AUTHOR ACCEPTED MANUSCRIPT

Oxytocin and brain activity in humans: A systematic review and coordinate-based meta-analysis of functional MRI studies

Sally A. Grace[1]*, Susan L. Rossell[1,2,3], Markus Heinrichs[4,5], Catarina Kordsachia[4], and Izelle Labuschagne[4]

1. Centre for Mental Health, Swinburne University of Technology, Melbourne, Australia
2. Monash Alfred Psychiatry Research Centre, Monash University, Melbourne, Australia
3. Psychiatry, St Vincent's Hospital, Melbourne, Australia
4. School of Psychology, Australian Catholic University, Melbourne, Australia
5. Department of Psychology, Albert-Ludwigs-University of Freiburg, Freiburg, Germany.

Correspondence:

Miss Sally Grace, Centre for Mental Health, Swinburne University of Technology, Melbourne, VIC 3122, Australia, Tel: +61 3 9214 8415, E-mail: sgrace@swin.edu.au

Word count: 9152 (total), 244 (abstract), 8908 (text)

Display items: 3 figures, 2 tables

Systematic review registration: PROSPERO CRD42017058656

Uncorrected statistical maps are available on NeuroVault (https://neurovault.org/collections/3713/). The brain activation coordinates, dataset and scripts to perform all of the analyses are available at https://osf.io/8ftzw/.

Table of contents

Abstract

Oxytocin (OXT) is a neuropeptide which has a critical role in human social behaviour and cognition. Research investigating the role of OXT on functional brain changes in humans has often used task paradigms that probe socioemotional processes. Preliminary evidence suggests a central role of the amygdala in the social cognitive effects of intranasal OXT (IN-OXT), however, inconsistencies in task-design and analysis methods have led to inconclusive findings regarding a cohesive model of the neural mechanisms underlying OXT's actions. The aim of this meta-analysis was to systematically investigate these findings. A systematic search of PubMed, PsycINFO, and Scopus databases was conducted for fMRI studies which compared IN-OXT to placebo in humans. First, we systematically reviewed functional magnetic resonance imaging (fMRI) studies of IN-OXT, including studies of healthy humans, those with clinical disorders, and studies examining resting-state fMRI (rsfMRI). Second, we employed a coordinate-based meta-analysis for task-based neuroimaging literature using activation likelihood estimation (ALE), whereby, coordinates were extracted from clusters with significant differences in IN-OXT versus placebo in healthy adults. Data were included for 39 fMRI studies that reported a total of 374 distinct foci. The meta-analysis identified task-related IN-OXT increases in activity within a cluster of the left superior temporal gyrus during tasks of emotion processing. These findings are important as they implicate regions beyond the amygdala in the neural effects of IN-OXT. The outcomes from this meta-analysis can guide *a priori* predictions for future OXT research, and provide an avenue for targeted treatment interventions.

Keywords: Systematic review; Meta-analysis; ALE; neuropeptides; neurochemistry; amygdala

1. Introduction

Oxytocin is a neuropeptide that has a critical role in human social behaviours; including social perception, social cognition, and social memory (Macdonald and Macdonald, 2010). For this reason, oxytocin research has garnered serious interest within the scientific community, popular press and general public (Bartz *et al*, 2011). Since the first study was published in 2005 (Kirsch *et al*, 2005), there has been a fourfold increase in neuroimaging studies on the neurobiological effects of oxytocin when administered intranasally (**Figure 1**). Yet, neuroimaging studies on intranasal oxytocin (IN-OXT) have thus far failed to produce consistent findings and have resulted in small effect sizes, leading to a debate as to whether there is a publication bias in IN-OXT research (Lane *et al*, 2016). Of greatest community interest, IN-OXT provides a unique therapeutic tool for conditions characterised by anxiety and social dysfunction such as social anxiety (Labuschagne *et al*, 2010) and autism (Domes *et al*, 2013). Thus, it is imperative that there is clear evidence supporting the central role for IN-OXT in social neuroscience.

Insert **Figure 1** about here.

At the time of writing this review, over 122 published fMRI studies have measured IN-OXT's involvement in human behaviour and cognition. However, determining the reliable neural correlates of IN-OXT has proven difficult when making qualitative comparisons across studies. It has been argued that individual research studies should be viewed as a single data point in the cumulative investigation of the respective field, and thus should be included in meta-analyses (Schmidt, 1992). To date, three meta-analyses have quantitatively examined the neural correlates of IN-OXT (Rocchetti *et al*, 2014; Wang *et al*, 2017; Wigton *et al*, 2015). Of these, two examined 11 fMRI studies (Rocchetti *et al*, 2014; Wigton *et al*, 2015), and found that the insula was the only reliably activated brain region after IN-OXT (Wigton *et al*, 2015). A more recent meta-analysis of 60 studies found that IN-OXT augments

the bilateral amygdala, caudate head, and superior temporal gyrus (Wang *et al*, 2017). However, close examination of the coordinates included by Wang *et al* (2017) suggests that the authors included coordinates of activation from region of interest (ROI) examinations. For our meta-analysis, we decided upon an alternate approach and applied a stringent inclusion criteria of studies that examined whole-brain activations of OXT in healthy adults only.

There are key points of difference when comparing the current meta-analysis with previous meta-analyses of IN-OXT (Rocchetti *et al*, 2014; Wang *et al*, 2017; Wigton *et al*, 2015). Specifically, the meta-analysis within the current review: (1) provides a coordinate-based meta-analysis to examine the neural correlates of task-based fMRI of IN-OXT research using an activation likelihood estimation (ALE) approach; and (2) focusses solely on whole-brain coordinates from peaks of task-based activation during fMRI to avoid bias from region-of-interest approaches. ALE is a widely used meta-analytic tool that quantitatively assesses voxel-wise neuroimaging foci (Eickhoff *et al*, 2009; Laird *et al*, 2005; Turkeltaub *et al*, 2002). ALE is one of many tools that can be used to achieve meta-analytic synthesis and has the benefit of exhaustive and unbiased inclusion criteria. However, it is not as statistically robust as other methods such as effect size SDM analyses (for a detailed review see, Radua and Mataix-Cols, 2012). Nonetheless, as opposed to narrative reviews, meta-analyses with stringent protocols such as ALE provide a less-biased review of the literature, and provide a worthwhile measure of the neural correlates of IN-OXT.

1.1. Aims of the study

First, we aimed to provide a systematic qualitative outline of all studies that have measured fMRI responses to IN-OXT in healthy humans or those with psychiatric disorders; covering both task-based fMRI and resting-state fMRI studies. Second, we employed an exploratory coordinate-based meta-analysis for task-based fMRI studies reporting whole-

brain activations using ALE. For the meta-analysis, we ran separate analyses focusing on tasks of emotion perception or processing, and those that probed other social cognitive processes such as trust and empathy. Additionally, we performed separate analyses for male and female samples, as well as subtraction analysis to determine if there was any specific gender difference in brain regions activated by IN-OXT.

2. Materials and Methods

The present study was pre-registered with PROSPERO (CRD42017058656) and has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA; Moher et al., 2009) (refer to **Supplementary Materials**). Following recommendations for neuroimaging reporting (Poldrack *et al*, 2017), uncorrected statistical maps are available on NeuroVault (https://neurovault.org/collections/3713/) and the brain activation coordinates used in the ALE meta-analyses as well as the dataset and scripts to perform the effect size meta-analyses are available at https://osf.io/8ftzw/.

2.1. Search Strategy

The literature was searched using the PubMed, PsycINFO, and Scopus databases, and by additional hand searches through reference lists of included studies. The search terms comprised ("oxytocin" OR "syntocinon") AND ("fMRI" OR "brain imaging" OR "functional magnetic resonance imaging" OR "MRI" OR "magnetic resonance imaging"). The search was limited to articles published from the first functional neuroimaging study of oxytocin (Kirsch *et al*, 2005) until February 2017.

2.2. Study selection and eligibility criteria

Two authors (SG and CK) screened all titles and abstracts in the electronic databases. Studies were included if they met the following eligibility criteria: (1) the full-text was

published in the English language; (2) used only human participants; (3) measured brain function using fMRI; (4) includes the use of exogenous OXT (e.g., nasal spray; IN-OXT); and (5) were peer-reviewed original articles. Articles were excluded that: (1) examined correlates of endogenous OXT (e.g., plasma levels, saliva levels, or measures OXTR receptor expression with functional brain activity); (2) used a single case-report; and (3) were reviews or meta-analyses of the literature.

2.1. Review method

We had two main goals: (1) to provide a systematic review of all studies that have examined task-based or resting-state fMRI responses to the administration of IN-OXT in both healthy and psychiatric populations; and (2) meta-analyse whole-brain foci from task-based studies of IN-OXT in healthy humans using ALE.

2.1.1. Data synthesis for systematic literature review

Firstly, studies that met eligibility criteria were subjected to a qualitative systematic review. The following data were extracted from all selected papers: patient characteristics (including sample size, handedness, and age and gender distribution); intervention dose or specifications; the procedure and design of the relevant fMRI technique; and brain regions implicated in the significant findings of the study. These data were broken down into: (1) task-based fMRI studies in healthy humans and in non-healthy clinical populations (**Table 1**); and (2) resting-state fMRI examinations in healthy humans and in non-healthy clinical populations (**Table 2**).

2.1.2. Activation likelihood estimation (ALE) meta-analysis

Secondly, the studies included in the systematic qualitative review were also assessed for relevant data for a meta-analysis. To ensure rigour, stringent inclusion criteria were applied. To be included in the meta-analysis, studies were required to: (1) report specific peak foci of activation in either Talairach or Montreal Neurological Institute (MNI) space; (2)

include a reasonable sample size (i.e., case studies of single subjects were excluded); and (3) reported peak activation coordinates from whole-brain analyses (i.e., could not employ region-of-interest analyses alone).

Ultimately, 39 of 122 examined studies were included in our meta-analyses (**Supplementary Table S3**). Of the included studies, 15 examined emotion perception or processing and 24 examined other social processes. Details of excluded studies are outlined in **Supplementary Table S1**.

2.2.1.1. Statistical meta-analyses

We used a quantitative, random-effects meta-analytic method known as activation likelihood estimation (ALE; Eickhoff *et al*, 2009; Laird *et al*, 2005; Turkeltaub *et al*, 2002; Turkeltaub *et al*, 2012) implemented in the software program GingerALE 2.3.6 (http://brainmap.org) using the most recent algorithm designed to minimize the impact of individual experiments (Turkeltaub *et al*, 2012). The ALE algorithm tests for clustering of peak foci from different experiments included in the meta-analysis. As a part of the analysis, a full-width half maximum (FWHM) Gaussian blur is modelled for each respective foci in each experiment, adjusted for sample size, which together provides and ALE activation map of all studies across the brain. These ALE maps are then assessed against a null-distribution map, thus assessing above-chance clustering of activation foci between studies, enabling random-effects inference (Eickhoff *et al*, 2009; Turkeltaub *et al*, 2012). Based on recommendations (Eickhoff *et al*, 2012), we applied a stringent threshold of $p < 0.05$, 1000 thresholding permutations, and a cluster size > $15mm^3$; which is considered to offer protection against false positives, while providing adequate power levels to reliably detect differences in activation. Notably, there are still no methods to correct for ALE difference maps for multiple comparisons (Eickhoff *et al*, 2011), and given the small number of papers in the sub-sample analyses (8-24 experiments), an uncorrected threshold of $p < 0.05$ is

considered conservative. Therefore, for the subtraction and conjunction analyses we applied stringent threshold of FDR pN < 0.01, 1000 thresholding permutations, and a cluster size > 100mm^3. All peak voxel coordinates are reported in Montreal Neurological Institute (MNI) space. For consistency, for all studies where peak voxels were originally reported in Talairach space, we transformed coordinates into MNI space using the icbm2tal transformation function implemented within the GingerALE software package (Laird *et al*, 2010; Lancaster *et al*, 2007). To display the results, maps were computed separately for the clusters of activations and deactivations. The creation of the final figures for presentation here was performed in the MRIcron software package using standard MNI brain templates (http://www.mccauslandcenter.sc.edu/crnl/mricron/).

2.2.1.2. Sub-analyses

Using the statistical methods described above, a series of ALE analyses were conducted on a final set of 39 studies. We first performed an analysis comparing IN-OXT and placebo (PBO) contrasts (i.e., OXT>PBO, OXT<PBO). For the sub-analyses, we conducted separate *emotion processing* (*n* = 15 studies) and other *social processing* (*n* = 24 studies) analyses. Also, gender analyses were performed on males (*n* = 29 studies) and females (*n* = 8 studies) separately. For each of the sub-analyses categories, we performed the ALE analyses for the contrasts of OXT>PBO and PBO>OXT to separately identify whether activity was increased or decreased by IN-OXT. Three studies (Chen *et al*, 2017; Feng *et al*, 2015; Gao *et al*, 2016) that were included in the overall analysis were not included in the gender analysis as they only provided foci or main effects of pooled samples of males and females or contrasts comparing males and females. All of our sub-analyses had a sample size that is required to obtain valid results from ALE analysis (*n*>8 studies, as reported in Wagner *et al*, 2014). However, we did not have enough statistical power to show a significant difference in the subtraction and conjunction analyses (*n*>15 studies) for all sub-analyses.

2.2.1.3. Estimating publication bias in meta-analytic results

Several methods were applied to reduce the risk of bias of within and across studies. First, to overcome the problem of a bias toward specific brain areas, only studies using a quantitative automated whole-brain analysis were included. Studies reporting results of region-of-interest approaches were not considered. As proposed in Eickhoff *et al* (2009) new algorithm, the number of patients included in each study was taken into account in data synthesis. We also performed a separate analysis of positive and negative findings separately.

Second, the Cochrane Collaboration's tool for assessing risk of bias (Higgins *et al*, 2011) was used to assess the within-study risk of bias in included studies systematically (**Supplementary Table S4**). Third, the bias toward publication of only positive results is a serious concern (the 'file drawer' problem; Rosenthal, 1991), particularly within the OXT literature (Lane *et al*, 2016; Leng and Ludwig, 2016). Publication bias was visually inspected via a funnel plot (standard error plotted against effect size) and performing an Egger's regression test for funnel plot asymmetry (Egger *et al*, 1997). If the null hypothesis for this test is rejected ($p<0.05$), it indicates that a publication bias exists in the model and can be corrected by the Trim and Fill method that is used to adjust for publication bias (Duval and Tweedie, 2000). Details on effect size calculations and methodology are described in the Supplementary Methods.

3. Results I: neuroimaging systematic review

3.1. Study selection

A total of 922 articles were identified. Following removal of duplicates, 671 remained and were screened by title and abstract. As a result, 591 were excluded based on identifying at least one feature of the article that warranted exclusion. A total of 122 articles were selected for full-text review, after which 82 studies were identified for inclusion in this

systematic review. A flowchart of this selection process is displayed in the supplementary material in **Figure S1**.

3.2. Study characteristics

Fifty-five studies investigated task-based functional brain activation in IN-OXT in healthy populations (**Table 1**), 18 examined task-based functional brain activation in non-healthy populations (**Table 1**), seven studies investigated functional differences using resting-state fMRI in healthy populations (**Table 2**), and two studies investigated functional differences using resting-state fMRI in non-healthy clinical populations (**Table 2**). Overall, these articles yielded a total of 3950 participants, age ranged from 8-85 years, the ratio of males to females was 5:2, with 19 of these studies including both male and female participants in their samples. The clinical groups examined included generalised social anxiety disorder (GSAD; n = 3), autism spectrum disorder (ASD; n = 8), post-traumatic stress disorder (PTSD; n = 4), depression (n = 1) and schizophrenia (n = 1). Of these studies, all administered an acute dose of IN-OXT via nasal spray method with the exception of one study that used a unique breath powered device (Quintana *et al*, 2016), and one study that measured cumulative dosages of home IN-OXT users (Kovacs and Keri, 2015). Dosages ranged from 16-76 international units (IU; M = 25.91 IU, SD = 8.09 IU), with the most common dosage being 24 IU (n = 61).

3.3. Oxytocin and task-related brain activation

In this section, we systematically discuss the significant regions of interest activated in our included studies that examined task-based activation using fMRI in healthy (**Table 1**) and non-healthy populations (**Table 1**), covering a total of 72 articles that include significant findings from both region-of-interest and whole-brain analyses. Please refer to **Supplementary Table S2** for a summary of the specific brain areas modulated by each study.

Insert **Table 1** about here

3.4. Regional activation

3.4.1. Amygdala

Of the 73 articles using task-based fMRI, 39 reported significant augmentation of amygdala region-of-interest activity by IN-OXT and three studies reported significant whole-brain differences, making it the most consistent region of IN-OXT action in the human brain. Twenty-five studies showed a task-related *decrease* in amygdala activation following an acute dose of IN-OXT. When broken down into task type: 14 studies showed a decrease in amygdala responses to emotive faces or aversive stimuli (Domes *et al*, 2007; Domes *et al*, 2013; Eckstein *et al*, 2015; Gamer *et al*, 2010; Kanat *et al*, 2015a; Kanat *et al*, 2015b; Kirsch *et al*, 2005; Koch *et al*, 2016a; Labuschagne *et al*, 2010; Quintana *et al*, 2016; Radke *et al*, 2017; Rupp *et al*, 2014; Shin *et al*, 2015; Striepens *et al*, 2012); one to aversively conditioned stimuli (Petrovic *et al*, 2008); two in response to pain (Singer *et al*, 2008; Zunhammer *et al*, 2015); three studies showed a decrease in response to tasks that involved infant laughter and distress (Riem *et al*, 2011; Riem *et al*, 2016; Riem *et al*, 2012); and five studies that probe motivational processes such as monetary transactions and trust (Andari *et al*, 2016; Baumgartner *et al*, 2008; Chen *et al*, 2016; De Dreu *et al*, 2015; Rilling *et al*, 2014).

Conversely, 19 studies showed an *increase* in amygdala activation following IN-OXT. When broken down into task type: 14 studies used tasks that included facial emotion or aversive stimuli (Domes *et al*, 2013; Domes *et al*, 2014; Domes *et al*, 2010; Frijling *et al*, 2016; Gamer *et al*, 2010; Gordon *et al*, 2016; Grimm *et al*, 2014; Koch *et al*, 2016a; Lischke *et al*, 2012; Petrovic *et al*, 2008; Pincus *et al*, 2010; Shin *et al*, 2015), and 5 used tasks of social processes like empathy, trust and reward (Chen *et al*, 2017; Hu *et al*, 2015; Rilling *et al*, 2014; Rilling *et al*, 2012).

Importantly, individual (e.g., sex, psychopathology) and contextual differences (e.g., stimulus type or valence) appear to have moderating effect of IN-OXT on amygdala activation. First, gender may be an important moderator of IN-OXT's effects. In healthy females, four studies have shown IN-OXT induced increased activation of the amygdala for threatening, fearful or negative stimuli (Domes *et al*, 2010; Frijling *et al*, 2016; Lischke *et al*, 2012; Rilling *et al*, 2014). Whereas, five studies have found that IN-OXT was associated with a reduction of amygdala activity in females, in response to tasks that probe infant distress and laughter (Riem *et al*, 2011; Riem *et al*, 2016; Riem *et al*, 2012), negative images (Rupp *et al*, 2014), and social economic games (Rilling *et al*, 2014).

In contrast, in healthy males, attenuated amygdala responses to IN-OXT have been observed in 13 studies that include threatening or aversive stimuli (Eckstein *et al*, 2015; Gamer *et al*, 2010; Radke *et al*, 2017; Striepens *et al*, 2012), the experience of pain (Singer *et al*, 2008), facial emotion (Domes *et al*, 2007; Domes *et al*, 2013; Kanat *et al*, 2015a; Kirsch *et al*, 2005; Quintana *et al*, 2016), and social economic games (Baumgartner *et al*, 2008; Chen *et al*, 2017; De Dreu *et al*, 2015). Whereas, increases in amygdala activation following IN-OXT have also been observed in four studies of healthy males, on tasks of facial emotion perception (Gamer *et al*, 2010; Shin *et al*, 2015), conditioned fear (Petrovic *et al*, 2008), and in response to negative social interactions (Chen *et al*, 2017; Hu *et al*, 2015).

Direct within-study comparisons of males and females on amygdala responses to IN-OXT have found distinct gender differences. For example, Frijling *et al* (2016) found a significant sex interaction on amygdala reactivity, with women showing increased left amygdala reactivity after IN-OXT during an emotional face matching task. In contrast, when the same authors analysed the male and female samples together they found right amygdala responses to fearful faces. Further, Rilling *et al* (2014) found the opposite effect of gender in the left amygdala during the Prisoners Dilemma task. Whereby, IN-OXT treatment increased

the left amygdala response to cooperation in men whereas it decreased in women. Other than gender, it appears that valence has a large effect on amygdala reactivity as well. Gamer *et al* (2010) found that happy faces elicited a strong increase in activity within the lateral and dorsal regions of the anterior amygdala for happy faces but attenuated it for fearful faces.

It is important to consider these amygdala responses in the context of dynamic functional brain network changes. For example, while IN-OXT inhibited amygdala responses to aversive stimuli, a complementary connectivity analysis revealed that it increased functional coupling between the left amygdala, left anterior insula, and left IFG (Striepens *et al*, 2012). These findings suggest that the inhibition of the amygdala to aversive responses might be superficial and the insula might take on more of a mediating role in output behaviours such as empathy and memory for such stimuli (Striepens *et al*, 2012). This, in turn, could lead to the modulation of approach behaviours, for example towards in-group members or own-children. Furthermore, in a fear conditioning paradigm, Eckstein *et al* (2015) found that while right amygdala responses were reduced, using psychophysiological interactions analysis to assess the functional interplay of brain regions, IN-OXT increased functional connectivity (FC) of the right amygdala with left precuneus, which might suggest that IN-OXT upregulates PCC responses to fear-associated stimuli and in turn, downregulates the amygdala. Together, extant data in IN-OXT suggest that the amygdala has a dynamic role in increasing approach behaviours as well as modulating responses to aversive social stimuli and social situations.

Amygdala responses to IN-OXT have also been measured in psychiatric cohorts. Such studies have found that task-based activation in patient groups opposes that of matched healthy control samples. For example, in males with ASD, administration of IN-OXT increased right (Domes *et al*, 2013), left (Domes *et al*, 2014) and bilateral (Gordon *et al*, 2016) amygdala activation to emotive faces and voices, which consequently resembled the

pattern of activation of healthy controls under placebo, and could be interpreted as a "normalisation" effect within this cohort. Decreased amygdala responses to IN-OXT have also been observed in a social ball tossing game in ASD (Andari *et al*, 2016). A discrepancy here might reflect the nature of the task, as tasks that involve emotional stimuli in ASD are associated with underactive amygdala at baseline, reflected in blunted socio-effective processes in ASD cohorts. Additionally, differential modulation of IN-OXT on the right amygdala has been shown in borderline personality disorder, where increased activation in response to angry faces was reversed by IN-OXT, potentially reflecting reduced threat hypersensitivity in the disorder (Bertsch *et al*, 2013). Likewise, hyperactive amygdala responses and connectivity to emotional faces have been restored (i.e., resemble healthy controls at baseline) by IN-OXT administration in those with GSAD (Gorka *et al*, 2015; Labuschagne *et al*, 2010), PTSD (Koch *et al*, 2016a) and schizophrenia (Shin *et al*, 2015). Altogether, these data suggest that IN-OXT might be a promising pharmacological agent through targeting and altering abnormal amygdala function in these disorders.

3.4.2. Anterior cingulate cortex

Of the studies reported, 13 reported alterations of ACC activity following IN-OXT administration: seven found an *increase* and two found a *decrease* in ACC activation following IN-OXT. Preliminary data has shown attenuation of the ACC in males following IN-OXT during fMRI tasks of conditioned fear (Eckstein *et al*, 2016), positive responses of men to viewing images of their children (Li *et al*, 2017), and in response to female touch (Scheele *et al*, 2014a). In contrast, increased ACC following IN-OXT has also been observed in tasks of self-referential processing of disgust and stress (Eckstein *et al*, 2014; Scheele *et al*, 2014b), and increased dmPFC-ACC connectivity to self and other processing (Zhao *et al*, 2016).

IN-OXT's effect on the ACC might facilitate learning and the downregulation of fear related processes. For example, during a Pavlovian fear conditioning task, IN-OXT strengthened ACC responses to fear associated stimuli, and activation of the MCC in response to social-related fear stimuli (Eckstein *et al*, 2016). The authors suggest that IN-OXT specifically facilitates social fear conditioning, and as such, acts as an enhancer of adaptation to social contexts (Eckstein *et al*, 2016). This is important in the context of psychiatric disorders that involve maladaptive fear extinction, and preliminary research suggests that IN-OXT might be useful in the treatment of such disorders, for example, GSAD (Labuschagne *et al*, 2012) and PTSD (Koch *et al*, 2016a; Nawijn *et al*, 2017). Evidence from these studies suggests that IN-OXT restores mPFC and ACC hyperactivity in male GSAD patients, such that group differences observed at baseline were no longer observed under IN-OXT (Labuschagne *et al*, 2012). Beyond fear-related processes, the ACC and mPFC have also been implicated in improvements in verbal and facial emotion recognition in ASD following IN-OXT (Aoki *et al*, 2015; Watanabe *et al*, 2014). Together, the results discussed here provide support that the ACC may have a role in the prosocial and anxiolytic effects of IN-OXT.

3.4.3. Prefrontal cortex

Nine studies within the present review found significant augmentation of the PFC following IN-OXT. In males and females, significant *decreases* in mPFC activation have been observed in tasks that probe interpersonal relations, such as social economic games (Chen *et al*, 2017; Feng *et al*, 2015; Mickey *et al*, 2016) and judgements of self and others (Zhao *et al*, 2016). Interestingly, opposing effects of IN-OXT have been found between males and females, whereby IN-OXT activation of the mPFC was associated with increased positive social interactions in men, while decreased mPFC responses were associated with positive social interactions in females. Thus, these data might suggest that IN-OXT has

sexually dimorphic brain responses and similar behavioural outcomes. This is also consistent with studies that have found IN-OXT increases mPFC activation and socioemotional processing in ASD (Aoki *et al*, 2015; Watanabe *et al*, 2014).

Other tasks have elicited *increases* in mPFC activation following IN-OXT. First, IN-OXT increased mPFC activity and dampened amygdala activity in response to aversively conditioned stimuli (Eckstein *et al*, 2015), suggesting a mPFC-amygdala link in the potential cognitive downregulation of conditioned fear. Second, in a task of interpersonal space, dmPFC activation in males following IN-OXT was associated with approach and closeness to a friend, but also increased outgroup bias by increasing distance from an unfamiliar person (Cohen *et al*, 2017). Together, it appears that IN-OXT increases activity in the mPFC during interpersonal social tasks, which might reflect enhanced metallization processes (Rilling *et al*, 2004).

3.4.4. Inferior and orbitofrontal cortex

Eight studies within the present review found signifcant alterations of inferior frontal and OFC regions following IN-OXT administration. Of these studies, seven found an *increase* in healthy males and females. Specifically, in healthy females, increased OFC was observed whilst viewing facial emotion (Domes *et al*, 2010; Voorthuis *et al*, 2014) and in response to infant crying (Riem *et al*, 2011; Riem *et al*, 2014b). In healthy males, increased OFC was observed during self-processing (Scheele *et al*, 2014a). Moreover, in ASD samples relative to neurotypical healthy controls, IN-OXT was associated with increased inferior frontal activation during facial emotion recognition (Domes *et al*, 2014; Gordon *et al*, 2016). Moreover, Gordon *et al* (2016) found increased OFC-vmPFC-NAcc connectivity in individuals with ASD following IN-OXT, which might suggest an increase in social attentiveness through mPFC and OFC activation, which might translate into behavioural action through NAcc outputs. Despite differing effects, it appears that IN-OXT has an

influence on inferior frontal regions in mediating social processing, which may underlie some of IN-OXT's prosocial behavioural effects.

3.4.5. Insula

Eighteen studies within the present review reported significant insula mediation by IN-OXT, making it the second most consistent region of activation across the included studies. We identified nine studies that demonstrated an *increase* in insula activation following IN-OXT, three using a sample of healthy females (Riem *et al*, 2011; Riem *et al*, 2014a; Riem *et al*, 2014b), two using a sample of healthy males (Scheele *et al*, 2014a; Scheele *et al*, 2014b), and four in samples of patients with PTSD (Nawijn *et al*, 2016, 2017), depression (Pincus *et al*, 2010), and autism (Andari *et al*, 2016). Addditionally, increased functional connectivity of the insula was also observed in four studies (Gorka *et al*, 2015; Hu *et al*, 2015; Rilling *et al*, 2014; Rilling *et al*, 2012). IN-OXT was also associated with *decreases* in insula activity in six studies: two using samples of healthy females (Chen *et al*, 2017; Rilling *et al*, 2014); and four using healthy males (Bos *et al*, 2015; Chen *et al*, 2016; Eckstein *et al*, 2015; Gozzi *et al*, 2017).

The insula might have a role in prosocial effects of IN-OXT through its hypothesised role in self-awareness, emotional responses, and empathetic processes, and alongside the ACC, as part of a "salience network" (Menon and Uddin, 2010). IN-OXT induced activation of the insula might increase bottom-up detection of salient events and generate behavioural responses to social stimuli. For example, IN-OXT administration increased insula activity in response to negative social situations in males with ASD, potentially triggering arousal for subjective feelings of social pain (Andari *et al*, 2016).

In addition, the insula has been shown to play a role in increased empathy following IN-OXT. Riem *et al* (2011) also found an increase in insula and IFG activity, and a decrease in right amygdala activity in response to infant crying following IN-OXT administration.

Further, a meta-analysis found that of all the brain regions, the insula was the most robustly activated by IN-OXT administration, and did not show a significant modulation by sex (Wigton *et al*, 2015). However, in the present study, we identified evidence to suggest that this relationship is not as clear as previously thought. Namely, there is evidence to suggest that there is a female-specific reduction of insula activity following IN-OXT administration. For example, Rilling *et al* (2014) demonstrated increased activity in the insula, hippocampus and amygdala in men after IN-OXT administration, but decreased in women, suggesting that IN-OXT may enhance social reward and facilitate social bonding to a greater degree in men than women. In support, females have been shown to reliably deactivate the rACC, vlPFC and posterior insula following IN-OXT in both within-subject and between-subject designs of social interaction (Chen *et al*, 2017; Chen *et al*, 2016). This activation pattern was not evident in males, with males showing attenuated amygdala and anterior insula responses to negative social interaction in a within-subject study that did not survive a more robust within-subject designs (Chen *et al*, 2017; Chen *et al*, 2016). Further, in males, the functional connectivity of the amygdala and insula has been implicated in social learning tasks and might play a role attributing salience and reward value to social stimuli (Hu *et al*, 2015; Striepens *et al*, 2012). Also, there is evidence to suggest that IN-OXT administration reduces empathy-related activation in the left-insula in males (Bos *et al*, 2015). Together, these studies suggest that insula may mediate the social saliency of emotional information and empathetic concern associated with IN-OXT, however, as with other regions, it appears that this role differs across the sexes.

3.4.6. Midbrain and basal ganglia

We identified 11 studies that found task-related *increases* in midbrain and basal ganglia activation following IN-OXT, of these studies, three included a sample of healthy females (Gregory *et al*, 2015; Groppe *et al*, 2013; Scheele *et al*, 2016), six healthy males (Feng *et al*,

2015; Hu *et al*, 2015; Li *et al*, 2017; Mickey *et al*, 2016; Rilling *et al*, 2012; Scheele *et al*, 2013), one autism (Gordon *et al*, 2013), and one PTSD (Nawijn *et al*, 2016). *Decreases* were identified in three studies, two using a sample of healthy females (Chen *et al*, 2017; Feng *et al*, 2015), and one males (Wittfoth-Schardt *et al*, 2012).

The basal ganglia are crucial for reward processing and comprise the globus pallidus (GP), substantia nigra, putamen, caudate and ventral striatum (Hong and Hikosaka, 2008). It has been suggested that the caudate is particularly relevant to OXT research as it may help modulate how decisions are made based on preconceptions of trust (Wigton *et al*, 2015). In support of this view, several studies have found an increase in caudate responses following IN-OXT administration in males and females during tasks of face processing (Pincus *et al*, 2010), trust (Rilling *et al*, 2012), and parental attachment (Wittfoth-Schardt *et al*, 2012). Other authors suggest that the caudate connects with the amygdala to facilitate reward processing under social feedback, which has a role in the salience and reward of social information and learning, and might contribute to the enhanced emotional memory and social facilitatory processes of IN-OXT (Hu *et al*, 2015).

There is growing evidence to suggest that OXT enhances reward based activation of the dorsal striatum (including the caudate) in men. For example, when compared to placebo, IN-OXT augmented caudate responses to fathers viewing images of their children (Li *et al*, 2017), enhances responses to reciprocated cooperation from the opposite sex within the caudate and putamen (Feng *et al*, 2015), and increased NAcc and VTA activation whilst men viewed images of their long term romantic partners (Scheele *et al*, 2013). Further, when comparing IN-OXT to placebo, increased VTA responses have been observed in positive social situations in females but not males (Chen *et al*, 2017), in anticipation of monetary reward and loss (Groppe *et al*, 2013; Mickey *et al*, 2016), and whilst women viewed sexual and infant images (Gregory *et al*, 2015). Taken together, this suggests that IN-OXT guides

the detection of socially relevant cues. For example, in males, OXT increases romantic bonds by making their partner more attractive and rewarding compared to other women.

The midbrain connects with the central nucleus of the amygdala to mediate fear-related behaviour and arousal (LeDoux, 2000). Thus, IN-OXT might not only mediate amygdala function, but also facilitates coupling with other regions to mediate fear responses. For example, Baumgartner *et al* (2008) found that IN-OXT increased trust behaviours in a monetary game, which was associated with a significant reduction in BOLD signal within the amygdala and caudate, suggesting that neural systems responsible for mediating fear and reward processing modulate IN-OXT's effect on trust. Therefore, IN-OXT might facilitate social interaction by attenuating neural responses to socially salient cues. Furthermore, using a well-validated paradigm to robustly activate the amygdala with two classes of fearful visual stimuli, Kirsch *et al* (2005) found significant decoupling of the amygdala and midbrain under IN-OXT, which was more pronounced for socially relevant stimuli (i.e., faces). Altogether, these data suggest that, alongside the amygdala, IN-OXT may mediate fear-related responses via its reciprocal connections with midbrain regions.

Together, these results suggest a consistent role of IN-OXT for the midbrain and basal ganglia in reward processing, whereby IN-OXT enhances reward and salience from interpersonal relationships (e.g., cooperation, romantic, parental), and thus facilitates social bonding and attachment.

3.4.7. Temporal gyrus

We identified 10 studies that showed task-related increases in temporal activity following IN-OXT, six in females, two in healthy males, and two in autism. Thus, IN-OXT appears to have a relatively consistent effect on task-based activation within the temporal lobes in healthy females, particularly using tasks that probe empathetic processing or involve stimuli of a negative valence. For example, in female samples, increased superior temporal

gyrus (STG) and middle temporal gyrus (MTG) responses have been observed in response to happy and fearful faces (Domes *et al*, 2010), left anterior temporal responses to negative scenes (Lischke *et al*, 2012), and increased activity within the IFG, MTG and STG in response to infant distress (Voorthuis *et al*, 2014). The only study included in our systematic review that shows reduced temporal activity following IN-OXT administration in females was that of Hecht *et al* (2017), who implemented a dynamic social interaction game with animations of shapes playing, chasing or fighting, using a non-double-blind procedure. The reduced activation within the temporal lobes could be caused by the use of non-face and non-emotive stimuli, or limited by the non-blind experimental design. Together, these findings suggest that IN-OXT effects the processing of threatening stimuli and negative social situations within the temporal lobes in females.

In healthy males, there appears to be a task-based differential effect of IN-OXT on temporal responses. Namely, IN-OXT was associated with an increase in fusiform gyrus activity during a task of emotion recognition from eye and mouth stimuli (Domes *et al*, 2014), and fusiform and STG in the response phase of a learning task under social feedback (Hu *et al*, 2015). Together, this might reflect the enhanced processing of socially salient information. On the other hand, deactivations of the temporal lobe have been identified. Petrovic *et al* (2008) found decreased fusiform and amygdala responses to fear conditioned faces following IN-OXT, and Gozzi *et al* (2017) found decreased STG and temporoparietal junction (TPJ) activation during negative social feedback. When contrasting placebo to IN-OXT conditions, a decrease in temporal lobe and amygdala activity might reflect the downregulation of negative emotional experience by IN-OXT, and thus the potential anxiolytic effect that has been hypothesised. In support of this theory, research into males with ASD suggests that IN-OXT may enhance attentional processes for social information. Specifically, several studies have found an increase in fusiform and temporal regions

following IN-OXT in males and females with ASD (Andari *et al*, 2016; Gordon *et al*, 2013). Given that pathological social attentive processing characterises ASD, these results suggest that IN-OXT may promote neurotypical brain functioning in individuals with ASD in tasks of social and emotional perception.

Together, IN-OXT's augmentation of the temporal lobes might reflect the enhanced processing of social cues and mentalisation, which might contribute to enhanced emotion recognition following IN-OXT (Shahrestani *et al*, 2013).

3.4.8. Precuneus

We identified six studies that documented altered precuneus activity following IN-OXT: four studies that found *increases* in precuneus activation following IN-OXT; one study of healthy females found *decreased* precuneus activity; and changes to the functional connectivity of the precuneus have also been identified. Specifically, in an examination of functional brain connectivity in response to infant laughter, Riem *et al* (2012), found that IN-OXT enhances the functional connectivity between the amygdala, OFC, ACC, hippocampus, the precuneus and the middle temporal gyrus. Furthermore, Zhao *et al* (2016) found that IN-OXT was positively associated with vmPFC-PCC functional connectivity in males during self-referential processing. Moreover, Gordon *et al* (2013) found that IN-OXT significantly increased BOLD signal within the precuneus and PCC, and within other notable "social cognitive" regions (vmPFC, IFG, STG, right amygdala) in children with ASD during the processing of socially meaningful pictures. Suggesting that IN-OXT may impact on the salience of socially meaningful stimuli, and therefore facilitate social awareness in ASD. Chen *et al* (2016) found that IN-OXT attenuated BOLD responses within the PCC in women during social tasks that involved trusting other players. Together, these studies suggest that IN-OXT may exert its central effects through activating a "social cognitive" functional network that includes the amygdala, PFC and the PCC/precuneus.

3.4.9. Occipital cortex

Lastly, fMRI tasks have demonstrated the augmentation of the occipital cortex following IN-OXT administration in eight studies. Specifically, five studies that included samples of healthy males identified *increased* activation of the visual cortex whilst men viewed pictures of children (Li *et al*, 2017; Wittfoth-Schardt *et al*, 2012), in social feedback tasks (Hu *et al*, 2015), in response to social touch (Scheele *et al*, 2014a), and during prosocial interactions (Rilling *et al*, 2012). Further, in autistic males, IN-OXT enhanced visual cortex activity in response to faces more than geometric shapes (Andari *et al*, 2016). Together, occipital activation by IN-OXT complements the temporal lobe findings, suggesting that IN-OXT facilitates activation of early sites within the visual processing stream.

3.5. Oxytocin and resting-state brain connectivity

Insert **Table 2** about here.

Nine fMRI studies have examined IN-OXT's effect on the resting brain using resting-state fMRI (rsfMRI; see **Table 2** for an overview). Of the 9 rsfMRI studies presented, 8 used a seed-based approach to identify temporal correlations between the amygdala as an *a priori* region-of-interest and other voxels of the brain. Two studies used a similar approach and examined region-to-region connectivity. An early rsfMRI study examined a small sample of healthy males and demonstrated increased amygdala-prefrontal coupling after IN-OXT administration (Sripada *et al*, 2013), whereas another study suggested decreased coupling of the amygdala with the precuneus (Kumar *et al*, 2015), and that early life stress modulates amygdala-prefrontal connectivity (Fan *et al*, 2014). Similar patterns were observed in male patients with GSAD whereby IN-OXT administration had a normalising effect, as it reversed heightened amygdala-mPFC connectivity observed in the placebo session in GSAD patients

(Dodhia *et al*, 2014), compared to healthy controls who demonstrated an opposite pattern of connectivity. These early studies must be interpreted with caution, as they have included small samples of young male participants, and research involved female samples has brought to light gender and age specific effects of IN-OXT on brain activation at rest.

Namely, in a between-subject twin study of females, IN-OXT did not modulate amygdala-prefrontal connectivity but altered PCC-brainstem connectivity. Further, Ebner *et al* (2016) found significant treatment-by-age-by-sex variations on IN-OXT, asserting that IN-OXT not only has differing sex effects on rsFC but age variations as well. The effect was most evident in young females showing enhanced resting-state functional connectivity of the amygdala and mPFC, with no significant effects in young men and older females, and approaching significance in older men (Ebner *et al*, 2016).

Together, it is apparent from the small subsection of rsfMRI studies that IN-OXT may exert its behavioural and social cognitive effects by altering the connectivity between regions known for social and emotive processing (i.e., the amygdala, mPFC, ACC and precuneus/PCC).

4. Results II: Meta analytic results

We meta-analysed a total of 374 peak foci of activation or deactivation drawn from 39 studies (**Supplementary Table S3**). To retain a maximal amount of information, the meta-analysis collapsed data from 16 between-group and 22 within-group designs. Coordinate foci (n=2) from the included studies fell outside of the brain mask templates used with the GingerALE meta-analysis software. This is a normal occurrence when using exclusive meta-analytic template masks. The total number of foci included in the final meta-analyses was therefore 372. Analysis of 31 OXT>PBO contrast experiments (243 foci, 1420 participants)

revealed no significant clusters of convergence. Similarly, analysis of 19 PBO>OXT contrast experiments (135 foci, 652 participants) revealed no significant clusters of convergence.

4.1. Meta-analysis by task type

We separated the data by task type (see **Supplementary Table S3**) and conducted separate ALE meta-analyses on fMRI tasks that probed social and emotional processes. The ALE meta-analysis on 24 experiments (221 foci; 1124 participants) that probed social processes revealed no significant clusters of convergence. Likewise, no significant clusters were identified when we broke the social category down into OXT>PBO (16 experiments, 153 foci, 873 participants) and PBO>OXT (13 experiments, 66 foci, 539 participants) contrasts. The ALE meta-analysis on 15 experiments (151 foci, 491 participants) that probed emotional processes revealed no significant clusters overall or under the PBO>OXT contrast (7 experiments, 87 foci, 158 participants). However, for the OXT>PBO contrast (14 experiments, 72 foci, 506 participants), one significant cluster was identified within the left STG (MNI[-52,-8,-2], $k = 24mm^3$, extrema = 0.018, FWE $p < 0.05$; **Figure 2**). Suggesting that IN-OXT increases brain activity within the left STG during tasks that probe basic emotional processes.

Insert Figure 2 about here

4.2. Meta-analysis by gender

We then conducted separate ALE analyses on studies that reported foci for male and female samples. The ALE meta-analysis on all studies that reported foci from male participants alone (29 experiments, 279 foci, 1034 participants), and within the OXT>PBO (22 experiments, 142 foci, 855 participants) and PBO>OXT (14 experiments, 129 foci, 465 participants) contrasts, reported no significant clusters of convergence. Similarly, the ALE

meta-analysis on all studies that reported foci from female participants alone (8 experiments, 63 foci, 321 participants), and within the OXT>PBO (5 experiments, 53 foci, 143 participants) and PBO>OXT (5 experiments, 10 foci, 208 participants) contrasts, reported no significant clusters of convergence.

4.3. Publication bias

To assess the possibility of publication bias, we conducted several analyses. First, we used the Cochrane Collaboration's tool for assessing bias and identified no significant areas of risk (**Supplementary Table S4**). Second, we constructed a funnel plot derived from effect sizes (Cohen's *d*) from studies that reported *t* statistics. The methodology is detailed within the Supplementary Methods and these results are reported in **Supplementary Table S3**. The funnel plot indicated the presence of publication bias (**Figure 3**), and Egger's regression test for funnel plot asymmetry (Egger *et al*, 1997) confirmed that publication bias influenced the validity of the summary effect size of this meta-analysis across the included studies (p = 0.002). Thirdly, we employed the "trim and fill" methodology described by Duval *et al* (2000) to estimate the number of studies missing due to publication bias, which suggested that eight imputed studies are missing.

Insert Figure 3 about here

3. Discussion

The current review employed both a qualitative systematic and quantitative meta-analytic approach to identify the neural correlates of IN-OXT in humans. There were two main aims of the review: (1) provide a systematic summary of extant empirical research studies examining the association between IN-OXT administration, and task-based or resting-state functional brain activity; and (2) quantitatively investigate the neural correlates of IN-

OXT on task-based brain activation via meta-analysis, and explore gender and within-task differences in brain activation.

Current hypotheses regarding IN-OXT's mechanisms of action on human brain function broadly encompass a two-part model action (Bethlehem *et al*, 2013; Quintana *et al*, 2015). That is, a bottom-up anxiolytic effect that facilitates approach behaviour (Kemp and Guastella, 2011), and a top-down effect that increases the social salience of stimuli and increases reward from prosocial interactions (Bartz *et al*, 2011; Ma *et al*, 2016). The findings of our systematic review support this two-part model. First, alterations in brain function within the amygdala might contribute to the anxiolytic effect of IN-OXT (Bethlehem *et al*, 2013). Our systematic review revealed that IN-OXT consistently augmented the amygdala in both task-based and resting-state fMRI paradigms with region-of-interest approaches. Specifically, it appears that IN-OXT influences activation and functional connectivity of the amygdala in the regulation of negative affect. This pattern of brain activity might modulate stress and anxiety responses, and thus, facilitate approach behaviours. Further, our review found that IN-OXT increases functional decoupling of midbrain and basal ganglia with the amygdala, which might also help to mediate fear and anxiety responses.

Second, evidence that IN-OXT increases salience and reward from social stimuli are supported by increases in brain activity following IN-OXT within a "salience network"; comprising the amygdala, ACC and insula (Menon *et al*, 2010). Whilst also increasing salience to social information, these regions contribute to social decision making processes and down-regulating negative affect (Menon, 2011); which might also contribute to documented increases in approach behaviours in humans and animals following IN-OXT (Heinrichs *et al*, 2009). Our systematic findings also suggest that IN-OXT increases reward-based dopaminergic systems within the midbrain and basal ganglia that have a role in detecting socially relevant cues and providing a subsequent reward. This is particularly

relevant to human social interactions, as the increased salience and reward placed on social interactions, consequently leads to social bonding and attachment. In addition, the social salience hypothesis of IN-OXT is supported by behavioural evidence that IN-OXT promotes social cognition and facial emotion recognition in humans (Shamay-Tsoory and Abu-Akel, 2016). Our systematic finding of a consistent increase in activity within the temporal and occipital lobes supports this hypothesis, as increased activity within the temporal and occipital lobes might indicate increased early attentional processes directed to social information and encoding social relevant stimuli from faces. Third, our systematic review also found that IN-OXT changes brain activity in the default mode network, comprising the precuneus, PCC, mPFC, and IFG. Increased default-mode function has been associated with metallization, empathy, and self-referential processing, and thus has an indispensable role in social understanding of others (Li *et al*, 2014).

Alongside these studies examining the role of OXT in social behaviour in healthy adults, research is investigating the efficacy of IN-OXT in the treatment of several psychiatric disorders with prominent socio-behavioural dysfunction, such as GSAD (Labuschagne *et al*, 2010, 2012), ASD (Andari *et al*, 2016; Aoki *et al*, 2015; Gordon *et al*, 2013; Scheele *et al*, 2014a), and schizophrenia (Bartholomeusz *et al*, 2015; Macdonald and Feifel, 2012). Of note, IN-OXT appears to alter brain function in the three large-scale networks of psychopathological dysfunction proposed by Menon (2011). Specifically, Menon (2011) proposed that dysfunction in the central executive network (CEN; comprised of the PFC and posterior parietal cortex), the salience network (SN; comprised of the dorsal ACC and limbic structures) and the DMN (comprised of the PCC and medial PFC), each have a prominent role in several disorders including schizophrenia, depression, dementia and autism. Given that our systematic review demonstrated that IN-OXT alters brain function within regions comprising these networks, we speculate that the promising prosocial effects of IN-OXT

within psychopathology might originate from the alteration of IN-OXT on these large-scale brain networks. Together, these studies lend support for the role of OXT in "normalising" or restoring neurobiological dysfunction in these groups; however, if future treatments are to be established, a more defined role of IN-OXT on brain function needs to be established.

The findings of our meta-analysis revealed no significant clusters of activation or deactivation when including all foci from all included studies. These data provide little overlap with the findings of previous meta-analyses who found that the insula (Wigton *et al*, 2015) and amygdala (Wang *et al*, 2017) were the most reliably activated region after the administration of IN-OXT, independent of task design and gender. This suggests that when the results of region-of-interest investigations are excluded, these regions do not show consistent activation, and despite *a priori* hypothesis regarding the function of these regions in the behavioural effects of IN-OXT, this raises concern that region-of-interest approaches may be biasing the results of neuroimaging investigations in IN-OXT. However, when we performed a sub-analysis on studies that used tasks of basic emotional processes, we identified a cluster of activation within the left STG, suggesting partial support for the results of Wang *et al* (2017) who also found overall left STG activation using the same significance thresholding methods. Our meta-analytic finding of left STG activation by IN-OXT is unsurprising, as most emotion processing tasks in the OXT neuroimaging literature involve emotion identification from faces. Haxby *et al* (2000) emphasised that the STG encodes facial motion (e.g., eyebrows frowning or mouth smiling). Thus, increased activation of the STG by IN-OXT might contribute to the improved ability to recognise emotions from faces following IN-OXT administration (e.g., Guastella *et al*, 2010). Together, this suggests that independent of region-of-interest analysis approaches; the left STG is the most reliably activated brain region by IN-OXT.

The results of the systematic review underscore that the effect of IN-OXT on neural activity is different in women compared to men. This finding might be the result of gonadal steroid hormones influence on OXT. For example, men and women have varying levels of testosterone and estrogen, which modulate OXT receptor expression this has been shown to lead to differing distributions of receptors in the brain (Insel, 2010). Others have hypothesised that IN-OXT has an inverted "U-shaped" dose response relationship in men and women (Rilling *et al*, 2014). In this instance, women have higher CSF OXT levels than males, thus elevating brain OXT levels in women will result in levels reaching maximum threshold, producing a decrease in brain activity; whereas, men have lower CSF OXT levels at baseline, so administration of IN-OXT will increase, but not reach maximum levels, thereby increasing brain activity (Rilling *et al*, 2014). Nonetheless, the underlying factors for this gender disparity across both task-based and resting-state fMRI investigations remains unknown. Unfortunately, there is a tendency within OXT research to focus predominantly on males given complex sex-specific brain responses to IN-OXT (Wigton *et al*, 2015). Having a better understanding of the effects of IN-OXT in both males and females is particularly important due to the interest in IN-OXT as a potential therapeutic intervention for disorders such as ASD that have complex modulatory effects of sex (Domes *et al*, 2013; Meyer-Lindenberg *et al*, 2011).

There are other factors to consider when interpreting the divergent results across the studies presented within this review. Evidence from behavioural studies suggests that there is a context- and person-dependent nature of OXT (see, Bakermans-Kranenburg and van, 2013; Bartz *et al*, 2011, for detailed reviews). For example, several fMRI studies have demonstrated that effects of IN-OXT are shown to be modulated by early life stress (Fan *et al*, 2015; Grimm *et al*, 2014) and attachment style (Bartz *et al*, 2010; Riem *et al*, 2016). Further, those who have greater behavioural and brain deficits seem to benefit the most from IN-OXT

administration. For example, fathers who had less empathy for their child at baseline showed the greatest brain responses to IN-OXT which corresponded to increased attention directed to viewing pictures of their children (Li *et al*, 2017), and people who find it difficult to take pleasure in social situations seems to show greater IN-OXT responses to social cues in brain regions associated with reward (e.g., the VTA; Groppe *et al*, 2013). Together, suggesting that individuals with greater pathological dysfunction might benefit the most by IN-OXT.

5. Limitations

As with previous meta-analyses, ours was not without limitations. For example, while our meta-analytic technique was weighted by sample size, it did not account for several other moderating variables such as within versus between-subject designs, participants' age, effect size and the cluster sizes of the peak activation. In particular, previous research has demonstrated differing responses in between- versus within-subject designs (Chen *et al*, 2017), and our meta-analysis included data from 21 within-subject and 17 between-subject designs. While this is a balanced representation of each design type, we cannot contest that collapsing data across designs is entirely valid. Moreover, previous studies have indicated that the effect of oxytocin on brain activity might be dose-dependent (Quintana *et al*, 2016; Spengler *et al*, 2017). Due to methodological constraints of ALE, we were unable to add these variables as moderators in our analyses. Thus, we recommend that these moderating variables should be taken into consideration when performing future meta-analyses on IN-OXT. Furthermore, our meta-analysis was limited to analysing peak reported foci from whole-brain fMRI analyses that included different thresholding methods (see **Supplementary Table S1**). Future inclusion of main effects, even if they are not the primary outcome of the study, will greatly increase the statistical power of possible meta-analytic approaches in OXT neuroimaging literature. Making data openly available to share un-

thresholded whole-brain statistical maps will allow for more sophisticated and accurate meta-analyses. Likewise, pre-registering trials, declaring primary outcomes and statistical analysis techniques, and making data openly available will address these problems (see; Walum *et al*, 2016, for a detailed discussion). Following such recommendations, we have made available reported brain activation coordinates, analysis scripts and statistical maps (unthresholded) on open science platforms for use in future meta-analyses that can consider the effect of the above moderators in their analyses.

6. Conclusion

To conclude, we undertook a systematic review of all placebo-controlled studies examining IN-OXT and functional brain activity through fMRI in human participants. The results of our systematic review suggest that IN-OXT exerts its socio-behavioural and cognitive effects through modulating amygdala, midbrain, prefrontal, and temporal brain activity. Our meta-analytic finding suggests that the enhancement of emotion recognition by IN-OXT is driven by increased activity within the superior temporal gyrus. Future studies probing IN-OXT will benefit from task designs that probe gender and task-related effects specifically, as well move beyond region-of-interest analyses and investigate activity and connections between all voxels of the brain. Extending beyond current data, this undoubtedly will have a significant effect on the generalizability of findings, and have important relevance to using IN-OXT as a treatment in psychiatric and behavioural pathology.

7. Funding and disclosure

SG was supported by an Australian Government Research Training Program Scholarship. SG, IL and MH are investigators on a project examining the impact of oxytocin administration on social cognition and neural activity in ageing (ACURF Program Grant 20130000557). SG and SR are investigators on a project examining oxytocin on functional

brain activity in body dysmorphic disorder (BDBSF Project Grant 4000000098). MH gratefully acknowledges grant support from the German Research Foundation (DFG). The other authors declare that they have no known conflicts of interest.

8. Acknowledgements

SG, SR and IL were involved in the conceptualization of the work. SG and CK screened the abstracts. SG extracted and checked the data, prepared the data for meta-analysis, and drafted the manuscript with assistance from IL, MH and SR. All authors revised the manuscript and approved the final version.

References

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.

Aoki Y, Watanabe T, Abe O, Kuwabara H, Yahata N, Takano Y, *et al* (2015). Oxytocin's neurochemical effects in the medial prefrontal cortex underlie recovery of task-specific brain activity in autism: a randomized controlled trial. *Molecular psychiatry* **20**(4): 447-453.

Aoki Y, Yahata N, Watanabe T, Takano Y, Kawakubo Y, Kuwabara H, *et al* (2014). Oxytocin improves behavioural and neural deficits in inferring others' social emotions in autism. *Brain* **137**(Pt 11): 3073-3086.

Bakermans-Kranenburg MJ, van IJMH (2013). Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. *Transl Psychiatry* **3**(5): e258.

Bartholomeusz CF, Ganella EP, Labuschagne I, Bousman C, Pantelis C (2015). Effects of oxytocin and genetic variants on brain and behaviour: implications for treatment in schizophrenia. *Schizophrenia Research* **168**(3): 614-627.

Bartz J, Simeon D, Hamilton H, Kim S, Crystal S, Braun A, *et al* (2010). Oxytocin can hinder trust and cooperation in borderline personality disorder. *Social cognitive and affective neuroscience* **6**(5): 556-563.

Bartz J, Zaki J, Bolger N, Ochsner KN (2011). Social effects of oxytocin in humans: context and person matter. *Trends in cognitive sciences* **15**(7): 301-309.

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**(4): 639-650.

Bertsch K, Gamer M, Schmidt B, Schmidinger I, Walther S, Kastel T, *et al* (2013). Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. *The American journal of psychiatry* **170**(10): 1169-1177.

Bethlehem RA, van Honk J, Auyeung B, Baron-Cohen S (2013). Oxytocin, brain physiology, and functional connectivity: a review of intranasal oxytocin fMRI studies. *Psychoneuroendocrinology* **38**(7): 962-974.

Bos PA, Montoya ER, Hermans EJ, Keysers C, van Honk J (2015). Oxytocin reduces neural activity in the pain circuitry when seeing pain in others. *Neuroimage* **113**: 217-224.

Chen X, Gautam P, Haroon E, Rilling JK (2017). Within vs. between-subject effects of intranasal oxytocin on the neural response to cooperative and non-cooperative social interactions. *Psychoneuroendocrinology* **78**: 22-30.

Chen X, Hackett PD, DeMarco AC, Feng C, Stair S, Haroon E, *et al* (2016). Effects of oxytocin and vasopressin on the neural response to unreciprocated cooperation within brain regions involved in stress and anxiety in men and women. *Brain Imaging Behav* **10**(2): 581-593.

Cohen D, Perry A, Gilam G, Mayseless N, Gonen T, Hendler T, *et al* (2017). The role of oxytocin in modulating interpersonal space: A pharmacological fMRI study. *Psychoneuroendocrinology* **76**: 77-83.

De Dreu CK, Scholte HS, van Winden FA, Ridderinkhof KR (2015). Oxytocin tempers calculated greed but not impulsive defense in predator-prey contests. *Soc Cogn Affect Neurosci* **10**(5): 721-728.

Dodhia S, Hosanagar A, Fitzgerald DA, Labuschagne I, Wood AG, Nathan PJ, *et al* (2014). Modulation of resting-state amygdala-frontal functional connectivity by oxytocin in generalized social anxiety disorder. *Neuropsychopharmacology* **39**(9): 2061-2069.

Domes G, Heinrichs M, Glascher J, Buchel C, Braus DF, Herpertz SC (2007). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biol Psychiatry* **62**(10): 1187-1190.

Domes G, Heinrichs M, Kumbier E, Grossmann A, Hauenstein K, Herpertz SC (2013). Effects of intranasal oxytocin on the neural basis of face processing in autism spectrum disorder. *Biol Psychiatry* **74**(3): 164-171.

Domes G, Kumbier E, Heinrichs M, Herpertz SC (2014). Oxytocin promotes facial emotion recognition and amygdala reactivity in adults with asperger syndrome. *Neuropsychopharmacology* **39**(3): 698-706.

Domes G, Lischke A, Berger C, Grossmann A, Hauenstein K, Heinrichs M, *et al* (2010). Effects of intranasal oxytocin on emotional face processing in women. *Psychoneuroendocrinology* **35**(1): 83-93.

Duval S, Tweedie R (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**(2): 455-463.

Ebner NC, Chen H, Porges E, Lin T, Fischer H, Feifel D, *et al* (2016). Oxytocin's effect on resting-state functional connectivity varies by age and sex. *Psychoneuroendocrinology* **69**: 50-59.

Eckstein M, Becker B, Scheele D, Scholz C, Preckel K, Schlaepfer TE, *et al* (2015). Oxytocin facilitates the extinction of conditioned fear in humans. *Biol Psychiatry* **78**(3): 194-202.

Eckstein M, Markett S, Kendrick KM, Ditzen B, Liu F, Hurlemann R, *et al* (2017). Oxytocin differentially alters resting state functional connectivity between amygdala subregions and emotional control networks: Inverse correlation with depressive traits. *Neuroimage* **149**: 458-467.

Eckstein M, Scheele D, Patin A, Preckel K, Becker B, Walter A, *et al* (2016). Oxytocin Facilitates Pavlovian Fear Learning in Males. *Neuropsychopharmacology* **41**(4): 932-939.

Eckstein M, Scheele D, Weber K, Stoffel-Wagner B, Maier W, Hurlemann R (2014). Oxytocin facilitates the sensation of social stress. *Hum Brain Mapp* **35**(9): 4741-4750.

Egger M, Smith GD, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *Bmj* **315**(7109): 629-634.

Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT (2012). Activation likelihood estimation meta-analysis revisited. *Neuroimage* **59**(3): 2349-2361.

Eickhoff SB, Bzdok D, Laird AR, Roski C, Caspers S, Zilles K, *et al* (2011). Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. *Neuroimage* **57**(3): 938-949.

Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp* **30**(9): 2907-2926.

Fan Y, Herrera-Melendez AL, Pestke K, Feeser M, Aust S, Otte C, *et al* (2014). Early life stress modulates amygdala-prefrontal functional connectivity: implications for oxytocin effects. *Hum Brain Mapp* **35**(10): 5328-5339.

Fan Y, Pestke K, Feeser M, Aust S, Pruessner JC, Boker H, *et al* (2015). Amygdala-Hippocampal Connectivity Changes During Acute Psychosocial Stress: Joint Effect of Early Life Stress and Oxytocin. *Neuropsychopharmacology* **40**(12): 2736-2744.

Feng C, Hackett PD, DeMarco AC, Chen X, Stair S, Haroon E, *et al* (2015). Oxytocin and vasopressin effects on the neural response to social cooperation are modulated by sex in humans. *Brain Imaging Behav* **9**(4): 754-764.

Frijling JL, van Zuiden M, Koch SB, Nawijn L, Veltman DJ, Olff M (2016). Effects of intranasal oxytocin on amygdala reactivity to emotional faces in recently trauma-exposed individuals. *Soc Cogn Affect Neurosci* **11**(2): 327-336.

Gamer M, Zurowski B, Buchel C (2010). Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. *Proc Natl Acad Sci U S A* **107**(20): 9400-9405.

Gao S, Becker B, Luo L, Geng Y, Zhao W, Yin Y, *et al* (2016). Oxytocin, the peptide that bonds the sexes also divides them. *Proceedings of the National Academy of Sciences of the United States of America* **113**(27): 7650-7654.

Gordon I, Jack A, Pretzsch CM, Vander Wyk B, Leckman JF, Feldman R, *et al* (2016). Intranasal Oxytocin Enhances Connectivity in the Neural Circuitry Supporting Social Motivation and Social Perception in Children with Autism. *Scientific reports* **6**: 35054.

Gordon I, Vander Wyk BC, Bennett RH, Cordeaux C, Lucas MV, Eilbott JA, *et al* (2013). Oxytocin enhances brain function in children with autism. *Proc Natl Acad Sci U S A* **110**(52): 20953-20958.

Gorka SM, Fitzgerald DA, Labuschagne I, Hosanagar A, Wood AG, Nathan PJ, *et al* (2015). Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. *Neuropsychopharmacology* **40**(2): 278-286.

Gozzi M, Dashow EM, Thurm A, Swedo SE, Zink CF (2017). Effects of Oxytocin and Vasopressin on Preferential Brain Responses to Negative Social Feedback. *Neuropsychopharmacology* **42**(7): 1409-1419.

Gregory R, Cheng H, Rupp HA, Sengelaub DR, Heiman JR (2015). Oxytocin increases VTA activation to infant and sexual stimuli in nulliparous and postpartum women. *Horm Behav* **69**: 82-88.

Grimm S, Pestke K, Feeser M, Aust S, Weigand A, Wang J, *et al* (2014). Early life stress modulates oxytocin effects on limbic system during acute psychosocial stress. *Soc Cogn Affect Neurosci* **9**(11): 1828-1835.

Groppe SE, Gossen A, Rademacher L, Hahn A, Westphal L, Grunder G, *et al* (2013). Oxytocin influences processing of socially relevant cues in the ventral tegmental area of the human brain. *Biol Psychiatry* **74**(3): 172-179.

Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ, *et al* (2010). Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol Psychiatry* **67**(7): 692-694.

Haxby JV, Hoffman EA, Gobbini MI (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences* **4**(6): 223-233.

Hecht EE, Robins DL, Gautam P, King TZ (2017). Intranasal oxytocin reduces social perception in women: Neural activation and individual variation. *Neuroimage* **147**: 314-329.

Heinrichs M, von Dawans B, Domes G (2009). Oxytocin, vasopressin, and human social behavior. *Frontiers in neuroendocrinology* **30**(4): 548-557.

Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al* (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* **343**: d5928.

Hong S, Hikosaka O (2008). The globus pallidus sends reward-related signals to the lateral habenula. *Neuron* **60**(4): 720-729.

Hu J, Qi S, Becker B, Luo L, Gao S, Gong Q, *et al* (2015). Oxytocin selectively facilitates learning with social feedback and increases activity and functional connectivity in emotional memory and reward processing regions. *Hum Brain Mapp* **36**(6): 2132-2146.

Hu Y, Scheele D, Becker B, Voos G, David B, Hurlemann R, *et al* (2016). The Effect of Oxytocin on Third-Party Altruistic Decisions in Unfair Situations: An fMRI Study. *Scientific reports* **6**: 20236.

Insel TR (2010). The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior. *Neuron* **65**(6): 768-779.

Kanat M, Heinrichs M, Mader I, van Elst LT, Domes G (2015a). Oxytocin Modulates Amygdala Reactivity to Masked Fearful Eyes. *Neuropsychopharmacology* **40**(11): 2632-2638.

Kanat M, Heinrichs M, Schwarzwald R, Domes G (2015b). Oxytocin attenuates neural reactivity to masked threat cues from the eyes. *Neuropsychopharmacology* **40**(2): 287-295.

Kemp AH, Guastella AJ (2011). The role of oxytocin in human affect: a novel hypothesis. *Current Directions in Psychological Science* **20**(4): 222-231.

Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, *et al* (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **25**(49): 11489-11493.

Koch SB, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M (2016a). Intranasal Oxytocin Administration Dampens Amygdala Reactivity towards Emotional Faces in Male and Female PTSD Patients. *Neuropsychopharmacology* **41**(6): 1495-1504.

Koch SB, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M (2016b). Intranasal Oxytocin Normalizes Amygdala Functional Connectivity in Posttraumatic Stress Disorder. *Neuropsychopharmacology* **41**(8): 2041-2051.

Kovacs B, Keri S (2015). Off-label intranasal oxytocin use in adults is associated with increased amygdala-cingulate resting-state connectivity. *European psychiatry : the journal of the Association of European Psychiatrists* **30**(4): 542-547.

Kumar J, Völlm B, Palaniyappan L (2015). Oxytocin Affects the Connectivity of the Precuneus and the Amygdala: A Randomized, Double-Blinded, Placebo-Controlled Neuroimaging Trial. *International Journal of Neuropsychopharmacology* **18**(5).

Labuschagne I, Phan KL, Wood A, Angstadt M, Chua P, Heinrichs M, *et al* (2010). Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. *Neuropsychopharmacology* **35**(12): 2403-2413.

Labuschagne I, Phan KL, Wood A, Angstadt M, Chua P, Heinrichs M, *et al* (2012). Medial frontal hyperactivity to sad faces in generalized social anxiety disorder and modulation by oxytocin. *Int J Neuropsychopharmacol*: 1-14.

Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, *et al* (2005). ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. *Hum Brain Mapp* **25**(1): 155-164.

Laird AR, Robinson JL, McMillan KM, Tordesillas-Gutiérrez D, Moran ST, Gonzales SM, *et al* (2010). Comparison of the disparity between Talairach and MNI coordinates in functional neuroimaging data: validation of the Lancaster transform. *Neuroimage* **51**(2): 677-683.

Lancaster JL, Tordesillas‐Gutiérrez D, Martinez M, Salinas F, Evans A, Zilles K, *et al* (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM‐152 brain template. *Human brain mapping* **28**(11): 1194-1205.

Lane A, Luminet O, Nave G, Mikolajczak M (2016). Is there a publication bias in behavioural intranasal oxytocin research on humans? Opening the file drawer of one laboratory. *Journal of neuroendocrinology* **28**(4).

LeDoux JE (2000). Emotion circuits in the brain. *Annu Rev Neurosci* **23**: 155-184.

Leng G, Ludwig M (2016). Intranasal oxytocin: myths and delusions. *Biological psychiatry* **79**(3): 243-250.

Li T, Chen X, Mascaro J, Haroon E, Rilling JK (2017). Intranasal oxytocin, but not vasopressin, augments neural responses to toddlers in human fathers. *Horm Behav*.

Li W, Mai X, Liu C (2014). The default mode network and social understanding of others: what do brain connectivity studies tell us. *Frontiers in human neuroscience* **8**.

Lischke A, Gamer M, Berger C, Grossmann A, Hauenstein K, Heinrichs M, *et al* (2012). Oxytocin increases amygdala reactivity to threatening scenes in females. *Psychoneuroendocrinology* **37**(9): 1431-1438.

Ma Y, Shamay-Tsoory S, Han S, Zink CF (2016). Oxytocin and social adaptation: insights from neuroimaging studies of healthy and clinical populations. *Trends in cognitive sciences* **20**(2): 133-145.

Macdonald K, Feifel D (2012). Oxytocin in schizophrenia: a review of evidence for its therapeutic effects. *Acta Neuropsychiatr* **24**(3): 130-146.

Macdonald K, Macdonald TM (2010). The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. *Harvard review of psychiatry* **18**(1): 1-21.

Menon V (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in cognitive sciences* **15**(10): 483-506.

Menon V, Uddin LQ (2010). Saliency, switching, attention and control: a network model of insula function. *Brain structure & function* **214**(5-6): 655-667.

Meyer-Lindenberg A, Domes G, Kirsch P (2011). Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nature Reviews*.

Mickey BJ, Heffernan J, Heisel C, Pecina M, Hsu DT, Zubieta JK, *et al* (2016). Oxytocin modulates hemodynamic responses to monetary incentives in humans. *Psychopharmacology (Berl)* **233**(23-24): 3905-3919.

Nawijn L, van Zuiden M, Koch SB, Frijling JL, Veltman DJ, Olff M (2016). Intranasal oxytocin enhances neural processing of monetary reward and loss in post-traumatic stress disorder and traumatized controls. *Psychoneuroendocrinology* **66**: 228-237.

Nawijn L, van Zuiden M, Koch SB, Frijling JL, Veltman DJ, Olff M (2017). Intranasal oxytocin increases neural responses to social reward in post-traumatic stress disorder. *Soc Cogn Affect Neurosci* **12**(2): 212-223.

Petrovic P, Kalisch R, Singer T, Dolan RJ (2008). Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **28**(26): 6607-6615.

Pincus D, Kose S, Arana A, Johnson K, Morgan PS, Borckardt J, *et al* (2010). Inverse effects of oxytocin on attributing mental activity to others in depressed and healthy subjects: a double-blind placebo controlled FMRI study. *Frontiers in psychiatry* **1**: 134.

Poldrack RA, Baker CI, Durnez J, Gorgolewski KJ, Matthews PM, Munafò MR, *et al* (2017). Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nature Reviews Neuroscience* **18**(2): 115.

Preckel K, Scheele D, Eckstein M, Maier W, Hurlemann R (2015). The influence of oxytocin on volitional and emotional ambivalence. *Soc Cogn Affect Neurosci* **10**(7): 987-993.

Quintana DS, Alvares GA, Hickie IB, Guastella AJ (2015). Do delivery routes of intranasally administered oxytocin account for observed effects on social cognition and behavior? A two-level model. *Neuroscience & Biobehavioral Reviews* **49**: 182-192.

Quintana DS, Westlye LT, Alnaes D, Rustan OG, Kaufmann T, Smerud KT, *et al* (2016). Low dose intranasal oxytocin delivered with Breath Powered device dampens amygdala response to emotional stimuli: A peripheral effect-controlled within-subjects randomized dose-response fMRI trial. *Psychoneuroendocrinology* **69**: 180-188.

Radke S, Volman I, Kokal I, Roelofs K, de Bruijn ERA, Toni I (2017). Oxytocin reduces amygdala responses during threat approach. *Psychoneuroendocrinology* **79**: 160-166.

Radua J, Mataix-Cols D (2012). Meta-analytic methods for neuroimaging data explained. *Biology of Mood & Anxiety Disorders* **2**: 6-6.

Riem MM, Bakermans-Kranenburg MJ, Pieper S, Tops M, Boksem MA, Vermeiren RR, *et al* (2011). Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: a randomized controlled trial. *Biol Psychiatry* **70**(3): 291-297.

Riem MM, Bakermans-Kranenburg MJ, van IMH (2016). Intranasal administration of oxytocin modulates behavioral and amygdala responses to infant crying in females with insecure attachment representations. *Attach Hum Dev* **18**(3): 213-234.

Riem MM, Bakermans-Kranenburg MJ, Voorthuis A, van IMH (2014a). Oxytocin effects on mind-reading are moderated by experiences of maternal love withdrawal: an fMRI study. *Progress in neuro-psychopharmacology & biological psychiatry* **51**: 105-112.

Riem MM, van IMH, Tops M, Boksem MA, Rombouts SA, Bakermans-Kranenburg MJ (2012). No laughing matter: intranasal oxytocin administration changes functional brain connectivity during exposure to infant laughter. *Neuropsychopharmacology* **37**(5): 1257-1266.

Riem MM, van IMH, Tops M, Boksem MA, Rombouts SA, Bakermans-Kranenburg MJ (2013). Oxytocin effects on complex brain networks are moderated by experiences of maternal love withdrawal. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* **23**(10): 1288-1295.

Riem MM, Voorthuis A, Bakermans-Kranenburg MJ, van Ijzendoorn MH (2014b). Pity or peanuts? Oxytocin induces different neural responses to the same infant crying labeled as sick or bored. *Developmental science* **17**(2): 248-256.

Rilling JK, Demarco AC, Hackett PD, Chen X, Gautam P, Stair S, *et al* (2014). Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction. *Psychoneuroendocrinology* **39**: 237-248.

Rilling JK, DeMarco AC, Hackett PD, Thompson R, Ditzen B, Patel R, *et al* (2012). Effects of intranasal oxytocin and vasopressin on cooperative behavior and associated brain activity in men. *Psychoneuroendocrinology* **37**(4): 447-461.

Rilling JK, Sanfey AG, Aronson JA, Nystrom LE, Cohen JD (2004). The neural correlates of theory of mind within interpersonal interactions. *Neuroimage* **22**(4): 1694-1703.

Rocchetti M, Radua J, Paloyelis Y, Xenaki LA, Frascarelli M, Caverzasi E, *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**(10): 733-751.

Rosenthal R (1991). Meta-analytic procedures for social research. **6**.

Rupp HA, James TW, Ketterson ED, Sengelaub DR, Ditzen B, Heiman JR (2013). Lower sexual interest in postpartum women: relationship to amygdala activation and intranasal oxytocin. *Horm Behav* **63**(1): 114-121.

Rupp HA, James TW, Ketterson ED, Sengelaub DR, Ditzen B, Heiman JR (2014). Amygdala response to negative images in postpartum vs nulliparous women and intranasal oxytocin. *Soc Cogn Affect Neurosci* **9**(1): 48-54.

Scheele D, Kendnck KM, Khouri C, Kretzer E, Schläpfer TE, Stoffel-Wagner B, *et al* (2014a). An oxytocin-lnduced facilitation of neural and emotional responses to social touch correlates inversely with autism traits. *Neuropsychopharmacology* **39**(9): 2078-2085.

Scheele D, Plota J, Stoffel-Wagner B, Maier W, Hurlemann R (2016). Hormonal contraceptives suppress oxytocin-induced brain reward responses to the partner's face. *Soc Cogn Affect Neurosci* **11**(5): 767-774.

Scheele D, Striepens N, Kendrick KM, Schwering C, Noelle J, Wille A, *et al* (2014b). Opposing effects of oxytocin on moral judgment in males and females. *Hum Brain Mapp* **35**(12): 6067-6076.

Scheele D, Wille A, Kendrick KM, Stoffel-Wagner B, Becker B, Gunturkun O, *et al* (2013). Oxytocin enhances brain reward system responses in men viewing the face of their female partner. *Proc Natl Acad Sci U S A* **110**(50): 20308-20313.

Schmidt FL (1992). What do data really mean? Research findings, meta-analysis, and cumulative knowledge in psychology. *American Psychologist* **47**(10): 1173.

Shahrestani S, Kemp AH, Guastella AJ (2013). The Impact of a Single Administration of Intranasal Oxytocin on the Recognition of Basic Emotions in Humans: A Meta-Analysis. *Neuropsychopharmacology* **38**(10): 1929-1936.

Shamay-Tsoory SG, Abu-Akel A (2016). The Social Salience Hypothesis of Oxytocin. *Biological Psychiatry* **79**(3): 194-202.

Shin NY, Park HY, Jung WH, Park JW, Yun JY, Jang JH, *et al* (2015). Effects of Oxytocin on Neural Response to Facial Expressions in Patients with Schizophrenia. *Neuropsychopharmacology* **40**(8): 1919-1927.

Singer T, Snozzi R, Bird G, Petrovic P, Silani G, Heinrichs M, *et al* (2008). Effects of oxytocin and prosocial behavior on brain responses to direct and vicariously experienced pain. *Emotion (Washington, DC)* **8**(6): 781-791.

Spengler FB, Schultz J, Scheele D, Essel M, Maier W, Heinrichs M, *et al* (2017). Kinetics and dose-dependency of intranasal oxytocin effects on amygdala reactivity. *Biological Psychiatry*.

Sripada CS, Phan KL, Labuschagne I, Welsh R, Nathan PJ, Wood AG (2013). Oxytocin enhances resting-state connectivity between amygdala and medial frontal cortex. *The International Journal of Neuropsychopharmacology* **16**(02): 255-260.

Striepens N, Scheele D, Kendrick KM, Becker B, Schafer L, Schwalba K, *et al* (2012). Oxytocin facilitates protective responses to aversive social stimuli in males. *Proc Natl Acad Sci U S A* **109**(44): 18144-18149.

Striepens N, Schroter F, Stoffel-Wagner B, Maier W, Hurlemann R, Scheele D (2016). Oxytocin enhances cognitive control of food craving in women. *Hum Brain Mapp* **37**(12): 4276-4285.

Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA (2002). Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage* **16**(3 Pt 1): 765-780.

Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P (2012). Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. *Hum Brain Mapp* **33**(1): 1-13.

Voorthuis A, Riem MM, Van IMH, Bakermans-Kranenburg MJ (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 Res* **1580**: 151-159.

Wagner S, Sebastian A, Lieb K, Tüscher O, Tadić A (2014). A coordinate-based ALE functional MRI meta-analysis of brain activation during verbal fluency tasks in healthy control subjects. *BMC neuroscience* **15**(1): 19.

Walum H, Waldman ID, Young LJ (2016). Statistical and methodological considerations for the interpretation of intranasal oxytocin studies. *Biological psychiatry* **79**(3): 251-257.

Wang D, Yan X, Li M, Ma Y (2017). Neural substrates underlying the effects of oxytocin: A quantitative meta-analysis of pharmaco-imaging studies. *Social Cognitive and Affective Neuroscience*.

Watanabe T, Abe O, Kuwabara H, Yahata N, Takano Y, Iwashiro N, *et al* (2014). Mitigation of sociocommunicational deficits of autism through oxytocin-induced recovery of medial prefrontal activity: a randomized trial. *JAMA psychiatry* **71**(2): 166-175.

Wigton R, Radua J, Allen P, Averbeck B, Meyer-Lindenberg A, McGuire P, *et al* (2015). Neurophysiological effects of acute oxytocin administration: systematic review and meta-analysis of placebo-controlled imaging studies. *Journal of psychiatry & neuroscience : JPN* **40**(1): E1-22.

Wittfoth-Schardt D, Gründing J, Wittfoth M (2012). Oxytocin modulates neural reactivity to children's faces as a function of social salience.

Zhao W, Yao S, Li Q, Geng Y, Ma X, Luo L, *et al* (2016). Oxytocin blurs the self-other distinction during trait judgments and reduces medial prefrontal cortex responses. *Hum Brain Mapp* **37**(7): 2512-2527.

Zunhammer M, Geis S, Busch V, Eichhammer P, Greenlee MW (2016). Pain modulation by intranasal oxytocin and emotional picture viewing - a randomized double-blind fMRI study. *Scientific reports* **6**: 31606.

Zunhammer M, Geis S, Busch V, Greenlee MW, Eichhammer P (2015). Effects of intranasal oxytocin on thermal pain in healthy men: a randomized functional magnetic resonance imaging study. *Psychosom Med* **77**(2): 156-166.

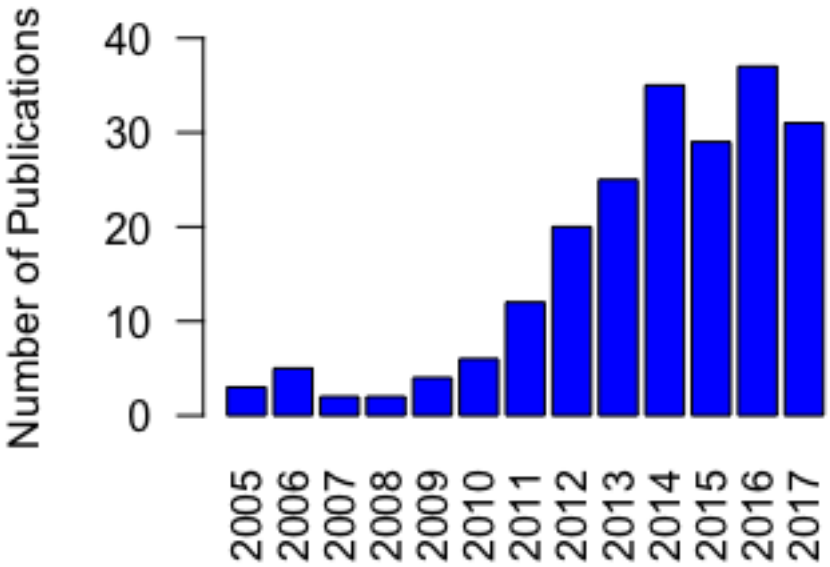

Figure 1. Number of PubMed articles with the keywords 'oxytocin' and 'fMRI'. Data collected using 'RISmed' R package. Information obtained 2 January 2018.

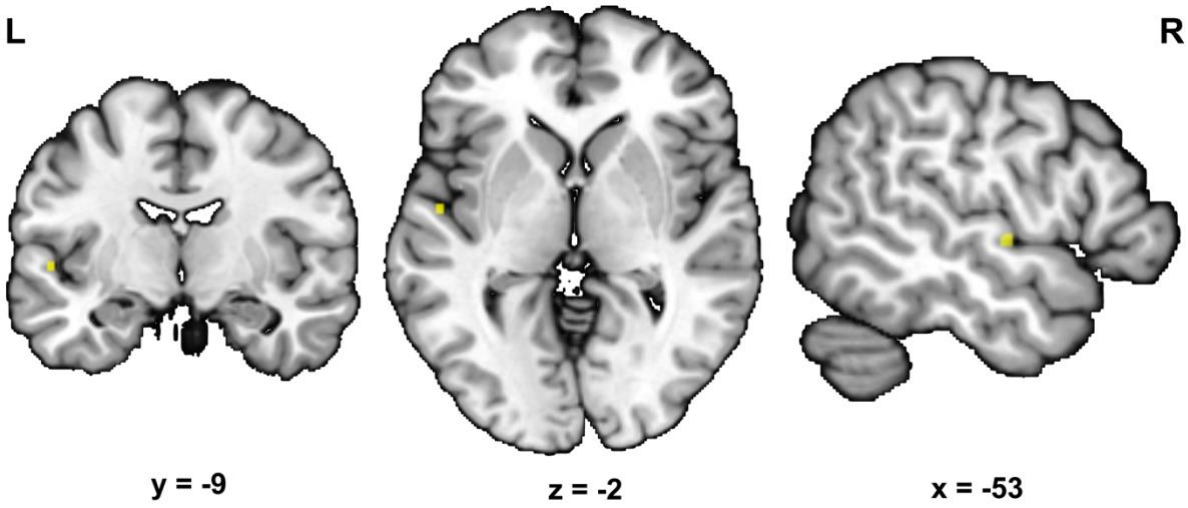

Figure 2. Meta-analytic findings: Left superior temporal gyrus cluster showing likelihood of increased brain activation after intranasal oxytocin (> placebo) in the overall analysis of studies of emotional processes. L = left, R = right.

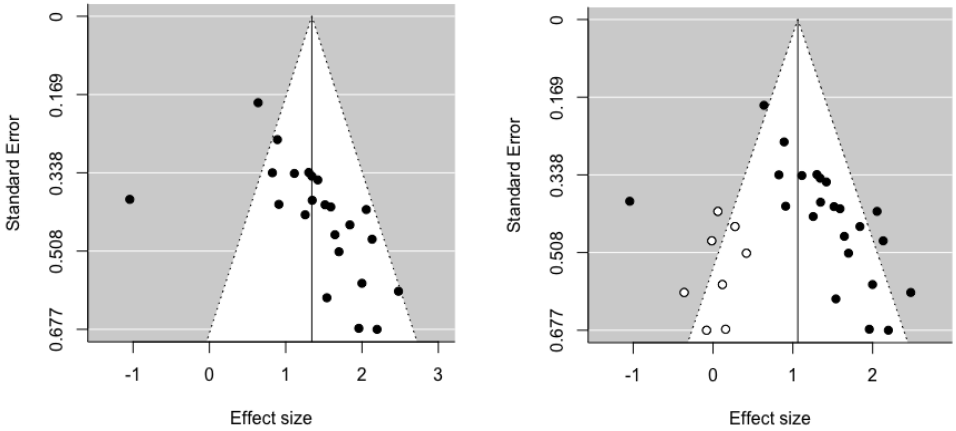

Figure 3. Funnel plot of study effect size plotted against standard error (left figure). Funnel plot after trim and fill method was applied (right figure). Filled circles indicate actual studies and unfilled circled indicate imputed studies.

Table 1. Characteristics of task-related fMRI studies in oxytocin in healthy populations that are included in the systematic review.

Reference	Sample size			Age (*M*±*SD*)	M/F	Paradigm/ stimulus	fMRI design				fMRI analysis	Main findings (OXT > PBO)
	N	OXT	PBO				Dose (IU)	Onset (mins)	Design	Task		
Studies using non-clinical populations												
Baumgartner *et al* (2008)	49	26	26	21.7±2.5	M	Trust game	24	50	BS	BD	WB ROI: amygdala, midbrain, caudate	↓ amygdala, midbrain, dorsal striatum (for sustained trust)
Bos *et al* (2015)	24	24	24	23.1	M	Empathy for pain with in- and out- groups	24	55	WS	ER	WB and ROI: insula, ACC MCC, the primary and secondary somatosensory cortices	↓ left insula (empathy for pain condition) opposite effect in non-pain condition
Chen *et al* (2016)	M: 153 F: 151	100	105	M: 20.7±2.2 F: 20.5±1.3	M/F	Prisoner's Dilemma game (trust game) played with same-sex partners (50% playing with human vs. 50% computer)	24	42	BS	ER	WB ROI: amygdala, anterior insula	Males: ↓ amygdala, anterior insula (for unreciprocated cooperation in human partners) Female: ↓ amygdala, anterior insula (for unreciprocated cooperation in non-human partners)
Chen *et al* (2017)	OXT-PBO 29 PBO-OXT	-	-	M: 20.9±1.6 F: 20.5±1.4	M/F	Prisoner's Dilemma game (trust game)	24	40	WS	ER	WB & ROI: Male: NA, CN; Female: hippocampus, vlPFC, PCC,	ROI: Females: ↓ vlPFC, rACC, PCC, post central gyrus, posterior

	30 PBO-PBO 31										rostral ACC, postcentral cortex, SMA, thalamus, insula, STG, MTG	insula (for reciprocated cooperation) Males: ↓ amygdala (for unreciprocated cooperation) WB: Females: ↓ VTA
Cohen *et al* (2017)	19	19	19	26.05±3.51	M	Comfortable interpersonal distance task	24	45	WS	BD	WB & ROI: right ACC, right posterior ACC, left mPFC, right parahippocampal gyrus	↓ dmPFC and a preference for greater distance for strangers ↑ dmPFC for friends
De Dreu *et al* (2015)	25	25	25	25.31	M	Predator-prey game	24	35	WS	BD	ROI: amygdala, SFG	↓ bilateral amygdala and SFG to predators but not prey
Domes *et al* (2007)	13	-	-	25.7±2.9	M	Emotional faces: happy, fear & angry	24	61	WS	BD	WB ROI: amygdala	↓ right amygdala (all faces)
Domes *et al* (2010)	16	-	-	24.2±2.5	F	Emotional faces: fearful, angry, happy, neutral	24	52.5	WS	BD	WB ROI: amygdala	↑ left amygdala, FG, STG (for fearful faces) ↑ IFG, vlPFC (for angry faces) ↑ IFG, FG (for happy faces)
Eckstein *et al* (2014)	60	30	30	24.67±3.89	M	Psychosocial stress task	24	30	BS	BD	WB ROI: ACC, amygdala	↑ ACC ROI ↑ precuneus, PCC

Eckstein *et al* (2015)	62	31	31	24.61±4.28	M	Fear conditioning	24	30	BS	ER	WB and ROI: mPFC, mid-PFC, amygdala	↓ right amygdala ↑ right MFG ROI (during early extinction) ↑ FC right amygdala-left precuneus (during late extinction) ↑ FC right PFC-right precuneus-left PCC (during early extinction)
Eckstein *et al* (2016)	97	31	31	24.45±4.02	M	Fear conditioning	24	30	BS	ER	WB ROI: amygdala, ACC, MCC	↑ ACC (for fear related stim) and MCC (social fear-related stim)
Fan *et al* (2015)	32	32	32	28.3±4.7	M	Psychosocial stress task	24	45	WS	BD	PPI: amygdala ROIs	OXT moderated amygdala-hippocampal FC in ps (asc. with emotional abuse in early life)
Feng *et al* (2015)	139	45	45	20.7	M	Prisoners dilemma	24	ns.	BS	ER	WB	No OXT main effects reported
Feng *et al* (2015)	186	89	97	20.7	M/F	Prisoners dilemma	24	ns.	BS	ER	WB	↑ left and right caudate/putamen, right frontal pole, left superior medial frontal cortex (↑ male, ↓ female)
Gamer *et al* (2010)	46	23	23	25.0±3.7	M	Emotional faces (explicit): fearful, happy, neutral	24	45	BS	BD	ROI: subregional amygdala and superior colliculi	↓ lateral & dorsal amygdala (for angry faces)

												↑ amygdala (for happy faces)
Gao *et al* (2016)	74	39	35		M/F	The First-Impression Task	24	40	BS	ER	WB gPPI ROI: amygdala, insula, ACC IFG	↑ left amygdala (females) ↓ left amygdala (males)
Gozzi *et al* (2017)	21	-	-	26.57	M	Negative social feedback task	24	45	WS	ER	WB	↓ right anterior insula, right FG, bilateral TPJ, posterior STS, supplementary motor area (negative>positive feedback)
Gregory *et al* (2015)	59	27	28	27.05±4.09	F	1-back matching task: Pictures of different categories (smiling infant, crying infant, sexual, positive, negative, neutral, and scrambled)	24	30	BS	ER	ROI: NAc and VTA	↑ VTA (all women: for images of crying infants and sexual images)
Grimm *et al* (2014)	32	-	-	28.4±4.5	M	Psychosocial stress task	24	25	WS	ER	WB ROI: pgACC, hippo, amygdala, insula, caudate, putamen, MCG, STG, Thalamus	↑ Hippocampus, ACC, amygdala, PHG, insula (asc. with early life stress - opposite in HC)

Groppe *et al* (2013)	28	14	14	26.64±5.55	F	Social incentive delay task (reward vs. punishment)	26	30	BS	BD	WB ROI: ventral tegmentum	↑ ventral tegmentum (in response to social reward or punishment)
Hecht *et al* (2017)	28	14	14	23.08±0.73	F	Animations of geometric shapes depicting either random movement or social interactions	24	40	WS	BD	WB	↓ DVS and occipital (associated with social attention)
Hu *et al* (2015)	54	-	-	19.80±1.49	M	Learning task with social feedback (emotional faces)	24	45	BS	BD	WB and ROI: amygdala, hippocampus	↑ OG, STG, Hippocampus (learning) ↑ right hippocampus, parrahippocampal gyrus, amygdala and left putamen and thalamus (social feedback) ↑ FC right amygdala- left insula-left caudate (social feedback)
Hu *et al* (2016)	41	-	-	25.10±3.88	M	Money transfer game (altruism): either punish a violator or help a victim	24	51	WS	ER	WB ROI: TPJ, MPFC, NAcc	↑ left TPJ (in response to others being helped i.e. ToM/mentalization process)
Kanat *et al* (2015b)	43	22	21	23.64±2.81	M	Eye-gaze fixed to mouth or eyes for emotional faces (angry, happy, neutral)	24	45	BS	BD	WB, PPI connectivity (left amygdala and left FG) and ROI: amygdala	↓ amygdala ROI (for angry eyes and happy mouths)

						vs. masking stimulus (scrambled face)						↓ VC and brain stem ↓ FC left amygdala-left FG (reversed under PBO)
Kanat *et al* (2015a)	43	22	21	24.11±3.01	M	Eye-gaze fixed to eyes for emotional faces (fearful or happy) vs. masking stimulus (scrambled face)	24	55	BS	BD	WB and ROI: amygdala	↓ right amygdala ROI (Eyes: fear>happy)
Kirsch *et al* (2005)	15	-	-	26.7±3.0	M	Fearful and threatening scenes and faces (implicit)	27	50	WS	BD	WB ROI: amygdala	↓ amygdala (for threatening stimuli) ↓ amygdala-midbrain FC
Li *et al* (2017)	31	15	16	32.8±4.7	M	Fathers view pictures of own & unknown children & unknown adults as they listen to infant cry stimuli	24	50	WS	BD	WB ROI: caudate, ACC, visual cortex	↑ caudate, midbrain, dACC, visual cortex
Lischke *et al* (2012)	14	-	-	23.79±2.32	F	Threatening and non-threatening scenes	24	45	WS	BD	WB ROI: amygdala	↑ right amygdala ROI (for negative relative to neutral scenes) ↑ left anterior temporal lobe

Mickey *et al* (2016)	20	-	-	22±2	M	Money incentive/reward task	24	49	WS	BD	WB ROI: NAc, VTA, midbrain	↑ midbrain ROI ↓ mPFC (anticipation of loss)
Petrovic *et al* (2008)	27	15	12	24.85	M	Fear conditioning, emotive faces	32	45	BS	ER	WB ROI: amygdala, FFA, insula, ACC, OFC	OXT admin abolished fear conditioning associated with MTG and ACC ↓ amygdala and FG (for aversively conditioned faces)
Preckel *et al* (2015) - Experiment 1	48	24	24	24.6±4.56	M	Moral judgement task (stories)	24	45	BS	BD	WB	↓ ACC, PCC, precuneus, MCC (moral>non-moral)
Preckel *et al* (2015) - Experiment 2	22	22	22	26.73±3.60	M	Short sentences of moral infidelity	24	45	WS	BD	WB ROI: OFC, ACC	↓ ACC (neutral>sexual)
Quintana *et al* (2016)	16	-	-	23.81±3.33	M	Participants viewed angry, happy and neutral faces whilst asked questions relating to emotional valence and trust of the face displayed	8 IU BPD 24 IU BPD 1 IU IV	40	WS	BD	ROI: amygdala	8 IU BPD: ↓ right amygdala (in response to happy, neutral and angry faces)

Radke *et al* (2017)	52	24	28	22.4±3.0	M	Approach-avoidance task	24	45	BS	BD	WB ROI: amygdala PPI: aPFC-amygdala	↓ amygdala during threat approach
Riem *et al* (2011)	42	21	21	29.07±7.56	F	Response to infant crying	24	36	BS	BD	WB ROI: amygdala	↓ right amygdala (infant crying > control) ↑ INS, IFG (infant crying > control)
Riem *et al* (2012)	44	22	22	28.71±6.93	F	Response to infant laughter	24	40	BS	BD	WB PPI ROI: amygdala, ventral striatum/ nucleus accumbens, IFG, insula	↓ bilateral amygdala (infant laughter > control) ↑ FC of amygdala-OFC-ACC-Hipp-Prec-SMG-MTG (laughter > control)
Riem *et al* (2016)	42	21	21	29.00±7.4	F	Responses to infant crying	16	35	BS	ER	ROI: amygdala	↓ right amygdala ROI (cry>control)
Riem *et al* (2014a)	50	25	25	N.A.	F	RMET	16	60	BS	ER	WB ROI: insula, IFG, STG	↑ left STG, left insula
Riem *et al* (2014b)	50	26	24	19.66±1.47	F	Responses to infant crying	16	35	BS	BD	WB ROI: left insula, left IFG, right amygdala	↑ left insula and IFG ROI (bored cry<sick cry) ↑ right amygdala (high pitched cry) ↓ right amygdala (lower pitched cry)
Rilling *et al* (2012)	91	27	36	20.2	M	Iterated Prisoner's Dilemma task (trust game)	24	42	BS	ER	WB ROI: amygdala, CN	↑ left amygdala, CN (for

												reciprocated cooperation)
Rilling *et al* (2014)	58	29	29	N.A.	F	Iterated Prisoner's Dilemma task (trust game)	24	42	BS	ER	WB ROI: amygdala, CN	↓ left amygdala, hippocampus, insula (opposite to previous study in men; Rilling et al., 2012)
Rupp *et al* (2013)	53	14/14	13/12	26.95±5.19	F	1-back matching task: sexual & infant vs control pictures	24	30	BS	BD	WB ROI: amygdala	No main effect of OXT
Rupp *et al* (2014)	53	14/14	13/12	26.95±5.19	F	1-back matching task: Negative vs control pictures	24	30	BS	BD	WB ROI: amygdala	↓ right amygdala (nulliparous women)
Scheele *et al* (2013)	20	-	-	25.50±2.99	M	Passive viewing of photographs of the partner, a matched, unfamiliar woman, and houses	24	30	WS	ER	WB ROI: VTA, NAcc, caudate, lentiform nucleus	↑ left NAcc (partner > unfamiliar face)
Scheele *et al* (2014a)	40	40	40	25.75±3.82	M	Photograph of female/male experimenter coupled with closeness to experimenter condition (home/baseline, close, touch)	24	30	WS	ER	WB ROI: pregenual ACC, OFC, ventral striatum, midbrain	↑ insula, precuneus, pACC, OFC (associated with enhanced experience of female touch)

Scheele *et al* (2016)	40	40	40	24.38±3.26	F	Pair bonding: Passive viewing of partner, matched unknown men, familiar woman, matched unknown woman	24	30	WS	BD	WB ROI: NAcc and VTA	↑ left and right precuneus ↑ bilateral NAcc and VTA ROI (women not on HC)
Scheele *et al* (2014b)	23	23	23	25.57±3.29	M	Self-referential emotional face matching	24	30	WS	BD	WB ROI: insula	↑ ACC, MCC, precuneus (disgust>neutral) ↑ insula ROI (disgust>neutral)
Singer *et al* (2008)	20	-	-	24.6±3.2	M	Pain exposure (self or observed)	32	45	WS	ER	WB ROI: amygdala	↓ amygdala (for experienced pain in selfish individuals)
Striepens *et al* (2012)	70	35	35	24.5±3.0	M	Viewing aversive vs neutral pictures and verbal description (noun describing picture)	24	45	BS	ER	WB PPI ROI: amygdala	↓ bilateral amygdala (negative stimuli) ↑ FC between left amygdala-insula-IFG
Striepens *et al* (2016)	31	31	31	25.35±4.37	F	The regulation of food craving using cognitive control	24	45	WS	ER	WB ROI: MFG	↑ precuneus, cingulate, precentral gyrus, STG (in cognitive control condition) ↑ MFG ROI

Voorthuis *et al* (2014)	50	25	25	19.66±1.45	F	Face emotion recognition on infant faces	16	55	BS	ER	WB ROI: anterior insula, IFG, STG, OFG, MTG	↑ IFG, STG, MTG (when watching infants emotion)
Wittfoth-Schardt *et al* (2012)	19	-	-	39.3±6.2	M	Viewing pictures from own, familiar and unfamiliar children vs. fixation cross	24	30	WS	ER	WB PPI ROI: amygdala	↓ left GP (own children) ↓ FC left GP (own children & unfamiliar children) ↑ right caudate (own children>other children)
Zhao *et al* (2016)	38	18	20	22.83±0.34	M	Self-referential judgement task: adjective traits placed on mother, self, classmate, or stranger	40	45	BS	BD	WB ROI: dmPFC, vmPFC PPI: dmPFC, vmPFC	↓ dmPFC, vmPFC (during self and other trait judgements) ↓ FC ACC-vmPFC, PCC (associated with self-esteem)
Zunhammer *et al* (2016)	36	36	36	24.9	M	Thermo-visual training task: hot-non-painful and hot-painful heat applied whilst viewing emotive faces (positive, neutral, negative) vs. scrambled images (baseline)	32	40	WS	BD	WB	No main effect of OXT on brain function

Zunhammer *et al* (2015)	30	-	-	24.9	M	Thermal threshold test: Hot-non-painful and hot-painful heat applied	76	40	WS	BD	WB ROI: amygdala	↓ bilateral amygdala (all temperatures)

Studies using clinical populations

Reference	***N***	**Clinical Sample**	**Healthy Sample**	**Age (*M*±*SD*)**	**Gender**	**Paradigm/ stimulus**	**Dose (IU)**	**Onset (mins)**	**Design**	**Task**	**fMRI analysis**	**Main findings (OXT > PBO)**
Andari *et al* (2016)	20	20 ASD	-	26.37±8.45	M/F	Social ball-tossing game and face-matching task (neutral vs. shapes)	24	30	WS	BD	WB ROI: VC, FG, OFC, caudate, amygdala, hippocampus	Face-matching task: ↑ OG, FG (for faces) Ball game: ↓ amygdala, hippocampus
Aoki *et al* (2014)	20	20 ASD	-	30.8±6.0	M	Sally-Anne task – infer others beliefs	24	40	WS	ER	WB ROI: insula, STG, dmPFC	↑ right insula ROI ↑ cuneus, right ATG, right IFG, ring insula
Aoki *et al* (2015)	48	31 ASD	17 HC	30.8±6.0	M	Movies shown with males and females showing different facial expressions and prosody (positive vs. negative)	24	40	WS	ER	ROI (vmPFC/ACC, dmPFC) correlated with magnetic resonance spectroscopy of N-acetlyaspartate (NAA) in vmPFC	↑ vmPFC/ACC related to N-acetlaspartate levels
Bertsch *et al* (2013)	81	40 BPD	41 HC	24.4±4.7	F	Emotional face recognition task	26	45	BS	BD	ROI: amygdala	↓ amygdala angry faces /

												↑ amygdala happy faces (BPD>HC: "normalize")
Domes *et al* (2013)	18	14 ASD	14 HC	24.0±6.9	M	Facial discrimination task (neutral vs. houses)	24	45	WS	ER	WB ROI: amygdala localizer seed	PBO>OXT: ↓ right amygdala, FG, inferior OG (ASD > HC) OXT>PBO: ↑ right amygdala (ASD > HC) "normalization"
Domes *et al* (2014)	18	14 ASD	14 HC	24.0±6.9, 18-31 years	M	Facial emotion recognition task six (anger, fear, disgust, happiness, sadness, and surprise) presented with verbal label (50% correct/incorrect)	24	45	WS	ER	WB and ROI: AAL amygdala	↑ left amygdala (ASD > HC)
Frijling *et al* (2016)	41	41 trauma exposed individuals	-	35.6±11.5	M/F	Emotional face matching task	40	45	BS	BD	WB ROI: amygdala	↑ right amygdala (fearful faces) ↑ left amygdala (neutral faces: female>male)
Gordon *et al* (2013)	21	21 ASD	-	13.2±2.7	M/F 18/3	RMET - Judgments of socially (eyes) and nonsocially (vehicles) meaningful pictures	24 (for 16-19 yr/old) 18 (12-15	30	WS	BD	WB	↑ the dorsal and ventral striatum, precuneus, PCC, left inferior parietal lobule, left posterior superior temporal sulcus, left

							yr/old) 12 (7-11 yr/old					parahippocampal gyrus, and right premotor cortex (eyes > vehicles)
Gordon *et al* (2016)	21	21 ASD	-	13.16±2.79	M/F	Biological motion and vocal affect perception task	24 (for 16-19 yr/old) 18 (12-15 yr/old) 12 (7-11 yr/old)	ns.	WS	BD	WB PPI	↑ NAcc-prefrontal (vmPFC/OFC) during biological motion perception ↑ FC NAcc-primary auditory cortex (happy>angry) ↑ FC NAcc-precuneus
Gorka *et al* (2015)	36	18 GSAD	18 HC	18-55	M	Emotional face matching task: fearful, angry, happy vs. shapes (implicit)	24	45	WS	BD	WB ROI: middle cingulate and insula PPI: amygdala	GSAD>HC: ↑ FC left amygdala-bilateral insula ("normalising" effect) GSAD>HC: ↑ FC left amygdala-mid/dACC
Labuschagne *et al* (2010)	36	18 GSAD	18 HC	29.4±9.0	M	Emotional faces (implicit): fearful, angry, happy vs. shapes	24	45	WS	BD	WB ROI: amygdala	↓ amygdala (for fearful stimuli; GSAD > HC)
Labuschagne *et al* (2012)	36	18 GSAD	18 HC	29.4±9.0	M	Emotional face matching task: fearful, angry, happy vs. shapes (implicit)	24	45	WS	BD	WB	↓ mPFC, ACC (for sad faces; GSAD > HC), 'reversing' pattern observed at PBO

Nawijn *et al* (2016)	72	35 PTSD	37 trauma exposed HC	39.92±9.91	M/F	Money incentive delay task: manipulates anticipation of monetary reward and loss	40	50	WS	BD	WB ROI: bilateral striatum, insula and ACC	↑ striatum, dACC, insula (reward>loss)
Nawijn *et al* (2017)	72	35 PTSD	37 trauma exposed HC	39.92±9.91	M/F	Social incentive delay task: participants are rewarded or punished with presentation of a happy face or an angry face	40	Ns.	WS	ER	WB ROI: amygdala and anterior insula	↑ anterior insula (in response to social reward feedback) – reversed from PBO – "normalizing" ↑ right putamen (for social reward)
Pincus *et al* (2010)	17	8 depressed	9 HC	35.5±10.62	M/F	RMET	40	10	WS	ER	WB	↑ STG, MFG, ACC, insula (depression > HC) ↑ STG, ACC, amygdala (HC > depression)
Koch *et al* (2016a)	80	40 PTSD	40 HC	39.96±9.93	M/F	Emotional face-matching task	40	45	WS	BD	ROI: left and right amygdala	group*drug effect in left amygdala ROI (↓ PTSD, ↑HC; "normalisation")
Shin *et al* (2015)	36	16 SZ	16 HC	32.0±7.8	M	Emotional faces (fearful, happy, neutral) vs. fixation cross (control condition)	40	45	WS	BD	ROI: amygdala	SZ ↓, HC ↑ amygdala (for emotional faces)
Watanabe *et al* (2014)	33	33 ASD	-	28.5±5.9	M	Film of actors speaking emotional words with emotional	24	40	WS	ER	WB ROI: ACC, dmPFC, IFG,	↑ dmPFC and ACC

				face expression and affective prosody – decision made about congruent/non-congruent emotions	AI, Amygdala, STP PPI: ACC, dmPFC	↑ FC dmPFC-ACC

Note. OXT = oxytocin, PBO = placebo, AVP = arginine vasopressin, HC = healthy control group, N = sample size and within group characteristics, M/F = gender distribution of sample (males/females), HC = healthy control group, ASD = autism spectrum disorder, GSAD = generalized social anxiety disorder, PTSD = post-traumatic stress disorder, SZ = schizophrenia, BPD = borderline personality disorder, IN = intranasal, BPD = breath powered device, IV = intravenous injection, SNP = single-nucleotide polymorphism, BS = between subjects, WS = within subjects, FC = functional connectivity, WB = whole-brain analysis, ROI = region-of-interest analysis, PPI = psychophysiological interaction analysis (brain connectivity), AAL = Automated Anatomical Labelling system used for amygdala seed GSAD = generalized social anxiety disorder, ASD = autism spectrum disorder, SZ = schizophrenia, BD = bipolar disorder, RMET = reading the mind in the eyes task, BST = brain stem, FG = fusiform gyrus, STG = superior temporal gyrus, IFG = inferior frontal gyrus, DS = dorsal striatum, GSAD = generalized social anxiety disorder, mPFC = medial prefrontal cortex, ACC = anterior cingulate cortex, MCC = mid cingulate cortex, smFG = superior middle frontal gyrus, CN = caudate nucleus, OFC = orbitofrontal cortex, Hipp = hippocampus, Pre-c = precuneus, SMG = supramarginal gyrus, MTG = middle temporal gyrus, GP = globus pallidus, FPC = frontopolar cortex, OG = occipital gyrus, TPJ = temperoparietal junction, STS = superior parietal sulcus. N.A. = data not available.

Table 2. Characteristics of resting-state fMRI studies in oxytocin in healthy and clinical populations that are included in the systematic review**.**

Reference	Sample Size			Age (*M*±*SD*)	M/F	Methods			Analysis	Main findings (OXT > PBO)
	N	OXT	PBO			Dose	Design	rsFC Paradigm		
Studies using non-clinical populations										
Ebner *et al* (2016)	79 (40 young vs. 39 older)	79	79	Young sample: 18-31 years, Older sample: 63-81 years	M/F	24 IU	BS	Duration: ~8min, 70-90min post spray Instructions: Relax and to look at a white fixation cross on a black screen	Region-to-region connectivity between mPFC and amygdala ROIs	Young female: ↑ rsFC amygdala–mPFC (not observed in young men or older adults, however, a trend was observed in older men)
Eckstein *et al* (2017)	79	27	52	24.27±4.16	M	24 IU	BS	Duration: ~6 min, 30 min post spray Intructions: Lie still with eyes closed but without falling asleep	Subregional amygdala (CeM, BLA, SF) to whole-brain	↑ rsFC left total amygdala-dmPFC-right IPL ↑ rsFC left BLA-dlPFC-right IPL ↑ rsFC right BLA-cerebellum ↑ rsFC CeM-cerebellum ↑ rsFC right SF-PFC ↓ rsFC CeM-lingual gyri-left PG-right OG
Fan *et al* (2014)	18	18	18	27.8±4.4	M	24 IU	WS	Duration: ~8 min, 45 min post spray Instructions: Rest silently, watch a white fixation cross against a black background, remain relaxed and awake	ROI: amygdala AAL seed to whole-brain	OXT administration did not modulate the association between increment in severity of emotional abuse and rsFC of right amygdala with pregenual/subgenual ACC and dorsal mPFC

Kovacs *et al* (2015)	82	41 OXT 'misusers'	41 HC (matched for age, education, gender)	OXT: 25.0±10.3, HC: 26.1±8.1	M/F	Frequency and dose recorded of oxytocin users (cumulative dose)	BS	Duration: ~5 min Instructions: Fixate on point on screen, let mind wander without falling asleep	ROI: amygdala AAL seed to whole-brain	OXT>HC: ↑ rsFC right amygdala-dorsal ACC (associated with higher estimated cumulative oxytocin dose)
Kumar *et al* (2015)	15	15	15	23.20±4.17	M	24 IU	WS	Duration: ~5 min, 45 min post spray Instructions: Keep eyes open, focus on fixation cross on screen	ROI: amygdala AAL to whole-brain	↓ bilateral amygdalae-precuneus rsFC ↓ degree centrality of the precuneus ↓ localized connectivity of right amygdala
Riem *et al* (2013)	44	44	44	28.98±7.48	F	16 IU	BS	Duration: ~6min, 35 mins post spray Instructions: Eyes closed	ROI: Amygdala, insula and PCC seeds to whole-brain	OXT>PBO: ↑ rsFC PCC-brainstem PBO>OXT: ↓ rsFC cerebellum-postcentral gyrus (only in participants who were classified as having low maternal love withdrawal)
Sripada *et al* (2013)	15	15	15	30.70±10.60	M	24 IU	WS	Duration: ~3 min, 45 min post spray Instructions: Relax and keep eyes closed, without falling asleep	Analysis: ROI, amygdala AAL seed to whole-brain	OXT>PBO: ↑ rsFC bilateral amygdala-ACC/mPFC
Studies using clinical populations										
Dodhia *et al* (2014)	36	18 GSAD	18 HC	GSAD: 29.89±10.2 HC: 19.39±9.0	M	24 IU	WS	Duration: ~3 min, 45 min post spray Instructions: Eyes closed, relax and let mind wander, without falling asleep	ROI, amygdala AAL seed to whole-brain	GSAD>HC: ↑ rsFC of bilateral amygdala-rostral ACC/mPFC

Koch *et al* (2016b)	76	36 PTSD	HC 40	39.96	F	40 IU	WS	Duration: ~5 min, 72.51 (4.03) min post spray Instructions: Relax and let mind wander, with open eyes	Subregional amygdala (BLA & CeM) connectivity to insula vmPFC, dmPFC, MFG, OFC and ACC masks	Male PTSD>HC: ↑ rsFC CeM-left vmPFC Female PTSD>HC: ↓ rsFC BLA-dACC (opposite to PBO, "normalizing" effect)

Note. Data represented as mean(SD). OXT = oxytocin, HC = healthy control group, N = sample size and within group characteristics, M/F = gender distribution of sample (males/females), PTSD = post-traumatic stress disorder, GSAD = generalized social anxiety disorder, AVP = arginine vasopressin, ROI = region-of-interest, AAL = Automated Anatomical Labelling system used for amygdala seed, rsFC = resting-state functional connectivity, BLA = basolateral amygdala, CeM = centromedial amygdala, SF = superficial amygdala, vmPFC = ventromedial prefrontal cortex, dmPFC = dorsalmedial prefrontal cortex, MFG = middle frontal gyrus, OFC = orbitofrontal cortex, IFG = inferior frontal gyrus, ACC = anterior cingulate cortex, STG = superior temporal gyrus, IPL = inferior parietal lobule.