



RESEARCH ARTICLE

Oxytocin Affects the Connectivity of the Precuneus and the Amygdala: A Randomized, Double-Blinded, Placebo-Controlled Neuroimaging Trial

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Abstract

Background: Although oxytocin is one of the most widely studied neuropeptides in recent times, the mechanistic process by which it modulates social-affective behavior in the brain is not yet clearly understood. Thus, to understand the neurophysiological basis of oxytocin effects, we used resting-state functional MRI to examine the effects of intranasal oxytocin on brain connectivity in healthy males.

Methods: Using a randomized, double-blinded, placebo-controlled, crossover design, 15 healthy male volunteers received 24 IU intranasal oxytocin or placebo prior to resting-state functional MRI acquisition at 3T.

Results: We found that oxytocin significantly reduced the degree centrality of the right precuneus ($P < .05$). Oxytocin also reduced connectivity between the bilateral amygdalae and between the right precuneus and the right and left amygdala ($P < .05$). Although there were no significant changes in regional homogeneity at the whole brain level, posthoc results showed a reduction involving the right precuneus ($P < .05$).

Conclusions: These results show that oxytocin affects one of the key centers in the brain for social cognition and introspective processing, the precuneus, and enhances our understanding of how oxytocin can modulate brain networks at rest. An improved understanding of the neurophysiological effects of oxytocin can be important in terms of evaluating the mechanisms that are likely to underlie the clinical responses observed upon long-term oxytocin administration.

Keywords: oxytocin, resting-state, amygdala, precuneus, fMRI

Introduction

Oxytocin (OXT) is one of the most widely studied neuropeptides in recent times, mainly because of its potential ability to modulate different aspects of human social cognition such as emotional recognition (Shahrestani et al., 2013), evaluation of trustworthiness (Lambert et al., 2014), and fear-processing (Fischer-Shofty et al., 2010; Acheson et al., 2013). During the past few years, researchers have explored the use of OXT as a

potential treatment for disorders characterized by social deficits. For instance, both preclinical and clinical studies have explored the effect of OXT on autistic spectrum disorders (Chang et al., 2013; Gordon et al., 2013; Teng et al., 2013; Anagnostou et al., 2014), anxiety disorders (Slattery and Neumann, 2010), schizophrenia (Pederson et al., 2011; Averbach et al., 2012; Feifel et al., 2012; Davis et al., 2013), and depression (MacDonald et al., 2013;

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Mah et al., 2014). Although these studies indicate that OXT could be a promising therapeutic tool, the mechanism behind its modulation of social-affective behavior in the brain is not yet fully understood.

The neurophysiology of OXT can be evaluated in vivo using neuroimaging studies (Meyer-Lindenberg et al., 2011; Zink and Meyer-Lindenberg, 2012; Bethlehem et al., 2013). A number of functional MRI (fMRI) studies suggest that the amygdala, an important social cognitive center in the brain, is a main target for OXT-mediated effects. Even a single-dose administration of OXT has a notable influence on the stimulus-induced responses and connectivity of the amygdala (Kirsch et al., 2005; Domes et al., 2007; Domes et al., 2010; Gamer et al., 2010). However, fMRI studies have predominantly focused on the effect of OXT on blood-oxygen-level dependent (BOLD) responses induced by stimulus presentation. These task-based studies differ in terms of their experimental design and paradigms and have also found variable results. Task-free assessment of brain connectivity using resting-state fMRI can be very useful in such situations in that it would be possible to investigate the fundamental neurocircuitry of the brain without the confounding influence of task load, between-group differences in task performance, and learning effects. To our knowledge, only one study so far has examined the functional connectivity of the resting brain under OXT in healthy males. Sripada et al. (2013), using functional connectivity analysis, showed that the connectivity of the amygdala and the rostral medial prefrontal cortex might be altered by OXT (Sripada et al., 2013). Along with regions such as the precuneus, posterior-cingulate cortex, and lateral parietal cortex, medial prefrontal cortex forms an extended network called the default mode network (DMN). The DMN, originally considered to be a task-negative network that contributes to maintaining a resting brain state, is now recognized to be relevant for processing social and affective stimuli in addition to its contribution to self-processing (Amft et al., 2014).

Understanding the influence of OXT on the localized and distributed intrinsic brain connectivity patterns at rest will be crucial to understand how the procognitive and social effects of OXT are mediated. To understand the mechanisms of action of OXT, we looked at resting-state connectivity of the brain under intranasal OXT administration in male healthy volunteers. We studied the effect of OXT on the net connectivity of every grey-matter voxel using voxel-wise degree centrality (DC) (Buckner et al., 2009) and on the localized connectivity within the neighbourhood of every grey-matter voxel using regional homogeneity (ReHo) (Zang et al., 2004). In addition, we also tested the hypothesis that OXT alters the resting state functional connectivity (Fc) of the amygdala with the rest of the brain, especially the regions constituting the DMN.

Methods

Participants

Fifteen healthy male participants were recruited for this study (mean age [SD]: 23.20 [4.17], range: 18–33; handedness: right = 14, left = 1) via posters put up in and around the University of Nottingham and email messages circulated through departments. We applied the following exclusion criteria using a volunteer screening telephone questionnaire: (1) lifetime history of substance dependence or harmful use in the past 6 months, (2) history of head trauma or medical conditions likely to have appreciable neurological or psychiatric effects, (3) personal or family history of psychiatric disorders, (4) contraindications for MRI safety assessed using a standard safety questionnaire, and

(5) contraindications for OXT administration (eg, history of heart disorders, migraines, nasal problems, or known allergy to intranasal applications). Participants were recruited after a clinician checked and approved questionnaire answers. Informed consent was obtained from all participants, and an inconvenience allowance was paid in accordance with the ethical approval from the University of Nottingham Medical School Ethics Committee.

Study Design

This study employed a randomized, double-blinded, placebo-controlled, crossover design, where all 15 participants were scanned on 2 different days under 2 conditions, OXT and placebo, with a minimum 1-week washout period between the 2 scan days. Conditions were randomized and counter-balanced using a freely available online randomizer tool, and spray bottles were labelled as A or B and put into envelopes that were labelled with participant identification and session number (1 or 2) in order to keep both researchers and participants blind. Participants were asked to not consume any alcohol for 48 hours prior to appointments and also to refrain from smoking and having any food or caffeinated products for 2 hours before appointments.

Participants were given either an intranasal spray of OXT (24 IU or 40.32 mg; Syntocinon-spray; Novartis, Switzerland) or placebo (a saline nasal spray). Participants were shown how to use the spray and then asked to self-administer it. They were asked to spray 3 puffs in each nostril, each puff consisting of 4 IU, followed by deep breaths, consistent with previous studies (Kirsch et al., 2005; Domes et al., 2007; Sripada et al., 2013). A 45-minute wait period followed the spray administration to allow for the maximum physiological (Kirsch et al., 2005; Domes et al., 2007) and pharmacokinetic effects of OXT (Born et al., 2002). After this period, participants were taken to the MRI scanner where they completed an anatomical and a resting-state fMRI scan. Participants also completed the Positive and Negative Affect Schedule on arrival and before going into the scanner, that is, 45 minutes after intranasal spray administration, to measure the behavioral effects of OXT on mood.

Image Acquisition

All scans were conducted at Sir Peter Mansfield Magnetic Resonance Centre, University of Nottingham using a 3T Philips Achieva MR Scanner (Philips Medical Systems, Best, The Netherlands). The resting-state fMRI acquisition lasted for 5 minutes, wherein participants were asked to keep their eyes open and focus on a fixation cross on the screen. The echo-planar images (EPis) were acquired using a 32-channel head coil with SENSE factor 1 in the anterior-posterior direction, echo time (TE) of 35 ms, flip angle of 85°, and 240 × 240 × 112-mm field of view. A 3 × 3 mm in-plane resolution was used with a slice thickness of 3.5 mm and a repetition time (TR) of 2000 ms. At each dynamic time point, a volume dataset was acquired consisting of 32 contiguous axial slices in descending order. Then 150 time points were acquired during this resting-state paradigm. An anatomical T1 MPRAGE image was also acquired for each subject with a 1-mm isotropic resolution, 256 × 256 × 160 matrix, TE/TR of 2.2/4.5 ms, shot interval of 3000 ms, flip angle of 8°, and SENSE factor 1 for image registration.

Data Preprocessing

Resting-state data were preprocessed using Data Processing Assistant for Resting-State fMRI (Chao-Gan and Yu-Feng, 2010). The first 5 volumes of functional images were discarded to allow

for the stability of the longitudinal magnetization. Data were then slice-time corrected and spatially realigned to the first image of the remaining dataset. Movement parameters were assessed for each participant, and Friston 24 approach was used for correcting the effects of head motion. This model makes use of the 6 head motion parameters, 6 head motion parameters one time point before, and the corresponding 12 squared values (Friston et al., 1996). This has been shown to be superior to other model-based approaches of motion correction, particularly in reducing motion-BOLD relationships at the individual level (Yan et al., 2013). Nuisance covariates white matter and cerebrospinal fluid signal were regressed out before further processing.

Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL)-based normalization using each subject's structural image was carried out (voxel size $3 \times 3 \times 3$ mm), and the functional scans were smoothed using a Gaussian kernel of 8 mm full-width at half-maximum. After this, linear detrending and filtering using a band-pass filter (0.01–0.08 Hz) was done to eliminate low-frequency fluctuations and high-frequency noise. Finally, data were scrubbed to further correct for movement artefacts using frame-wise displacement (0.5 mm) (Power et al., 2012) with a nearest neighbor interpolation approach to further reduce spurious movement-induced correlations. These preprocessing steps were used to run the Fc and DC analyses. ReHo was initially computed from unsmoothed functional images in native space, as spatial smoothing before ReHo computation can result in a spurious increase in the local connectivity and ReHo intensity (Tian et al., 2012; Zuo et al., 2013). This was followed by detrending, band-pass filtering, spatial normalization, and smoothing with the same parameters as above.

In addition to the correction for frame-wise displacement, subjects with a high degree of head motion (>3 mm and 3 degree) were excluded. Two participants who formed the excluded group (EG) did not differ from the included group (IG) in terms of age (mean [SD] of EG = 23.50 [7.77] years, IG = 23.15 [3.91], $P = .91$) or intelligence quotient (mean [SD] of EG = 84.0 [12.0], IG = 96.46 [12.46], $P = .69$). There was no difference between the EG and IG in Positive and Negative Affect Schedule within-subject change scores for positive affect under OXT (mean [SD] of EG = 2.00 [0.00], IG = 0.69 [4.15], $P = .27$), positive affect under placebo (mean [SD] of EG = -0.50 [6.36], IG = -0.23 [2.35], $P = .96$), negative affect under OXT (mean [SD] of EG = 0.50 [2.12], IG = -0.30 [1.70], $P = .55$), or negative affect under placebo (mean [SD] of EG = 0.50 [0.70], IG = 0.07 [1.70], $P = .74$). The included subjects were well matched for the total proportion of frames, with displacement >0.5 mm in either arm of the study (proportion of frames [SD] displaced after OXT = 13.5% [14%]; PLA = 13.2% [16%]; within-subjects $F = 0.013$, $P = .91$)

and for the mean displacement across the 3 translation and 3 rotation axes, quantified in accordance with Power et al. (2012) (frame-wise displacement [SD] after OXT = 0.34 [0.21]; PLA = 0.47 [0.75]; within-subjects $F = 0.78$, $P = .39$).

Derived Measures of Connectivity

As our primary hypothesis was related to the influence of OXT on the Fc of the amygdala, right and left Automated Anatomical Labelling (AAL) masks were used separately to compute Fc (Tzourio-Mazoyer et al., 2002). Pearson's correlation coefficients were computed between the mean time-series of all voxels included within each region of interest and every voxel in the brain for each subject. The correlation coefficients were normalized using Fisher's r -to- z transformation.

To compute DC, for each voxel (i), a value representing the number of voxels in the rest of the brain showing a correlation above a specified threshold (absolute value of $r > 0.25$) with (i). This threshold was chosen in line with previous work (Buckner et al., 2009; Palaniyappan and Liddle, 2014; Zhou et al., 2014) and represents an effect size that eliminates counting of voxels with low temporal correlation that may result from noise in resting fMRI (Buckner et al., 2009). The DC and ReHo maps were z -transformed using respective mean values obtained from all voxels contained within subject-specific grey matter masks. For DC, Fc, and ReHo measures, voxelwise paired t tests with a family-wise error (FWE) cluster-wise correction ($P < .05$) and an inclusion threshold of $P < .05$ were undertaken to study group-level differences between OXT and placebo trials.

Results

OXT significantly reduced the DC in a single cluster centered on the right precuneus (Montreal Neurological Institute (MNI) coordinates of the peak of the significant cluster = 18, -60, 27; FWE-corrected $P = 0.015$, 1113 voxels). There were no other significant changes in DC with OXT, though at a more lenient statistical threshold (peak intensity $T = 2.3$, extent $k = 50$ voxels), other regions showing altered DC were noted (Supplementary Material).

OXT significantly reduced the Fc between bilateral amygdala seeds and a single cluster that included the right precuneus (left amygdala seed: MNI coordinates of the peak of the significant cluster = 18, -60, 27; FWE corrected $P = .026$, 1806 voxels; right amygdala seed: MNI coordinates of the peak of the significant cluster = 15, -45, 3; FWE corrected $P < .001$, 1267 voxels). These clusters are shown in Figure 1. OXT did not produce any other significant changes in Fc of the amygdala compared with

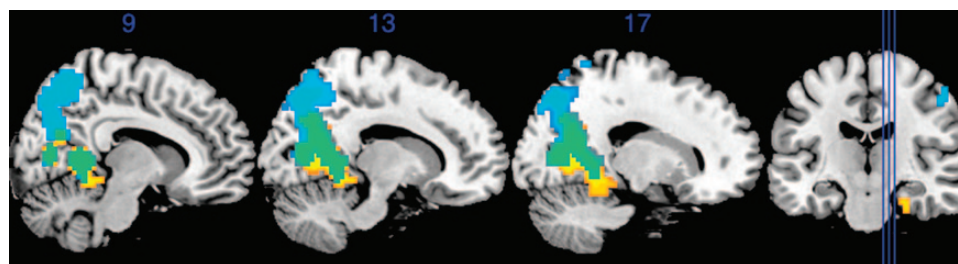


Figure 1. Effect of oxytocin (OXT) on the functional connectivity of the left and right amygdala. Clusters showing a decrease in functional connectivity with the left amygdala (blue) and right amygdala (red-yellow) under OXT administration compared with placebo. Regions in green show reduced connectivity with both right and left amygdala (overlap). The clusters that survived correction for multiple testing were centred around MNI coordinates 18, -60, 27 (1806 voxels, FWE corrected $P = .026$) for right amygdala and 15, -45, 3 (1267 voxels, FWE corrected $P < .001$) for left amygdala, both corresponding to right precuneus. To display the extended distribution of this cluster a height threshold $T = 2.3$ and an extent threshold $k = 50$ are used in this figure. Other regions showing a differential effect of OXT at this threshold ($T = 2.3, k = 50$) are displayed in Supplementary Tables 3 and 4. The statistical maps are displayed on a template structural image provided with MRICRON software.

placebo, though at a more lenient statistical threshold (peak intensity $T = 2.3$, extent $k = 50$ voxels), other regional changes in Fc were also noted (Supplementary Material).

The ReHo analysis did not yield any significant results at the whole brain level. At a more lenient statistical threshold (peak intensity $T = 2.3$, extent $k = 50$ voxels), regional changes in ReHo were notable (Supplementary Material). When a posthoc search within bilateral amygdala was conducted, a significant reduction in the ReHo was noted in the right amygdala in OXT trials compared with the placebo (MNI coordinates of the peak of the significant cluster = 30, 3, -21; few-corrected peak level $P = .036$, $T = 3.64$), but no significant changes in ReHo were observed in the left amygdala. A similar posthoc analysis of ReHo changes within the Automated Anatomical Labelling precuneus masks did not produce any significant results.

OXT did not have any significant effect on positive or negative affect. These results are presented in Table 1.

Discussion

Using resting state fMRI connectivity analysis, we investigated the neurophysiological effect of OXT administration in healthy male volunteers. Our results indicate that intranasal OXT affects one of the core centers in the brain that is crucial for social cognition and introspective processing: the precuneus. The precuneus is a part of the DMN, with an important role in mentalizing and self-referencing, thus forming a constituent part of the so-called social brain (Mars et al., 2012; Cabanis et al., 2013; Amft et al., 2014; Utevsky et al., 2014). OXT not only reduced the connectivity between bilateral amygdala and the precuneus but also resulted in a generalized reduction in the connectivity of the precuneus. In addition, OXT also reduced the localized connectivity of right amygdala.

In this study, the DC of the right precuneus was significantly reduced after the administration of OXT. In normal circumstances, several regions including the precuneus act as hubs that show a high DC. These hubs are highly connected to many other regions in the brain, potentially facilitating the integration of connectivity between spatially distinct functional systems (Buckner et al., 2009). A single dose of OXT shows the potential to affect this intrinsic systems-level hub architecture, at least for a short time, by reducing the centrality of one of the core hubs.

Our results also show that OXT affects the localized connectivity of the amygdala, as measured by ReHo, which reflects the temporal synchrony of the BOLD response within a particular region and is a measure of intraregional brain connectivity. A number of neuroimaging studies involving facial emotion

processing tasks implicate the modulation of amygdala as a key effect of OXT administration (Meyer-Lindenberg et al., 2011; Riem et al., 2012). In general, these studies suggest that OXT “dampens” the activity of amygdala and thus may have a prosocial effect by either reducing negative reactions to social cues and/or reducing (aversive) associative learning in response to socially relevant cues (Petrovic et al., 2008). Our observation of reduced localized connectivity (ReHo) in amygdala in repose to OXT suggests that the amygdala-modulating effect of OXT occurs even in the absence of emotion-processing constraints.

We also observed a dissociation (decreased connectivity) between the amygdala and the precuneus hub in response to OXT. In the absence of socially relevant external stimuli, the dissociation of amygdala from the task-negative, DMN region (precuneus) may reduce the involvement of amygdala-related activity in internal mentation (Andrews-Hanna, 2012) or associative memory processes in which precuneus plays an important role (Murray and Kensinger, 2014). It is important to note that the connectivity of precuneus and amygdala increases during social task-processing (exposure to infant laughter) in female volunteers exposed to OXT compared with placebo (Riem et al., 2012). These 2 observations when taken together suggest that OXT modulates the interaction between amygdala and precuneus in a context-specific manner.

Our results are particularly relevant in light of the fact that OXT is now being considered as a treatment option for a number of conditions. For instance, an increase in DC in the precuneus was found in individuals with autistic spectrum disorders and attention deficit hyperactivity disorder (Di Martino et al., 2013). Similarly, abnormalities in the resting-state Fc between the amygdala and precuneus have been observed in anxiety-related disorders. Higher connectivity between amygdala and precuneus was shown to be correlated with current post-traumatic stress disorder (PTSD) symptoms and was also a predictor of PTSD after a trauma (Lanius et al., 2010), whereas an increase in Fc between these 2 regions was found in patients with panic disorder (Pannekoek et al., 2013). Comparing these outcomes with the results obtained from our study (ie, a reduction in DC of the right precuneus and a decrease in Fc between the amygdala and the precuneus), it appears as if the mechanistic process by which OXT potentially improves social cognition is by acting on these altered connections within the limbic/social-affective network seen in these disorders.

Despite a similar protocol and the same dose of OXT, results obtained from this study do not correspond with those reported in the one other paper on the resting-state Fc of OXT in healthy males (Sripada et al., 2013). Even when we undertook a motivated search within the small volume of a 6-mm sphere centered on

Table 1. Effect of OXT on Positive and Negative Affect

	Baseline Score Between-Subject Mean (SD)	After-Effect Between-Subject Mean (SD)	Change Score (After-Effect Minus Baseline) Within Subject Mean (SD)	Paired Samples T Test Change Score
OXT positive affect	30.31 (5.31)	31.00 (6.96)	0.69 (4.15)	P = .43
Placebo	30.38 (5.33)	30.15 (7.18)	-0.23 (2.35)	
Positive affect				P = .55
OXT negative affect	11.92 (2.25)	11.62 (2.69)	-0.30 (1.70)	
Placebo	13.08 (5.46)	13.15 (4.96)	0.07 (1.70)	
Negative affect				

Abbreviation: OXT, oxytocin.

Positive and negative affect scores were calculated using the Positive and Negative Affect Schedule (PANAS). PANAS was administered upon arrival (baseline score) and 45 min after intranasal spray administration (after-effect score). The change score was calculated by subtracting the after-effect score from the baseline score for each subject individually. These within-subject change scores for OXT and placebo were then used to perform 2 paired samples t tests (one each for positive and negative affect) to test whether there were any significant differences in the change in affect as a result of OXT administration.

the coordinates identified by Sripada et al. (MNI coordinates: -4, 32, -4; small volume correction (SVC) search FWE corrected at threshold $P < .05$), we did not observe any OXT-related increase in connectivity from either amygdalae seeds. Reasons for this could be differences in acquisition times and preprocessing strategies. In Sripada et al.'s (2013) study, the resting-state acquisition lasted only 3 minutes, whereas our study used a 5-minute-long paradigm. Although short scanning period need not necessarily induce or reduce connectivity, it has been shown that this results in poor reliability of connectivity patterns (Birn et al., 2013). Additionally, we used a stringent head-motion correction (Friston 24) followed by correction for micro-movements using scrubbing (Power et al., 2012). Lack of appropriate motion correction has been associated with the appearance of spurious connectivity patterns (Power et al., 2012). In contrast to Sripada et al. who used EPI normalization, we used DARTEL-based spatial normalization. EPI normalization could affect group-level statistics, particularly in brain regions where signal dropouts do not match the EPI template (eg, the ventromedial prefrontal regions where the main effect was observed by Sripada et al.) (Huang et al., 2010). This may induce localization errors, reducing both the detection sensitivity and repeatability of reported group differences in connectivity metrics. The observation that the precuneus shows an overall reduction in connectivity indexed by DC as well as reduced connectivity with amygdala seed region when OXT is administered adds validity to our report. Despite the differences from Sripada et al. (2013), there is a broad agreement between both studies in that the resting-state amygdala connectivity is altered after OXT administration. Interestingly, results similar to ours have been observed with the administration of allopregnanolone in healthy volunteers (Sripada et al., 2014). Allopregnanolone is a neurosteroid that has been shown to modulate OXT expression in rats (Blyth et al., 2000; Widmer et al., 2003), and it appears as though the neurophysiology of allopregnanolone is closely linked to that of OXT. Studies focusing on both the precuneus and amygdala are likely to provide better insights into the network-level mechanism by which OXT affects affiliative behavior.

Several limitations need to be taken into account when interpreting our reported findings. The sample size in this study was quite small, and studies with larger sample sizes would need to be carried out in order to determine whether or not the results obtained from this study are robust and can be replicated. Several brain regions that have previously been implicated in social cognition and OXT-mediated effects showed a trend towards altered centrality and ReHo but were not sufficiently large in effect to survive the correction for multiple comparisons in this sample. These results, reported in the [Supplementary Material](#), will require further inspection in larger samples. Moreover, as this study included only male volunteers, we cannot generalize these findings to females. Results from a resting-state Fc study of the influence of OXT on females showed no effect of OXT on the Fc of the amygdala (Riem et al., 2013). Hence, it is important to note that intranasal OXT might have varied neurophysiological effects on males and females.

OXT is a promising agent currently being tested for clinical efficacy for the affiliative dysfunctions seen in a variety of psychiatric disorders (Bora et al., 2009). Most of these trials involve the administration of oXT as a therapeutic agent without any explicit social-cognitive training in combination. Thus, understanding the “resting-state” effects of OXT is crucial to evaluate the mechanisms that are likely to underlie the clinical responses observed upon regular administration of OXT. The lack of a mechanistic understanding of how novel therapeutic agents work has been highlighted as an important hurdle in the

successful development of new treatment approaches (Insel et al., 2013). This study adds to our current understanding of how OXT can modulate brain networks at rest and raises the possibility for a wider role for OXT in disorders of connectivity involving the core hubs of human connectome.

Supplementary Material

For supplementary material accompanying this paper, visit <http://www.ijnp.oxfordjournals.org/>

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Statement of Interest

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