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Intranasal oxytocin modulates neural functional connectivity during human social interaction

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Abstract

Oxytocin (OT) modulates social behavior in primates and many other vertebrate species. Studies in non-primate animals have demonstrated that, in addition to influencing activity within individual brain areas, OT influences functional connectivity across networks of areas involved in social behavior. Previously, we used fMRI to image brain function in human subjects during a dyadic social interaction task following administration of either intranasal oxytocin (INOT) or placebo, and analyzed the data with a standard general linear model. Here, we conduct an extensive re-analysis of these data to explore how OT modulates functional connectivity across a neural network that animal studies implicate in social behavior. OT induced widespread increases in functional connectivity in response to positive social interactions among men and widespread decreases in functional connectivity in response to negative social interactions among women. Nucleus basalis of Meynert, an important regulator of selective attention and motivation with a particularly high density of OT receptors, had the largest number of OT-modulated connections. Regions known to receive mesolimbic dopamine projections such as the nucleus accumbens and lateral septum were also hubs for OT effects on functional connectivity. Our results suggest that the neural mechanism by which OT influences primate social cognition may include changes in patterns of activity across neural networks that regulate social behavior in other animals.

Keywords

fMRI; oxytocin; network; functional connectivity; sex differences

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INTRODUCTION

Oxytocin (OT) is known to modulate social behavior across a wide range of vertebrate species (Goodson & Thompson, 2010). In non-human primates, peripheral OT levels are associated with a variety of prosocial behaviors (Ziegler & Crockford, 2017), and experimental manipulation of OT levels has been shown to influence social behavior (Brosnan et al., 2015; Cavanaugh, Carp, Rock, & French, 2016; Dal Monte, Noble, Costa, & Averbeck, 2014; Kotani et al., 2017; Lefevre et al., 2017; Mustoe, Cavanaugh, Harnisch, Thompson, & French, 2015; Putnam, Roman, Zimmerman, & Gothard, 2016; Taylor & French, 2015). In humans, intranasal OT (INOT) administration has been reported to facilitate multiple prosocial behaviors, including parental caregiving (Naber, van Ijzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010; Rilling & Young, 2014; Weisman et al., 2013; Weisman, Zagoory-Sharon, & Feldman, 2012) pair-bonding (Scheele et al., 2013), trust and cooperation (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; De Dreu, 2012; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). However, concerns have been raised about potentially high false positive rates given that many studies are underpowered to detect estimated effect sizes (Walum, Waldman, & Young, 2016).

Research with non-human primates has begun to shed light on the neural mechanisms for these effects of OT on social behavior. For example, infusion of OT into the basolateral amygdala increases the frequency of prosocial decisions in rhesus macaque monkeys (Chang et al., 2015), and OT injected into the lateral ventricle of rhesus macaques provokes serotonin release and increased 5-HT 1A (serotonin 1A) receptor availability in several limbic brain areas (Lefevre et al., 2017). Research in humans has also investigated the mechanisms of OT action through combining intranasal OT administration with fMRI. Studies show that INOT increases activation in the striatum in the context of both cooperation and pair-bonding (Feng et al., 2014; Scheele et al., 2013), consistent with augmentation of the reward value of these stimuli. In addition, multiple studies have found INOT to attenuate amygdala responses to face stimuli (Domes et al., 2007; Gamer, Zurowski, & Buchel, 2010; Kirsch et al., 2005; Labuschagne et al., 2010; Quintana et al., 2016), which may be a neural mechanism for increased trust (Baumgartner et al., 2008).

Most intranasal OT fMRI studies have been conducted in men. However, in the few cases where both sexes have been studied, there is evidence for robust sex differences. Whereas INOT decreased amygdala activation to threatening faces in men, it increased amygdala activation in women (Domes et al., 2007; Domes et al., 2010). Furthermore, while INOT augmented striatal activation to cooperative social interactions among men, it did the opposite in women (Feng et al., 2014). INOT also attenuated the amygdala and anterior insula response to negative social interactions among men but not women (Chen et al., 2015). These sex differences in OT effects in humans are consistent with sexually differentiated effects of OT on social cognition and behavior in rodents (Dumais & Veenema, 2016).

Although research with non-human primates is able to probe the neural mechanisms of OT action in more detail than is possible in humans, human neuroimaging research has the advantage that the whole brain can be studied at once, and with greater anatomical

resolution than is possible for smaller non-human primate brains. This becomes particularly important when investigating OT effects on functional connectivity. The fMRI findings discussed above refer to effects of INOT on activation maxima within individual brain regions. However, it is also possible to examine how INOT influences distributed patterns of brain activation, as well as the interactions between different regions using functional connectivity analyses. Previously, we conducted a double-blind, placebo-controlled, pharmaco-functional magnetic resonance imaging (fMRI) study in which 304 healthy normal subjects were randomized to treatment with either 24 IU (international units) intranasal OT (n=100), 20 IU intranasal AVP (n=100) or placebo (PL, n=104) and imaged with fMRI as they played an interactive social decision-making task known as the iterated Prisoner's Dilemma (PD) game with same-sex partners. Approximately half of all subjects were female (50M/50F for OT, 49M/51F for AVP, 54M/50F for Placebo). Our data analysis was a standard general linear model (GLM) approach focused on the effects of intranasal OT and AVP on the response of individual voxels to positive (reciprocated cooperation) and negative (unreciprocated cooperation) social interactions. Here, with the same data set, we instead ask whether OT modulates functional connectivity following cooperative and non-cooperative interactions in the iterated PD game. Most OT fMRI functional connectivity analyses explore connectivity across the entire brain which requires extensive correction for multiple comparisons. Here we instead focus our analysis on a largely subcortical network based on a network identified in rodent studies known as the social behavioral neural network (SBNN). The SBNN includes the lateral septum, the midbrain periaqueductal gray and adjacent tegmentum, the anterior hypothalamus, the ventromedial hypothalamus, the medial preoptic area of the hypothalamus and the medial extended amygdala. Each node within the SBNN is reciprocally interconnected with all of the others, all nodes have neurons that contain gonadal hormone receptors, and each of these areas is involved in more than one social behavior (Newman, 1999). In addition, OT receptors are found throughout the SBNN. According to the SBNN concept, a specific social behavior is an emergent property of the pattern of activity within and across the network and not the result of turning a specific structure in the network "on" or "off" (Albers, 2012). The value of this approach is demonstrated by a recent study in male prairie voles in which an OXTR antagonist blocked mating-induced partner preference formation, even though it had no effect on mating-induced increases in immediate early gene expression within a social salience network (SSN) that overlaps with the SBNN. Critically, however, the OXTR antagonist did disrupt mating-induced increases in functional connectivity across the SSN. Thus, mating-induced, OT-mediated increases in functional connectivity may contribute to male pair-bond formation (Z. V. Johnson et al., 2016; Z.V. Johnson & Young, 2017). We therefore predicted that INOT would lead to widespread increases in functional connectivity in men in response to cooperative interactions in the PD game. However, given previous evidence for opposing effects of OT on activation maxima in men and women, we predicted that INOT might decrease functional connectivity among women.

METHODS

Many methodological details have already been described in (Chen et al., 2015), but for completeness are summarized again here.

2.1 Subjects

In total, 153 men and 151 women from the Emory University community between the ages of 18 and 22 (mean (SD) = 20.7 (2.2) years for men, and 20.5 (1.3) years for women) were randomized(at a ratio of 1:1:1) to treatment with either intranasal oxytocin (n=50 for men, n=50 for women), placebo (PL, n=54 for men, n=50 for women) or intranasal vasopressin (AVP, n=49 for men, n=51 for women). Following previous studies that have reported social cognitive effects of intranasal OT and AVP administration (MacDonald et al., 2013; Thompson, George, Walton, Orr, & Benson, 2006), the OT group self-administered 24 IU oxytocin (Syntocinon-Spray, Novartis), and the AVP group self-administered 20 IU of AVP (American Reagents Laboratory, Shirley, NY, USA). Randomization was performed by the Emory Investigational Drug Service (IDS) using Research Randomizer (http://www.randomizer.org), which randomizes each subject by using the method of randomly permuted blocks.

All potential subjects completed a full medical history questionnaire. All subjects gave written informed consent, and the study was approved by the Emory University Institutional Review Board and the U.S. Food and Drug Administration. The research adhered to the legal requirements of the United States of America, and adhered to the American Society of Primatologists' Principles for the Ethical Treatment of Primates. In this paper, our analyses are focused on the OT and PL groups, to the exclusion of the AVP group. Eight male subjects (OT n=4, and PL n=4) were excluded from the neuroimaging analysis due to excessive motion (>1.5 mm), missing data or to abnormal brain anatomy that precluded accurate spatial normalization to the template image in standardized space. Two female subjects (OT n=2) were excluded from the neuroimaging analysis due to excessive motion. The final sample size for analysis was n=46 men and n=48 for women in the OT group, and n=50 men and n=50 women in the PL group.

2.2. Exclusion criteria and information on OT safety and adverse events

Please see (Chen et al., 2015).

2.3 Prisoner Dilemma Game

The iterated Prisoner's Dilemma (PD) game is a model for relationships based on reciprocal altruism. In the game, two players choose to either cooperate or defect and receive a payoff that depends upon the interaction of their respective choices. The game version we use here is a sequential-choice PD game in which player 1 chooses and player 2 is then able to view player 1's choice before making his own choice. Each of the four outcomes is associated with a different payoff. Player cooperation followed by partner cooperation (CC) pays $2 to both player and partner, player cooperation followed by partner defection (CD) pays $0 to the player and $3 to the partner, player defection followed by partner defection (DD) pays $1 to both player and partner, and player defection followed by partner cooperation (DC) pays $3 to the player and $0 to the partner. All subjects first completed a PD tutorial and two practice trials (see supplementary materials). We aimed to start both the task and fMRI scan at 40 min after drug administration. In actuality, this time period averaged 42 min across subjects (see supplementary materials). Prior to the start of each game, the visual display inside the scanner showed a picture of the partner the subject was about to play the game

with. While being scanned with fMRI, subjects played 30 rounds of a sequential-choice, iterated PD game in four separate runs (see supplementary materials for complete timeline of the PD game). For two runs, subjects were told they were playing with a human partner (a same sex confederate that was introduced to the subject prior to the experiment). For the other two runs, subjects were told they were playing with a computer partner. In actuality, subjects were always playing with a pre-programmed computer algorithm described in (Rilling et al., 2012). For both human and computer partners, in one of the two sessions, subjects played in the role of first mover (player 1) and their partner played in the role of second mover (player 2). In the other session, roles were reversed. The order of human and computer sessions was counterbalanced across subjects so that half of the subjects were scanned in the order: player 1 with human partner (H1), player 2 with human partner (H2), player 1 with computer partner (C1), player 2 with computer partner (C2), and the other half were scanned in the order: C1, C2, H1, H2. In this paper, we restrict our analyses to the player 1 data from each subject. After scanning, subjects were asked several questions about their experience during the PD game. Subjects were compensated with a total of approximately $120; the exact amount was obtained by multiplying the total earnings across both runs by 2/3.

2.4 Neuroimaging Data Collection

A T1-weighted structural image and blood-oxygenation-level-dependent (BOLD) functional MRI images were collected for each subject using a 3 Tesla Siemens Trio MRI scanner (Siemens Medical System, Malvern, PA, USA).

High-resolution T1-weighted images were acquired using a 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence with a GRAPPA factor of 2. The T1 scan protocol, optimized for 3 Tesla, used the following imaging parameters: a repetition time/inversion time/echo time (TR/TI/TE) of 2600/900/3.02 ms, a flip angle of 8°, a volume of view of 256×256×176 mm^3, a matrix of 256×256×176, and isotropic spatial resolution of 1.0×1.0×1.0 mm^3, one average. Total T1 scan time was approximately 5 minutes.

During fMRI scanning, subjects performed 30 rounds of a sequential-choice, iterated PD game with both putative human partners and computer partners. T2*-weighted images were collected using an Echo-Planar Imaging (EPI) sequence for BOLD fMRI. EPI images were collected in an interleaved fashion with the following imaging parameters selected to minimize susceptibility and distortion artifacts in the orbitofrontal cortex: TR=2000 ms, TE=28 ms, matrix=64 X64, FOV=224mm, in-plane resolution 3.5mm, slice thickness=2.5mm, and 34 axial slices with a gap of 1.05mm in between.

2.5 Neuroimaging Data Analysis

Two different types of analyses were conducted on BOLD signals within anatomically defined ROIs (regions of interest) that compose our modified social behavioral neural network: 1) Multivariate analysis of variance (MANOVA) was used to test for effects of treatment (OT vs PL), sex (M vs F) and their interaction on the BOLD responses across the network for both CC and CD outcomes, and 2) Task-based functional connectivity among the ROIs was estimated with a generalized psychophysiological interaction (gPPI) analysis

(McLaren, Ries, Xu, & Johnson, 2012) and compared across drug treatment (OT vs PL) in both men and women. We focused on CC and CD outcomes, and not DC and DD outcomes, because we were specifically interested in how INOT modulated the neural response to positive and negative social interactions in the form of reciprocated (CC) and unreciprocated (CD) cooperation.

2.5.1 Definition of ROIs within the social behavioral neural network—Our modified social behavioral neural network (mSBNN) included brain regions from both the SBNN (amygdala, lateral septum, ventral tegmental area) (Newman, 1999) and the social salience network (SSN) (ventral tegmental area, amygdala, nucleus accumbens, and orbitofrontal cortex) (Z. V. Johnson, Walum, Xiao, Riefkohl, & Young, 2017) as defined in rodents. We also included the insula given its widespread involvement in human social cognition (Rilling & Sanfey, 2011; Singer, Critchley, & Preuschoff, 2009) as well as the nucleus basalis of Meynert (NBM) given its high density of OXTR in humans and non-human primates (Freeman et al., 2014; Loup, Tribollet, Dubois-Dauphin, & Dreifuss, 1991). The nucleus accumbens (NAc), amygdala (AMY) and insula (INS) were defined using the Harvard-Oxford Subcortical Structural Atlas and Harvard-Oxford Cortical Structural Atlas implemented in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) with 50% probability as the threshold. The orbitofrontal cortex (OFC) was defined using FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki) (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002; Fischl et al., 2004). For each subject, the Lateral and Medial OFC were segmented based on the Desikan-Killiany Cortical Atlas (Desikan et al., 2006) in FreeSurfer and then combined into an OFC ROI. Then, the OFC ROI of each individual subject was converted into the MNI (Montreal Neurological Institute) space and averaged across subjects. Finally, the OFC was defined by setting 50% probability as a threshold. Nucleus basalis of Meynert (NBM), lateral septum (SEP) and ventral tegmental area (VTA) were manually defined based on the coordinates and anatomy of these ROIs and surrounding brain structures, referring to the "Atlas of the Human Brain" (Mai, Paxinos, & Voss, 2008). All the ROIs were defined in the MNI space (supplementary figure 1).

2.5.2 BOLD responses of regions within the modified social behavioral neural network—fMRI data were preprocessed as described previously (Chen et al., 2015). The preprocessed data were analyzed using the general linear model (GLM) for univariate statistical analysis. For each individual run, a separate GLM was constructed to examine the neural response to both the epoch in which the choice to cooperate or defect was made, as well as to the epoch in which the game outcome was revealed. More specifically, the following regressors were defined for each run of each subject: (1) the beginning epoch when round number and the partner's face or a picture of the computer were displayed, (2) the choice epoch when the subject chose to cooperate (Choice C), (3) the choice epoch when the subject chose to defect (Choice D), (4) CC outcomes, (5) CD outcomes, (6) DC outcomes, and (7) DD outcomes. The individual-level GLM was implemented using FILM (FMRIB's Improved Linear Model). Motion parameters were not included in the GLM. After the ROIs defined above were converted back to individual subject space, beta values from the GLM analysis were averaged across the voxels within each ROI for both CC and

CD outcomes. At the group level, averaged beta values of the ROIs were compared using MANOVA and t-tests in IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY).

2.5.3 Task-based functional connectivity within the social behavioral neural network—For each seed ROI (one of the ROIs defined above, converted to individual subject space), a GLM for the gPPI analysis was constructed that included: averaged time series of white matter and CSF signals for each subject, motion parameters for each subject, the averaged time series of the seed ROI, the interaction between the CC outcome regressor and the seed time series, and the interaction between the CD outcome regressor and the seed time series. After conversion to MNI space, beta values for the interaction variables were used in t-tests between the OT and PL groups. Since we were specifically interested in pair-wise interactions between nodes of the social behavioral neural network, type I errors were controlled using "Voxel Thresholding" with corrected voxel p of 0.05 and "Pre-threshold masking" with a target ROI as the mask (i.e., a small volume correction). Target ROIs with more than 5 voxels that passed this multiple comparison correction were reported in this paper. This group level analysis was conducted separately for all 182 possible pairs of seed (n=14) and target (n=13) ROIs across the network, and repeated for each of the four sex (M, F) by outcome (CC, CD) combinations.

Other methodological details that are not directly related to the theme of this manuscript, such as the preparation and the administration of drugs, monitoring of vital signs, *Positive and Negative Affect Schedule* (PANAS) ratings, and confederate introductions, are described in (Rilling et al., 2012).

RESULTS

3.1 BOLD responses of regions within the modified social behavioral neural network

Two-way MANOVA revealed no significant effect of OT, sex or their interaction on the overall pattern of activation across the mSBNN in response to either CC or CD outcomes. In addition to the two-way MANOVA analysis, we also examined the effect of OT separately for each of the four sexes by outcome combinations using 1-way MANOVA, but this multivariate analysis did not reveal any significant effects of OT on the network's response to either CC or CD outcomes, in either males or females. Despite not affecting activation across the overall network, OT did have effects on individual brain areas within the network. For CC outcomes in females, OT decreased activation in right NAc, left insula, bilateral OFC and right lateral septum ($p<0.05$, figure 1a). For CC outcomes in males, OT had no effect on activation in any individual region (figure 1b). For CD outcomes in females, OT had no effect on activation in any individual region (figure 1c). Finally, for CD outcomes in males, OT decreased activation in bilateral amygdala and left VTA ($p<0.05$, figure 1d).

3.2 Task-based functional connectivity within the modified social behavioral neural network

For CC outcomes in females, gPPI analysis showed that OT modulated 9 out of 182 possible connections in the mSBNN. OT increased connectivity in five of these connections and decreased connectivity in four connections (fig 2a). There was no significant difference

between the proportion of upregulated and downregulated connections (χ^2 (1) = 0.21, p>0.05). For CC outcomes in males, OT modulated 23 out of 182 possible connections, increasing connectivity in 22 of those, and decreasing connectivity in only one (fig 2b, supplementary figure 2), a difference that was highly statistically significant (χ^2 (1) = 37.51, p<0.0001). The lateral septum and basal nucleus (NBM) showed the greatest number of connectivity changes, being involved in 9 and 13 connections that were positively modulated by OT, respectively. Both of these regions were involved in more upregulated connections than expected if such connections were equally distributed across all network nodes (basal nucleus χ^2 (1) = 9.29, p=0.002; lateral septum χ^2 (1) = 3.81, p=0.05).

For CD outcomes in females, OT modulated 19 out of 182 possible connections, decreasing connectivity in 18 of these while increasing connectivity in only one (fig 2c), a difference that was highly statistically significant (χ^2 (1) = 29.62, p<0.0001). The nucleus accumbens showed the greatest number of connectivity changes, being involved with 10 connections that were negatively modulated by OT. This proportion was larger than expected if the 18 negatively modulated connections were equally distributed across all network nodes (χ^2 (1) = 6.56, p=0.01). Finally, for CD outcomes in males, OT modulated 9 connections, increasing 8 and decreasing only one (figure 2d), a difference that was also statistically significant (χ^2 (1) = 10.29, p=0.001). In this case, there was an obvious focus on the lateral septum, which was involved in 8 connectivity changes, including 7 positive and 1 negative change. The proportion of positive changes for the lateral septum was greater than expected if positive changes were equally distributed across network nodes (χ^2 (1) = 8.04, p=0.005).

DISCUSSION

Although INOT did not alter the pattern of activation across the mSBNN in response to either positive (CC) or negative (CD) social interactions, it profoundly altered the pattern of connectivity across the network and these effects differed markedly between male and female participants. For CC outcomes, INOT treatment led to widespread increases in functional connections in males, and a smaller number of both increases and decreases in functional connections in females. On the other hand, for CD outcomes, INOT treatment led to widespread decreases in functional connections in females, and a smaller number of mostly increases in functional connections among males.

Research in non-human animals suggests that the SBNN and related neural networks encode social information in a highly dynamic, distributed manner, with behavior most strongly linked to the pattern of neural activity across the network, rather than the activity of individual loci in that network (Goodson & Kabelik, 2009; Z.V. Johnson & Young, 2017). For example, a study in zebra fish showed that while immediate early gene expression in individual nodes of a social decision-making network (SDN) could not differentiate among three different social behavioral states, functional connectivity among the nodes could (Teles, Almeida, Lopes, & Oliveira, 2015). In this case, functional connectivity is measured by correlated gene expression between brain areas across individuals. In addition, a recent study in prairie voles showed that endogenous OT can modulate functional connectivity across a social salience network (SSN) which may explain the ability of OT to facilitate male partner preference formation (Z. V. Johnson et al., 2016). Sociosexual interactions led

to increased immediate early gene expression across all nodes of a pair bonding network, however treatment with an OTR antagonist (OTA) had no effect on expression in any of these regions. On the other hand, sociosexual interactions also resulted in widespread increases in functional connectivity (correlated expression), which OTA significantly disrupted. Thus, disrupted network connectivity is postulated to explain the behavioral effects of OTA, namely impaired partner preference formation (Z. V. Johnson et al., 2016). Although not focused on the SBNN or SSN in particular, another prairie vole study found that, in response to stress, OT promoted functional coupling between the paraventricular nucleus and brain regions regulating both sympathetic (i.e. rostral ventrolateral medulla) and parasympathetic (i.e. dorsal vagal complex and nucleus ambiguous) branches of the autonomic nervous system (Yee et al., 2016).

One significant limitation of these non-human animal studies that examine immediate early gene expression is that they can only measure brain activity at a single point in time. In this case, “functional connectivity” refers to correlations in brain activity across individuals. Other methods, such as electrophysiology and neuroimaging, allow researchers to instead examine correlations among network nodes over time within individuals. Electrophysiology is limited in the number of brain areas that can be simultaneously recorded from. fMRI, though lacking the temporal resolution of electrophysiology, permits examination of connectivity in multiple brain areas simultaneously.

A number of previous fMRI studies have investigated the effect of INOT on resting state functional connectivity in healthy human subjects (Bethlehem et al., 2017; Dodhia et al., 2014; Ebner et al., 2016; Kumar, Vollm, & Palaniyappan, 2014; Riem et al., 2013; Sripada et al., 2012). A smaller number of studies have examined the effect of INOT on task-based functional connectivity as we do here. In one study, 24 IU INOT increased amygdala connectivity with orbitofrontal cortex, anterior cingulate, hippocampus, precuneus, supramarginal gyri, and middle temporal gyrus in nulliparous women as they listened to infant laughter (Riem et al., 2012). In another study, 24 IU INOT decreased amygdala connectivity with bilateral anterior insula during fearful face processing in healthy men (Gorka et al., 2015).

The above functional connectivity studies involve defining a seed region, such as the amygdala, and searching the whole brain for voxels in which connectivity with the seed region is modulated by OT. Whole brain exploratory analyses like these require correction for multiple comparisons across a very large number of voxels, which can lead to high type II error rates. An alternative approach is to limit the analysis to a small number of brain regions within an a-priori network of interest, as was done for the prairie vole analysis described above. This method ameliorates the multiple comparison problem, and crucially, also allows investigation of connectivity from each node to every other node within the network, rather than simply examining connectivity from one or two seed regions as has been done previously. It should also be noted that none of the previous studies have examined functional connectivity in subjects immersed in dyadic social interactions as we do here. Functional connectivity and its modulation by OT may well differ in the contexts of rest, exposure to social stimuli, and immersion in social interactions.

We observed marked sex differences in the effect of OT on functional connectivity within the mSBNN. This finding is consistent with accumulating evidence from both rodents and humans for sex differences in the OT system and its influence on brain and behavior (Dumais, Kulkarni, Ferris, & Veenema, 2017; Dumais & Veenema, 2016). Previously with these data, we found that 24 IU intranasal OT augments the caudate nucleus response to positive social interactions among men, but attenuates this response among women (Feng et al., 2015). Furthermore, OT attenuates the amygdala and anterior insula response to negative social interactions among men but not among women (Chen et al., 2015). Here, we add to our previous findings by demonstrating sex differences in OT modulation of functional connectivity within our mSBNN.

NBM was the mSBNN node with the largest number of OT-modulated connections. This may be due to NBM having a particularly high density of OXTR in humans (Loup et al., 1991). NBM is an important regulator of selective attention and motivation and contains OXTR in all nonhuman primates studied to date (Freeman & Young, 2016). OT modulation of NBM connectivity may therefore be a mechanism by which OT influences the salience of positive and negative social interactions. OT effects on NBM connectivity were highly lateralized for CD outcomes in women, where OT decreased left NBM connectivity with 6 different areas but had no effect on right NBM connectivity. This finding may be related to the results of a meta-analysis showing that several left hemisphere sub-cortical areas are more responsive to negative emotion in women than in men (Stevens & Hamann, 2012). In addition to NBM, other hubs for OT effects on functional connectivity were found in regions that receive mesolimbic dopamine projections (Assaf & Miller, 1977). In males, the lateral septum had the largest number of OT-modulated connections for CD outcomes and the second largest number of OT-modulated connections for CC outcomes (after NBM). In females, the nucleus accumbens had the largest number of OT-modulated connections for CD outcomes. However, OT largely increased connectivity from the lateral septum in males, while decreasing connectivity from NAc in females. Since both of these structures are critically involved in reward processing (Olds & Milner, 1954; Schultz, 2016), these data add support to our previous conclusion that 24 IU INOT may be increasing reward from positive social interactions in men and decreasing reward from positive social interactions in women (Feng et al., 2014). However, it will be important to further evaluate this conclusion at different doses in future studies.

OT increases in lateral septum connectivity in males are interesting given the high density of OT receptors in the human lateral septum (Loup et al., 1991). Similarly, the pair-bonding titi monkey, but not the polygynous rhesus monkey, has a high density of OT receptors in the lateral septum, and the lateral septum is strongly implicated in the pair-bonding behavior of male titi monkeys (Bales et al., 2017; Hinde et al., 2016; Hostetler et al., 2017; Maninger, Hinde, et al., 2017; Maninger, Mendoza, et al., 2017). The closely related nonapeptide, vasopressin (AVP), also acts in the lateral septum to promote both pair bond formation (Liu, Curtis, & Wang, 2001) and paternal caregiving in male prairie voles (Wang, Ferris, & De Vries, 1994). OT can bind to AVP receptors (Manning et al., 2012), and there is a high density of AVP receptors in the human lateral septum (Loup et al., 1991), so OT effects on lateral septum connectivity could conceivably be mediated by either OT or AVP receptors. In females, OT effects on connectivity were concentrated in the nucleus accumbens (NAc). In

parallel with high densities of OXTR in NBM and the lateral septum, recent evidence suggests high levels of *OXTR* expression in the human nucleus accumbens (Bethlehem et al., 2017), suggesting that NAc may also be a target for OT effects. In rodents, OT acts in NAc to promote both maternal caregiving (Numan, 2007) and pair bonding (Numan & Young, 2016; Young, Murphy Young, & Hammock, 2005). Collectively, these and our own findings raise the possibility that nonapeptide effects on prairie vole prosocial behavior involves changes in functional connectivity, as recently proposed (Z. V. Johnson et al., 2016; Z. V. Johnson et al., 2017; Z.V. Johnson & Young, 2017).

There were some significant effects of OT treatment on responses to CC and CD outcomes within individual ROIs (figure 1). Among women, OT decreased the response to the CC outcomes in several regions involved with salience and reward processing, including the lateral septum, NAc and OFC. In men, OT decreased the response to the CD outcomes in bilateral amygdala. Previously, using voxel-wise analyses in this same data set, we found INOT to decrease the response to positive social interactions (i.e., CC outcomes) in the caudate nucleus in women (Feng et al., 2014). We also found INOT to decrease the response to negative social interactions (CD outcomes) in the amygdala and anterior insula in men (Chen et al., 2016). The current ROI results therefore echo our previous conclusion that 24 IU INOT decreases the reward or salience of positive social interactions among women and decreases the stress of negative social interactions among men.

Although we corrected for multiple comparisons across voxels in our regions of interest for each individual connection that we examined, we did not correct for multiple comparisons across the number of examined connections because we were principally interested in whether OT affected the behavior of the network as a whole. As a result, caution should be exercised in interpreting OT effects on specific connections, as these are vulnerable to type I errors. Nevertheless, the finding that OT increases mSBNN connectivity in males in response to CC outcomes, and decreases mSBNN connectivity in females in response to CD outcomes seems robust since the number of OT-induced changes (23 and 19, respectively) were larger than what is expected by chance (182*0.05=9.1 connections), and since there was a highly significant difference between the proportion of positively and negatively modulated connections in each case. Moreover, there was strong statistical evidence that OT-induced connectivity changes were focused on specific network nodes (the lateral septum and basal nucleus in males and the nucleus accumbens in females).

There is growing interest in OT as a potential treatment for psychiatric disorders such Autism Spectrum Disorders (ASD), depression, schizophrenia and anxiety disorders (Macdonald & Feifel, 2013; Young & Barrett, 2015; Zink & Meyer-Lindenberg, 2012). Understanding the mechanism of OT action in the brain may be important for developing effective pharmacologic treatments. Our data suggest that in addition to examining OT effects on activation within individual brain areas, it will be important to examine OT effects on patterns of connectivity across neural networks to more fully appreciate OT effects on primate brain function.

Finally, just as rodent research has informed the human research described here, our human research has the potential to inform research being conducted in non-human primates. For

example, the basal nucleus (NBM) was the node with the largest number of OT-modulated connections in our study. Similar to humans, OXTR is expressed in the basal nucleus (NBM) in marmoset, titi and rhesus monkeys (Freeman & Young, 2016). Therefore, non-human primate researchers might focus their more targeted methodological approaches on NBM. In this way, human and non-human primate research on the neural mechanisms of OT can complement one another.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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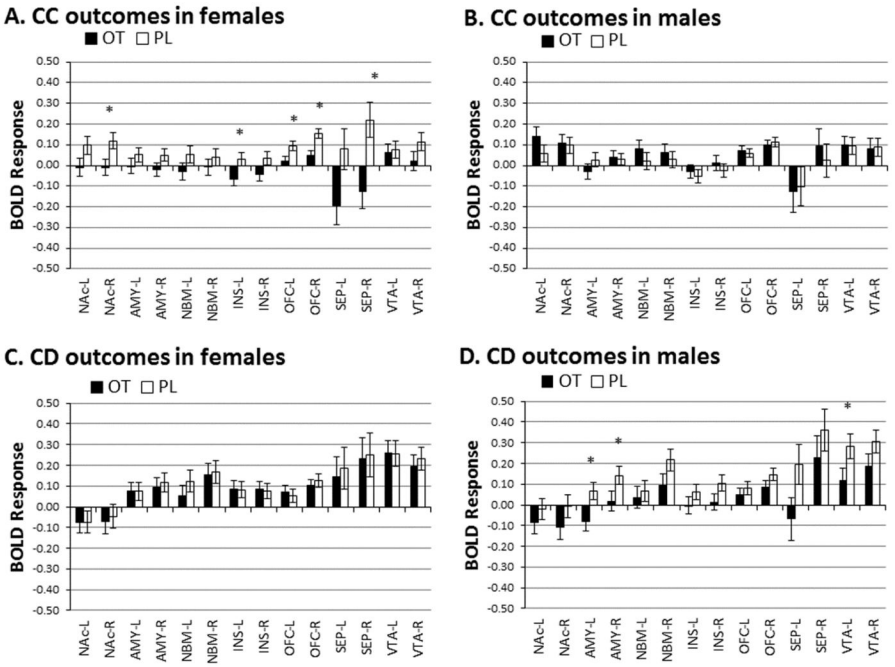

Figure 1.

Average BOLD fMRI response within each node of the social behavioral neural network as a function of treatment (OT vs PL) for a) CC outcomes in females, b) CC outcomes in males, c) CD outcomes in females and d) CD outcomes in males. * = $p<0.05$, error bars are 1 SE.

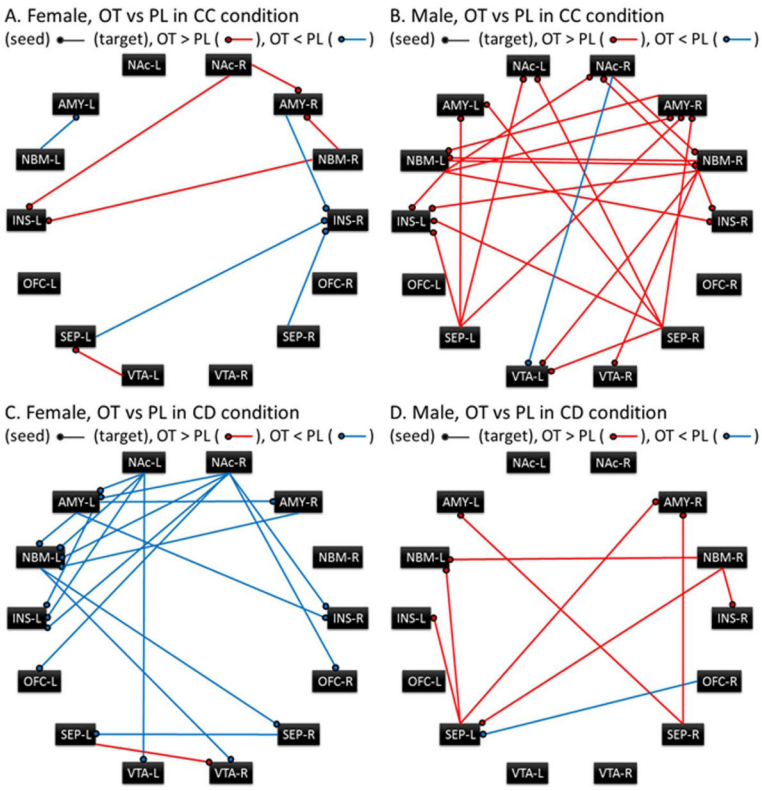

Figure 2.

OT modulation of functional connectivity across the mSBNN for a) CC outcomes in females, b) CC outcomes in males, c) CD outcomes in females, and d) CD outcomes in males.