytocin. (A) IN-OT increased activity in the left (lAmy) and right amygdala (rAmy) and left caudate (lCaud) whereas (B) decreased activity in bilateral amygdala (threshold: FWE $P < 0.05$, 1000 permutations, $k > 15\,mm^3$).

Comparison between patients and healthy volunteers

Given that the majority of IN-OT fMRI studies examined neural substrates mediating OT effects in healthy population, a key issue for OT clinical translation was to reveal the common and differential OT effects between patients and healthy volunteers. Thus we directly compared the effects of IN-OT between healthy volunteers and patients. We noticed that most studies examining OT effects on patients were conducted in males. Thus for the inclusion of studies in healthy population, only studies examining OT effect on males were included in this section for comparison to control for potential sex influences.

Conjunction and subtraction analyses on the 'OT < PL' contrasts revealed significantly IN-OT reduced bilateral amygdala activity (left: −19.8, −2.7, −15.7, $k = 816\,mm^3$; right: 18.9, −1, −13.6, $k = 208mm^3$) in both healthy volunteers and patients. Moreover, IN-OT decreased left amygdala (−24.3/−7.2/−12.5, $k = 544\,mm^3$, FDR $P < 0.01$) activity to a greater degree in patients than healthy volunteers. However, conjunction and subtraction analyses on the 'OT > PL' contrasts did not show significant similarities and differences in brain activity increased by IN-OT between patients and healthy volunteers.

OT effects on positive and negative social and affective processes

To reveal the neuropsychological mechanisms through which IN-OT influences social and affective processes, we analyzed IN-OT effects on healthy volunteers stratified by the valence of social and affective process (this analysis was only performed on healthy volunteers given the limited number of IN-OT fMRI studies on patients). During negative social and affective processes, IN-OT increased parahippocampus activity (26.8/1.2/−13.1, $k = 56\,mm^3$, FWE $P < 0.05$; based on 16 'OT > PL' contrasts, 72 activation coordinates), whereas decreased right amygdala (18.1/−5/−8, $k = 256\,mm^3$, FWE $P < 0.05$; ALE analysis on 21 'OT < PL' contrasts, 136 activation coordinates). During the positive social and affective processes, we found that IN-OT increased activity in the caudate head (−7.2/3.2/2.8, $k = 56\,mm^3$, FWE $P < 0.05$; ALE analysis on 17 'OT > PL' contrasts, 102

Table 1. The effects of IN-OT on brain activity in healthy volunteers and patients (threshold: FWE $P < 0.05$, 1000 permutations, $k > 15\,mm^3$)

Brain regions	Hemi.	BA	Weighted center			Volume (mm^3)	Number of contributors [a]
			x	y	z		
OT effects on healthy volunteers							
OT > PL (based on 41 contrasts, 250 coordinates, 36 studies)							
Amygdala	R		23.3	−2.2	−12.7	264	4
Caudate head	L		−8.1	3.5	2.5	120	2
Amygdala	L		−26	−0.8	−14	104	2
Superior temporal gyrus	L	21	−47.5	−0.5	−10.5	32	3
OT < PL (based on 36 contrasts, 228 coordinates, 35 studies)							
Amygdala (extending to GP)	R		17.2	−4.4	−8.7	408	3
OT effects on patients							
OT > PL (based on 14 contrasts, 114 coordinates, 12 studies)							
dorsal anterior cingulate	R	24	1	30	14	16	2
OT < PL (based on 7 contrasts, 33 coordinates, 7 studies)							
Amygdala	L		−21.7	−3.5	−15	432	4

GP, globus pallidus.
[a]The number of studies that contributed to each cluster.

activation coordinates), whereas no brain activity decreased by IN-OT was significant (FWE $P < 0.05$; ALE analysis on 13 'OT < PL' contrasts, 48 activation coordinates).

OT effects in healthy males and females

Conjunction and subtraction analyses on 'OT > PL' contrasts (male: 164 activation coordinates in 25 contrasts; female: 84 activation coordinates in 14 contrasts) were conducted to reveal significant similarities as well as differences in brain activity increased by IN-OT between healthy males and females (this analysis was also only performed on healthy volunteers given the limited number of IN-OT fMRI studies on patients). IN-OT increased right amygdala activity (23.7/−1.7/−11, $k = 128\,mm^3$) was overlapped in males and females. Conjunction and subtraction analyses on 'OT < PL' contrasts (male: 187 activation coordinates in 22 contrasts; female: 39 activation coordinates in 13 contrasts) showed that IN-OT decreased brain activity in the right amygdala (extending to medial GP; 17.3/−4.2/−9.1, $k = 656\,mm^3$, FDR $P < 0.01$) in both males and females. In addition, no brain activity increased or decreased by IN-OT was significantly different between males and females.

Discussion

The current study has uncovered several important findings. First, we showed converging evidence that IN-OT increased neural activity in the social and emotional networks, including bilateral amygdala, caudate head and STG, and decreased neural responses in the bilateral amygdala. The discrepant effects of IN-OT on the amygdala activity (i.e. both IN-OT induced increases and decreases) were discussed in the following section. Second, we showed that IN-OT decreased amygdala activity in both patients and healthy volunteers, but to a greater degree in patients than healthy volunteers. Moreover, the activations of different brain regions were increased by IN-OT in healthy and clinical populations. IN-OT increased neural activity in bilateral amygdala, left caudate head and STG activity in healthy individuals but increased dACC activity in patients. Third, we showed that the effect of IN-OT in healthy volunteers was modulated by valence. IN-OT increased parahippocampus activity, whereas decreased amygdala activity during negative social and affective processes. During positive social and affective processes, IN-OT increased caudate head activity. Finally, we showed common IN-OT effects on amygdala activity in males and females, and no significant sex-difference in OT effect was found. These findings have critical implications, providing convergent neural substrates underlying IN-OT effect, revealing similar and different OT effects on healthy and clinical populations, suggesting neuropsychological mechanisms underlying OT effects on social and affective processes, and confirming modulation of OT effect by valence.

Understanding of the discrepant directionality (i.e. increase or decrease) of the general OT effects on amygdala

We showed that, in the analysis of general OT effect, IN-OT resulted in both increases and decreases in bilateral amygdala activity. Such discrepant IN-OT effects on amygdala can be understood in further consideration of the modulation of the valence of social and affective processing. Specifically, we showed that the OT-decreased amygdala activity was only found in the meta-analytic analysis on the negative (but not positive) emotional and social processes. Moreover, we examined the studies contributing to the OT-induced amygdala activity change. We found that the OT-induced increases in the amygdala activity was mainly contributed by the contrasts examining IN-OT effects on positive social and affective processes (Gamer *et al.*, 2010; Rilling *et al.*, 2012,2014; Rupp *et al.*, 2013), whereas the OT-decreased amygdala activity was mainly contributed by contrasts on negative-valenced processes (Petrovic *et al.*, 2008; Labuschagne *et al.*, 2010; Bertsch *et al.*, 2013; Rupp *et al.*, 2014). Moreover, analysis from a more liberal threshold of FDR correction revealed that IN-OT increased amygdala activity during positive social and affective processes but decreased the amygdala activation during negative-valenced processes (see Supplementary Table S3). Amygdala has been recognized as the emotional hub (Kober *et al.*, 2008; Lederbogen *et al.*, 2011; Ma, 2015; Ma *et al.*, 2015b), also plays a key role in social interaction (Buchanan *et al.*, 2009) and processing social relevant stimuli (Bzdok *et al.*, 2011). The amygdala activity increased or suppressed by IN-OT may have different functional meanings. The IN-OT increased amygdala activity may suggest that IN-OT enhanced social functioning and/or increased positive experience from social processing. The decreased amygdala

activity by IN-OT may reflect the anxiolytic action of OT, suggesting that OT reduced negative affect processing for both healthy (Kirsch *et al.*, 2005; Domes *et al.*, 2007) and clinical populations (Labuschagne *et al.*, 2010; Andari *et al.*, 2016). Consistently our recent study suggested a cognitive mechanism of valence-specific IN-OT effects: the facilitation of learning from positive information and the reduction of learning from negative information (Ma *et al.*, 2016b). Given the differential roles of sub-regions of amygdala during social and affective processing (Davis *et al.*, 2010), it is of interest and critical importance for future research to further test the precise OT effects on different sub-regions of amygdala.

Neural supports for the social adaptation model of OT function

It has been proposed that OT promoted social adaptation through different neuropsychological mechanisms, such as reduction of negative affect, promotion of rewarding experiences from positive social interaction and facilitation of social salience (Ma *et al.*, 2016a). The current meta-analysis lent systematic neural support for these mechanisms underlying OT effects. The findings that IN-OT decreased amygdala activity during negative social and affective processing lent support for the negative affect-reduction mechanism, as this was a key region related to social stress and negative affect (LeDoux, 2000; Kober *et al.*, 2008; Ma *et al.*, 2014, 2015b; Ma, 2015). Thus, OT promoted social functioning through decreasing affective reaction caused by negative social interaction. The social rewarding experiences promotion mechanism would predict that IN-OT increased brain activity in the emotion-reactive network (amygdala, ACC; Phillips *et al.*, 2003; Killgore and Yurgelun-Todd, 2004; Kober *et al.*, 2008) and reward-related network (caudate, midbrain; Phillips *et al.*, 2003; Kober *et al.*, 2008; Liu *et al.*, 2011) during positive social and affective processes. Indeed, we showed that IN-OT convergently increased activity in the amygdala, caudate head and dACC. Moreover, IN-OT increased activation in the caudate head during positive social and affective processes, providing the neural basis for the social rewarding experiences promotion mechanism. The social salience mechanism would predict enhanced perceptual processing of social cues by IN-OT, independent of valence (Gordon *et al.*, 2013; Weisman and Feldman, 2013). We indeed found that IN-OT increased activity in the STG in healthy population, an important region involved in social cognitive processes (Blakemore, 2008). In addition, the IN-OT effect on STG activity might be independent of the valence of the processes, as we found that IN-OT increased STG activity was contributed by studies examining positive (Voorthuis *et al.*, 2014; Rilling *et al.*, 2014) or negative processes (Domes *et al.*, 2010; Riem *et al.*, 2011; Lischke *et al.*, 2012). Taken together, the OT effects on social functioning might be mediated by multiple neuropsychological mechanisms rather than underpinned by a uniform mechanism. These meta-analytic findings lend neural basis for our social adaptation model (Ma *et al.*, 2016a), proposing that the multifaceted roles of OT in social and affective processes improve the capability for social adaptation.

Comprehensive understanding of IN-OT effects in healthy and clinical population

The majority of OT-fMRI studies examined IN-OT effect in healthy population. Therefore, understanding the common and differential OT effects between healthy and clinical populations was critical for the clinical use of OT. The current meta-analysis provided a comprehensive understanding of OT effects in patients and healthy volunteers. First, convergent OT effects on the social and emotional networks were observed in both healthy and clinical populations. Specifically, IN-OT decreased bilateral amygdala activity in both patients and healthy volunteers, but IN-OT decreased left amygdala activity to a greater degree in patients than healthy volunteers. Moreover, IN-OT increased activity in different brain regions for patients and healthy volunteers. IN-OT increased activity in the amygdala, left caudate and STG for the healthy volunteers. However, OT-increased activity was found in the dACC for patients. These findings suggested selective IN-OT effects in patients and healthy volunteers. It should be noticed that currently only a limited number of OT-fMRI studies have examined IN-OT effect on brain function in patients, and the conjunction and subtraction analyses were performed on the two sets of imbalanced contrasts showing OT effects in patients and healthy volunteers. In addition, the more stringent threshold of FWE correction has not been developed for subtraction analysis in ALE analysis, the subtraction analysis was corrected by the FDR thresholding. Thus the OT effects on brain activity in patients and the comparison of OT effects between patients and healthy volunteers need to be further addressed by future research.

The next question was whether OT exhibited generic positive effects on various mental disorders (Churchland and Winkielman, 2012) or specific effects on different clinical groups (Guastella and MacLeod, 2012). To answer this question, we conducted separate ALE meta-analyses based on disorder types. Because OT-fMRI studies mainly examined OT effects on patients with ASD and SAD, we examined OT neural effects in ASD and SAD, respectively. ALE analysis on OT effects in ASD showed increased activity in the ACC and superior frontal gyrus (SFG) (Supplementary Table S4) and decreased activity in the amygdala. ALE analysis on OT effects in SAD patients showed decreased left amygdala activity by OT (Supplementary Table S4). These results supported the view of specific effects on different clinical groups, suggesting pro-social effect of OT for ASD and anxiolytic action of OT for SAD. Therefore, OT acts on different neuropsychological mechanisms in ASD and SAD, suggesting that therapeutic decisions regarding OT administration should be tailored to specific symptoms. However, it should be noted that this quantitative meta-analysis on the OT neural effect on ASD and SAD is based on a limited number of studies. Thus the conclusions should be interpreted cautiously and the OT effects on brain activity in clinical population need to be further confirmed with future research.

Moreover, OT effects may be modulated by the stage of the disorder. For example, recent OT-fMRI studies have shown that opposite OT effects on amygdala activity to emotional faces in with recently trauma-exposed (within 1-week post-trauma) individuals and PTSD patients. IN-OT increased amygdala activity to fearful faces in recently trauma-exposed women (Frijling *et al.*, 2016). However, OT reduced amygdala reactivity towards emotional faces in PTSD patients (Koch *et al.*, 2016). In addition, most of the published OT-fMRI studies and majority of clinical OT trials examine the effect of a single-dose OT administration. Only a limited number of clinical trials examined multiple-dose or chronic use of OT for mental disorders (see MacDonald and Feifel, 2013 for a summary). A recent OT-fMRI study (Watanabe *et al.*, 2015) has examined the clinical and neural effects of 6-week OT administration in ASD patients. While the authors showed that 6-week OT mitigated behavioral and neural responses in ASD, these effect sizes were not larger than a single

administration of OT. Thus, more clinical trials, as well as OT-fMRI studies, are needed to examine behavioral changes and neural effects by chronic OT administration, and the therapeutic potential of chronic OT needs to be further proven.

In conclusion, we have shown that OT increases neural activity in multiple nodes of the social and emotional network, and decreases neural responses in the emotional network, providing convergent neural evidence for anxiolytic and pro-social effects of OT. The common, but graded, OT effects on patients versus healthy volunteers support therapeutic promise to translate basic OT effects into clinical use for social functioning deficits. Moreover, the modulation of OT effect by the valence of social processes suggests that OT achieves anxiolytic and pro-social ends through different neuropsychological mechanisms. Thus we provide neural evidence supporting therapeutic effect of OT and highlight modulatory factors that would affect the application of OT in clinical practice.

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Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest. None declared.

References

Alvares, G.A., Hickie, I.B., Guastella, A.J. (2010). Acute effects of intranasal oxytocin on subjective and behavioral responses to social rejection. *Experimental and Clinical Psychopharmacology*, **18**, 316–21.

Andari, E., Richard, N., Leboyer, M., Sirigu, A. (2016). Adaptive coding of the value of social cues with oxytocin, an fMRI study in autism spectrum disorder. *Cortex*, **76**, 79–88.

Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H. (2013). Sniffing around oxytocin: Review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. *Translational Psychiatry*, **3**, e258.

Barraza, J.A. (2010). *The Physiology of Empathy: Linking Oxytocin to Empathic Responding*. The Claremont Graduate University.

Bartz, J.A., Hollander, E. (2008). Oxytocin and experimental therapeutics in autism spectrum disorders. *Progress in Brain Research*, **170**, 451–62.

Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N. (2011). Social effects of oxytocin in humans: context and person matter. *Trends in Cognitive Sciences*, **15**, 301–9.

Bartz, J.A., Zaki, J., Ochsner, K.N., *et al.* (2010). Effects of oxytocin on recollections of maternal care and closeness. *Proceedings of the National Academy of Sciences of United States America*, **107**, 21371–5.

Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron*, **58**, 639–50.

Bertsch, K., Gamer, M., Schmidt, B., *et al.* (2013). Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. *American Journal of Psychiatry*, **170**, 1169–77.

Bethlehem, R.A., van Honk, J., Auyeung, B., Baron-Cohen, S. (2013). Oxytocin, brain physiology, and functional connectivity: A review of intranasal oxytocin fMRI studies. *Psychoneuroendocrinology*, **38**, 962–74.

Blakemore, S.J. (2008). The social brain in adolescence. *Nature Reviews Neuroscience*, **9**, 267–77.

Buchanan, T.W., Tranel, D., Adolphs, R. (2009). The human amygdala in social function. In: Whalen, P.J., Phelps, E.A., editors. *The Human Amygdala*. New York: Guilford Press, pp. 289–318.

Bzdok, D., Langner, R., Caspers, S., *et al.* (2011). ALE meta-analysis on facial judgments of trustworthiness and attractiveness. *Brain Structure and Function*, **215**, 209–23.

Cardoso, C., Kingdon, D., Ellenbogen, M.A. (2014). A meta-analytic review of the impact of intranasal oxytocin administration on cortisol concentrations during laboratory tasks: Moderation by method and mental health. *Psychoneuroendocrinology*, **49**, 161–70.

Churchland, P.S., Winkielman, P. (2012). Modulating social behavior with oxytocin: How does it work? What does it mean? *Hormones and Behavior*, **61**, 392–9.

Davis, M., Walker, D.L., Miles, L., Grillon, C. (2010). Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology*, **35**, 105–35.

De Dreu, C.K., Greer, L.L., Handgraaf, M.J., *et al.* (2010). The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans. *Science*, **328**, 1408–11.

De Dreu, C.K., Greer, L.L., Van Kleef, G.A., Shalvi, S., Handgraaf, M.J. (2011). Oxytocin promotes human ethnocentrism. *Proceedings of the National Academy of Sciences of United States America*, **108**, 1262–6.

De Dreu, C.K. (2012). Oxytocin modulates cooperation within and competition between groups: An integrative review and research agenda. *Hormones and Behavior*, **61**, 419–28.

Domes, G., Heinrichs, M., Michel, A., Berger, C., Herpertz, S.C. (2007). Oxytocin improves "mind-reading" in humans. *Biological Psychiatry*, **61**, 731–3.

Domes, G., Kumbier, E., Heinrichs, M., Herpertz, S.C. (2014). Oxytocin promotes facial emotion recognition and amygdala reactivity in adults with Asperger Syndrome. *Neuropsychopharmacology*, **39**, 698–706.

Domes, G., Lischke, A., Berger, C., *et al.* (2010). Effects of intranasal oxytocin on emotional face processing in women. *Psychoneuroendocrinology*, **35**, 83–93.

Ebert, A., Kolb, M., Heller, J., Edel, M.A., Roser, P., Brüne, M. (2013). Modulation of interpersonal trust in borderline personality disorder by intranasal oxytocin and childhood trauma. *Social Neuroscience*, **8**, 305–13.

Eickhoff, S.B., Bzdok, D., Laird, A.R., Kurth, F., Fox, P.T. (2012). Activation likelihood estimation meta-analysis revisited. *Neuroimage*, **59**, 2349–61.

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping*, **30**, 2907–26.

Frijling, J.L., van Zuiden, M., Koch, S.B., Nawijn, L., Veltman, D.J., Olff, M. (2016). Effects of intranasal oxytocin on amygdala reactivity to emotional faces in recently trauma-exposed individuals. *Social Cognitive and Affective Neuroscience*, **11**, 327–36.

Gamer, M., Zurowski, B., Büchel, C. (2010). Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. *Proceedings of the National Academy of Sciences of United States America*, **107**, 9400–5.

Gordon, I., Vander Wyk, B.C., Bennett, R.H., *et al.* (2013). Oxytocin enhances brain function in children with autism. *Proceedings of the National Academy of Sciences of United States America*, **110**, 20953–8.

Guastella, A.J., MacLeod, C. (2012). A critical review of the influence of oxytocin nasal spray on social cognition in humans: Evidence and future directions. *Hormones and Behavior*, **61**, 410–8.

Guastella, A.J., Mitchell, P.B., Dadds, M.R. (2008). Oxytocin increases gaze to the eye region of human faces. *Biological Psychiatry*, **63**, 3–5.

Heinrichs, M., von Dawans, B., Domes, G. (2009). Oxytocin, vasopressin, and human social behavior. *Frontiers in Neuroendocrinology*, **30**, 548–57.

Klackl, J., Pfundmair, M., Agroskin, D., Jonas, E. (2013). Who is to blame? Oxytocin promotes nonpersonalistic attributions in response to a trust betrayal. *Biological Psychology*, **92**, 387–94.

Killgore, W.D., Yurgelun-Todd, D.A. (2004). Activation of the amygdala and anterior cingulate during nonconscious processing of sad versus happy faces. *Neuroimage*, **21**, 1215–23.

Kirsch, P., Esslinger, C., Chen, Q., *et al.* (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *Journal of Neuroscience*, **25**, 11489–93.

Kober, H., Barrett, L.F., Joseph, J., Bliss-Moreau, E., Lindquist, K., Wager, T.D. (2008). Functional grouping and cortical–subcortical interactions in emotion: A meta-analysis of neuroimaging studies. *Neuroimage*, **42**, 998–1031.

Koch, S.B., van Zuiden, M., Nawijn, L., Frijling, J.L., Veltman, D.J., Olff, M. (2016). Intranasal oxytocin administration dampens amygdala reactivity towards emotional faces in male and female PTSD patients. *Neuropsychopharmacology*, **41**, 1495–504.

Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, **435**, 673–6.

Labuschagne, I., Phan, K.L., Wood, A., *et al.* (2010). Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. *Neuropsychopharmacology*, **35**, 2403–13.

Laird, A.R., Eickhoff, S.B., Fox, P.M., *et al.* (2011). The BrainMap strategy for standardization, sharing, and meta-analysis of neuroimaging data. *BMC Research Notes*, **4**, 349.

Laird, A.R., Fox, P.M., Price, C.J., *et al.* (2005). ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. *Human Brain Mapping*, **25**, 155–64.

Lancaster, J.L., Tordesillas-Gutiérrez, D., Martinez, M., *et al.* (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Human Brain Mapping*, **28**, 1194–205.

Lederbogen, F., Kirsch, P., Haddad, L., *et al.* (2011). City living and urban upbringing affect neural social stress processing in humans. *Nature*, **474**, 498–501.

LeDoux, J.E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, **23**, 155–84.

Lieberman, M.D. (2005). Principles, processes, and puzzles of social cognition: an introduction for the special issue on social cognitive neuroscience. *Neuroimage*, **28**, 745–56.

Lieberman, M.D. (2007). Social cognitive neuroscience: a review of core processes. *Annual Review of Psychology*, **58**, 259–89.

Lischke, A., Gamer, M., Berger, C., *et al.* (2012). Oxytocin increases amygdala reactivity to threatening scenes in females. *Psychoneuroendocrinology*, **37**, 1431–8.

Liu, X., Hairston, J., Schrier, M., Fan, J. (2011). Common and distinct networks underlying reward valence and processing stages: A meta-analysis of functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, **35**, 1219–36.

Ma, Y., Li, B., Wang, C., *et al.* (2014). 5-HTTLPR polymorphism modulates neural mechanisms of negative self-reflection. *Cerebral Cortex*, **24**, 2421.

Ma, Y. (2015). Neuropsychological mechanism underlying antidepressant effect: A systematic meta-analysis. *Molecular Psychiatry*, **20**, 311–9.

Ma, Y., Liu, Y., Rand, D.G., Heatherton, T.F., Han, S. (2015a). Opposing oxytocin effects on intergroup cooperative behavior in intuitive and reflective minds. *Neuropsychopharmacology*, **40**, 2379–87.

Ma, Y., Li, B., Wang, C., Zhang, W., Rao, Y., Han, S. (2015b). Allelic variation in 5-HTTLPR and the effects of citalopram on the emotional neural network. *The British Journal of Psychiatry*, **206**, 385–92.

Ma, Y., Shamay-Tsoory, S., Han, S., Zink, C.F. (2016a). Oxytocin and social adaptation: Insights from neuroimaging studies of healthy and clinical populations. *Trends in Cognitive Sciences*, **20**, 133–45.

Ma, Y., Li, S., Wang, C., *et al.* (2016b). Distinct oxytocin effects on belief updating in response to desirable and undesirable feedback. *Proceedings of the National Academy of Sciences of United States America*, **113**, 9256–61.

MacDonald, K., Feifel, D. (2013). Helping oxytocin deliver: Considerations in the development of oxytocin-based therapeutics for brain disorders. *Frontiers in Neuroscience*, **7**, 35.

Marsh, A.A., Henry, H.Y., Pine, D.S., Blair, R.J.R. (2010). Oxytocin improves specific recognition of positive facial expressions. *Psychopharmacology*, **209**, 225–32.

Meinlschmidt, G., Heim, C. (2007). Sensitivity to intranasal oxytocin in adult men with early parental separation. *Biological Psychiatry*, **61**, 1109–11.

Meyer-Lindenberg, A., Domes, G., Kirsch, P., Heinrichs, M. (2011). Oxytocin and vasopressin in the human brain: Social neuropeptides for translational medicine. *Nature Reviews Neuroscience*, **12**, 524–38.

Mikolajczak, M., Gross, J.J., Lane, A., Corneille, O., de Timary, P., Luminet, O. (2010). Oxytocin makes people trusting, not gullible. *Psychological Science*, **21**, 1072–4.

Moskowitz, G.B. (2005). What does it mean to 'know' something?. *Social Cognition: Understanding Self and Others*. New York: Guilford Press, pp. 1–21.

Neumann, I.D. (2007). Stimuli and consequences of dendritic release of oxytocin within the brain. *Biochemical Society Transactions*, **35**, 1252–7.

Perry, A., Mankuta, D., Shamay-Tsoory, S.G. (2015). OT promotes closer interpersonal distance among highly empathic individuals. *Social Cognitive and Affective Neuroscience*, **10**, 3–9.

Petrovic, P., Kalisch, R., Singer, T., Dolan, R.J. (2008). Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. *Journal of Neuroscience*, **28**, 6607–15.

Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry*, **54**, 504–14.

Riem, M.M., Bakermans-Kranenburg, M.J., Pieper, S., *et al.* (2011). Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: A randomized controlled trial. *Biological Psychiatry*, **70**, 291–7.

Riem, M.M., Bakermans-Kranenburg, M.J., Voorthuis, A., van IJzendoorn, M.H. (2014). Oxytocin effects on mind-reading are moderated by experiences of maternal love withdrawal: An fMRI study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **51**, 105–12.

Rilling, J.K., DeMarco, A.C., Hackett, P.D., *et al.* (2014). Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction. *Psychoneuroendocrinology*, **39**, 237–48.

Rilling, J.K., DeMarco, A.C., Hackett, P.D., *et al.* (2012). Effects of intranasal oxytocin and vasopressin on cooperative behavior and associated brain activity in men. *Psychoneuroendocrinology*, **37**, 447–61.

Rocchetti, M., Radua, J., Paloyelis, Y., *et al.* (2014). Neurofunctional maps of the 'maternal brain' and the effects of oxytocin: A multimodal voxel-based meta-analysis. *Psychiatry and Clinical Neurosciences*, **68**, 733–51.

Rupp, H.A., James, T.W., Ketterson, E.D., Sengelaub, D.R., Ditzen, B., Heiman, J.R. (2013). Lower sexual interest in postpartum women: Relationship to amygdala activation and intranasal oxytocin. *Hormones and Behavior*, **63**, 114–21.

Rupp, H.A., James, T.W., Ketterson, E.D., Sengelaub, D.R., Ditzen, B., Heiman, J.R. (2014). Amygdala response to negative images in postpartum versus nulliparous women and intranasal oxytocin. *Social Cognitive and Affective Neuroscience*, **9**, 48–54.

Scheele, D., Kendrick, K.M., Khouri, C., *et al.* (2014). An oxytocin-induced facilitation of neural and emotional responses to social touch correlates inversely with autism traits. *Neuropsychopharmacology*, **39**, 2078–85.

Shahrestani, S., Kemp, A.H., Guastella, A.J. (2013). The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: A meta-analysis. *Neuropsychopharmacology*, **38**, 1929–36.

Shamay-Tsoory, S.G., Fischer, M., Dvash, J., Harari, H., Perach-Bloom, N., Levkovitz, Y. (2009). Intranasal administration of oxytocin increases envy and schadenfreude (gloating). *Biological Psychiatry*, **66**, 864–70.

Stavropoulos, K.K., Carver, L.J. (2013). Research review: Social motivation and oxytocin in autism–implications for joint attention development and intervention. *Journal of Child Psychology and Psychiatry*, **54**, 603–18.

Turkeltaub, P.E., Eickhoff, S.B., Laird, A.R., Fox, M., Wiener, M., Fox, P. (2012). Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. *Human Brain Mapping*, **33**, 1–13.

Turkeltaub, P.E., Messing, S., Norise, C., Hamilton, R.H. (2011). Are networks for residual language function and recovery consistent across aphasic patients? *Neurology*, **76**, 1726–34.

van IJzendoorn, M.H., Bakermans-Kranenburg, M.J. (2012). A sniff of trust: Meta-analysis of the effects of intranasal oxytocin administration on face recognition, trust to in-group, and trust to out-group. *Psychoneuroendocrinology*, **37**, 438–43.

Voorthuis, A., Riem, M.M., van IJzendoorn, M.H., Bakermans-Kranenburg, M.J. (2014). Reading the mind in the infant eyes: Paradoxical effects of oxytocin on neural activity and emotion recognition in watching pictures of infant faces. *Brain Research*, **1580**, 151–9.

Watanabe, T., Kuroda, M., Kuwabara, H., *et al.* (2015). Clinical and neural effects of six-week administration of oxytocin on core symptoms of autism. *Brain*, **138**, 3400–12.

Weisman, O., Feldman, R. (2013). Oxytocin effects on the human brain: Findings, questions, and future directions. *Biology Psychiatry*, **74**, 158–9.

Wigton, R., Radua, J., Allen, P., *et al.* (2015). Neurophysiological effects of acute oxytocin administration: Systematic review and meta-analysis of placebo-controlled imaging studies. *Journal of Psychiatry & Neuroscience*, **40**, E1–22.

Winslow, J.T., Insel, T.R. (2004). Neuroendocrine basis of social recognition. *Current Opinion in Neurobiology*, **14**, 248–53.

Yao, S., Zhao, W., Cheng, R., Geng, Y., Luo, L., Kendrick, K.M. (2014). Oxytocin makes females, but not males, less forgiving following betrayal of trust. *International Journal of Neuropsychopharmacology*, **17**, 1785–92.

Zink, C.F., Meyer-Lindenberg, A. (2012). Human neuroimaging of oxytocin and vasopressin in social cognition. *Hormones and Behavior*, **61**, 400–9.