Title: Oxytocin enhances intrinsic corticostriatal functional connectivity in women

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Abstract

Background
Oxytocin may influence various human behaviors and the connectivity across subcortical and cortical networks. Previous oxytocin studies are male-biased and often constrained by task-based inferences. Here we investigate the impact of oxytocin on resting state connectivity between subcortical and cortical networks women.

Methods
We collected resting state fMRI data on 26 typically-developing women following intranasal oxytocin administration using a double-blind placebo-controlled crossover design. Independent components analysis (ICA) was applied to examine connectivity between networks. An independent analysis of oxytocin receptor (*OXTR*) gene expression in human subcortical and cortical areas was carried out to determine plausibility of direct oxytocin effects on *OXTR*.

Results
In women, *OXTR* was highly expressed in striatal and other subcortical regions, but showed modest expression in cortical areas. Oxytocin increased connectivity between corticostriatal circuitry typically involved in reward, emotion, social-communication, language, and pain processing. This effect was 1.39 standard deviations above the null effect of no difference between oxytocin and placebo. This oxytocin-related effect on corticostriatal connectivity covaried with autistic traits, such that oxytocin-related increase in connectivity was stronger in individuals with higher autistic traits.

Discussion
Oxytocin strengthens corticostriatal connectivity in women, particularly with cortical networks that are involved in social-communicative, motivational, and affective processes. This effect may be important for future work on neurological and psychiatric conditions (e.g., autism, chronic pain), particularly through highlighting how oxytocin may operate differently for subsets of individuals.

Significance statement

This is the first study to examine how oxytocin affects corticostriatal connectivity in humans, and specifically in women. This is important given oxytocin could impact neural circuitry differently in males and females. Here, we show that oxytocin increases connectivity between corticostriatal circuitry involved in a number of social-communicative, motivational, and affective processes that are implicated in certain neuropsychiatric conditions (e.g., autism). This effect is bolstered by independent evidence that oxytocin receptor gene expression is high in striatal regions and modest in cortical areas. These results may have potential implications for personalized treatment, as oxytocin-related effects on connectivity may vary substantially between individuals.

Introduction

Oxytocin is a neuropeptide hormone involved in sexual intercourse, childbirth and parent-infant bonding, affecting reward processing, anxiety and social salience (Bethlehem et al., 2014). Oxytocin is not necessarily a 'pro-social' hormone, as effects are highly context- and person-dependent (Bartz et al., 2011; Bethlehem et al., 2014). Oxytocin has received substantial interest as a potential treatment for psychiatric conditions such as autism (Meyer-Lindenberg, 2008), although clinical trials show modest effects (Watanabe et al., 2013, 2015; Yatawara et al., 2015). Given the marked heterogeneity in autism (Lai et al., 2013) it is possible that the benefits of oxytocin may vary substantially between individuals. For example, on-average oxytocin improves eye contact during naturalistic social interaction, but the largest effects occur for individuals who typically make the least amount of eye contact (Auyeung et al., 2015). Thus, in evaluating oxytocin's therapeutic potential, we must move towards a more precise understanding of how its effects may vary across individuals.

We have theorized that the widespread effects of oxytocin on complex human social behavior may be due to distributed influence at a neural circuit level (Bethlehem et al., 2013). Although oxytocin acts directly at a local level via the oxytocin receptor (*OXTR*), it can potentially affect widespread circuit-level dynamics via connections to areas that are densely populated with *OXTR*. One way to test the hypothesis that oxytocin affects circuit-level organization in the human brain is through oxytocin-administration studies within the context of in-vivo measurement of intrinsic functional brain organization (i.e. connectome organization) with resting state fMRI (rsfMRI) data. While there are a number of existing neuroimaging oxytocin-administration studies (Bethlehem et al., 2013), most have relied on task-based fMRI paradigms and largely focus on males. In the oxytocin literature there is a prominent bias towards males, and one that affects much of neuroscience and medical research (Beery and Zucker, 2011). Sex differences in the *OXTR* system are documented (Kramer et al., 2004; Dumais and Veenema, 2015; Ebner et al., 2016), suggesting that findings in males may not generalize to females. Because oxytocin is viewed as a potential pharmacotherapy for conditions like autism, and given that sex may play a large moderating roles in drug effectiveness (Zagni et al., 2016), it is essential to begin examining how oxytocin operates in the female brain.

The majority of studies investigating how oxytocin affects the human brain use task-based fMRI paradigms. While task-based studies are important for targeting specific psychological processes, examination of oxytocin-related effects may be neuroanatomically constrained to specific circuits. Examination of functional connectivity using rsfMRI data allows for task-independent assessment of oxytocin's effect on intrinsic functional brain organization across the entire connectome. The small number of existing rsfMRI oxytocin-administration studies (Sripada et al., 2013; Watanabe et al., 2015; Ebner et al., 2016; Koch et al., 2016) use seed-based analyses that do not allow for hypothesis-free examination across the connectome. Thus, a more unconstrained approach could provide novel insights into oxytocin-related effects on connectome organization.

Here we use independent components analysis (ICA) to examine how connectivity between-circuits (i.e. between-component connectivity) (Smith et al., 2013, 2015) differs across oxytocin and placebo. To facilitate our understanding of oxytocin-effects on connectivity in the human brain we analyzed two publicly available post-mortem human brain gene expression datasets to answer the question of how the oxytocin receptor (*OXTR*) is expressed across a variety of subcortical and cortical areas in the human brain. We predicted

that oxytocin would have largest impact on connectivity between the densely *OXTR*-populated striatum and cortical circuits. Furthermore, we predicted that impact of oxytocin on connectivity would vary as a function of variation in autistic traits, with larger effects for individuals with higher levels of autistic traits (Auyeung et al., 2015).

Methods

Participants and procedure

All research was conducted in accordance with the Declaration of Helsinki and the study had received ethical approval from the NHS Research Ethics Service (NRES Committee East of England – Cambridge Central; REC reference number 14/EE/0202). This study was exempt from clinical trials status by the UK Medicines and Healthcare Regulatory Agency (MHRA).

In a double-blind randomized placebo-controlled cross-over design, 26 women (age: 23.6±4.6 years, range [21-50]) received an oxytocin nasal spray (24 IU, 40.32 µg, Syntocinon-spray; Novartis, Switzerland) in one session and placebo in the other session. The sprays were administered 40 minutes prior (Born et al., 2002) to undergoing resting-state fMRI imaging. Sessions were separated by at least one week when participants were on hormonal contraceptive (19/26). When participants were not on hormonal contraceptive (7/26) both sessions took place in the early follicular phase of the menstrual cycle. Exclusion criteria included pregnancy; smoking; a diagnosis of bipolar, obsessive-compulsive, panic or psychotic disorder; use of any psychoactive medication within one year prior to the study; substance dependence; epilepsy; and being post-menopausal.

The participants were instructed to abstain from alcohol and caffeine on the day of testing and from food and drink, except water, for 2 hours before spray administration. On arrival all participants were informed about the nature of the study and were given the opportunity to ask any questions for clarification. Written informed consent was obtained from all participants. Prior to the first session participants completed the Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001) and the Empathy Quotient (EQ) (Baron-Cohen and Wheelwright, 2004). At the start of the first session, participants were administered the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) and National Adult Reading Test (NART; Nelson, 1982).

Before administration of the nasal spray a medical examination including measurements of blood pressure, heart rate, general wellbeing and short medical history was conducted. A pregnancy test was also administered to avoid any potential effects of OXT. A medical professional provided a prescription and remained in attendance to manage any potential adverse effects from the spray. The participants received either the active or placebo nasal spray (three puffs per nostril, alternating between sides 4IU, 6.72 µg each). Heart rate and blood pressure were also continually monitored during scanning. One participant reported feeling slightly light-headed after the first MRI session. Post-hoc un-blinding revealed that this occurred during the placebo condition. No other side effects were reported. After administration of the nasal spray participants were prepared for MRI scanning and the anatomical MRI commenced approximately 30 minutes after administration, followed by the resting-state sequence 40 minutes after oxytocin administration. This study was part of a larger project and subjects subsequently performed 3 short computerized tasks in the scanner that are not reported here.

To understand whether oxytocin or some other placebo-related effect that explains any drug-related differences in connectivity, we utilized an independent dataset of age-matched typical females in order to ascertain what are the normative baseline between-component connectivity effects. Our logic here is that if normative connectivity looks similar to patterns we see during placebo, then we can reasonably infer that oxytocin is the primary reason for the induced change in connectivity and not due to some placebo-related change and no effect of oxytocin. This independent dataset consisted of 50 females whom were slightly older but did not statistically differ in age (mean age 31.6±12.2, Wilcoxon rank-sum test: W = 764.5, p = 0.117) collected on the same scanner and which used a similar multi-echo EPI sequence for data collection (Morris et al., 2016).

Image acquisition

MRI scanning was done on a 3T Siemens MAGNETOM Tim Trio MRI scanner at the Wolfson Brain Imaging Centre in Cambridge, UK. For the oxytocin-dataset, a total of 270 resting-state functional volumes were acquired with a multi-echo EPI (Kundu et al., 2012) sequence with online reconstruction (repetition time (TR), 2300 ms; field-of-view (FOV), 240 mm; 33 oblique slices, alternating slice acquisition, slice thickness 3.8 mm, 11% slice gap; 3 echoes at TE = 12, 29, and 46 ms, GRAPPA acceleration factor 2, BW=2368 Hz/pixel, flip angle, 80°). Anatomical images were acquired using a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence (TR, 2250 ms; TI, 900 ms; TE, 2.98 ms; flip angle, 9°; matrix 256×256×256, FOV 256 mm). For the independent rsfMRI dataset on age-matched females, data was acquired on the same 3T scanner and with a multi-echo EPI sequence that was similar to the oxytocin-dataset (TR, 2470 ms; FOV, 240 mm; 32 oblique slices, alternating slice acquisition, slice thickness 3.75 mm, 10% slice gap; 4 echoes at TE = 12, 28, 44, and 60 ms, GRAPPA acceleration factor 3, BW=1698 Hz/pixel, flip angle, 78°).

Image processing

Multi-echo functional images were pre-processed and denoised using the AFNI integrated multi-echo independent component analysis (ME-ICA, meica.py v3, beta1; http://afni.nimh.nih.gov) pipeline (Kundu et al., 2013). This pipeline included: skull-stripping of the anatomical MPRAGE image and warping it to the MNI anatomical template, co-registration of the first TE functional data to compute motion correction and for anatomical-functional co-registration, deobliquing of functional data, 12-paramater affine anatomical-functional co-registration using the local Pearson correlation and T2* weights (lp-t2s) cost function. Each TE functional dataset was slice-time corrected and spatially aligned through application of the anatomically derived alignment matrix using nonlinear warping to MNI space (MNI152 template) with AFNI 3dQwarp. No temporal filtering or smoothing was applied to the data.

Next, functional data were decomposed into independent components (ICs) as part of the ME-ICA pipeline. Subsequently, ICs were categorized as BOLD or non-BOLD based on their weightings measured by Kappa and Rho values, respectively. Because BOLD signal changes are linearly dependent on echo time (TE), a characteristic of the T2* decay, TE dependence of BOLD signal is used to dissociate BOLD from non-BOLD signal using the pseudo-*F*-statistic, Kappa. ICs that scale strongly with TE have high Kappa scores (Kundu et al., 2013). Conversely, non-BOLD ICs are identified by TE independence measured by the pseudo-*F*-statistic, Rho. By removing non-BOLD ICs, data are denoised for motion, physiological and scanner artefacts in a robust manner based on physical principles (Kundu et al., 2013; Evans et al., 2015). One session for one subject had to be excluded due to technical

difficulties in the realignment procedure. This subject was removed from subsequent analyses.

Gene expression analysis

To better characterize subcortical and cortical brain regions in terms of *OXTR* gene expression, we analyzed RNAseq data in the Allen Institute BrainSpan atlas (http://www.brainspan.org) and the Genotype-Tissue Expression (GTEx) consortium dataset (http://www.gtexportal.org/home/). The BrainSpan atlas covers a number of cortical areas the might provide insights into potential cortical targets of oxytocin expression, whereas the GTEx dataset does not have many regionally-specific areas of the cortex (only BA9 and BA24) and mostly includes more detailed information on several subcortical brain regions. In these analyses we used all postnatal (birth to 79 yrs.) samples in each dataset, stratified by biological sex. *OXTR* was isolated and plots were produced to descriptively indicate expression levels across brain regions. Expression levels in both datasets were summarized as Reads Per Kilobase of transcript per Million mapped reads (RPKM). To examine whether *OXTR* expression levels were significantly elevated in each brain region, we compared expression levels against zero and, as a more conservative test, against another tissue from GTEx where we would not expect *OXTR* to be expressed (i.e. skin). These tests were carried out using permutation t-tests (1000 permutations) implemented with the perm.t.test function in R.

Group Independent Components Analysis and Dual Regression

To assess large-scale intrinsic functional organization of the brain we first utilized the unsupervised data-driven method of independent component analysis (ICA) to conduct a group-ICA followed by a dual regression to back-project spatial maps and individual time series for each component and subject. Both group-ICA and dual regression were implemented with FSL's MELODIC and Dual Regression tools (www.fmrib.ox.ac.uk/fsl). For group-ICA, we constrained the dimensionality estimate to 30, as in most cases with low-dimensional ICA, the number of meaningful components can be anywhere from 10-30 (Smith et al., 2013). Some components were localized primarily to white matter and although likely may be driven by true BOLD-related signal (due to high ME-ICA kappa weighting), were not considered in any further analyses. The 22 out of 30 components which were manually classified as primarily localized to gray matter and were clearly not noise-driven components were taken further into analyses of between-component connectivity.

Between-Component Connectivity Analysis

Time courses for each component and subject were used to model between-component connectivity during placebo and oxytocin administration. This was achieved by constructing a correlation matrix of the 22 non-noise components for each subject. Connectivity strength in this correlation matrix was measured as the correlation coefficient after running robust regression (Wager et al., 2005) (https://github.com/canlab/RobustToolbox), to mitigate bias from outlier time points. We then tested for difference in connectivity strength for placebo versus oxytocin with a paired-sample t-test for each between-component connection. Correction for multiple comparisons was achieved via Bonferroni correction at a family-wise error rate of 5%. For component pairs that survived multiple comparison correction, we computed a difference score between oxytocin and placebo on the Fisher z-transformed correlation statistics (Steiger, 1980). This difference score indicates the size of oxytocin-related connectivity enhancement, with larger scores indicating larger enhancement of connectivity from oxytocin, whereas scores near 0

indicate no difference in connectivity between oxytocin and placebo. To report an effect size for any oxytocin-related effects on connectivity, we computed effect size as the mean of the difference score divided by the standard deviation of the difference score. This effect size is analogous to Cohen's d and indicates the magnitude of effect above a null effect of 0 in units of standard deviation. We also used this difference score to test for association with autistic traits as measured by the AQ using robust regression. In past work we have observed that oxytocin tends to have larger effects on individuals have higher levels of autistic traits (Auyeung et al., 2015). Therefore, we made the directional prediction that oxytocin-related effects on connectivity would be positively correlated with autistic traits.

Large-Scale Reverse Inference with Cognitive Decoding in NeuroSynth

To better characterize the components showing an oxytocin-related effect on connectivity we used the decoder function in NeuroSynth (Yarkoni et al., 2011) to compare the whole-brain component maps with large-scale automated meta-analysis maps within NeuroSynth. The top 100 terms (excluding terms for brain regions) ranked by the correlation strength between the component map and the meta-analytic map were visualized as a word cloud using the wordcloud library in R, with the size of the font scaled by correlation strength.

Results

Oxytocin Receptor (*OXTR*) Gene Expression in the Female Human Brain

Expression profiles of *OXTR* in women derived from the GTEx dataset reveal broad expression across subcortical regions, but with notable enrichments particularly in nucleus accumbens, substantia nigra, and the hypothalamus (Figure 1). All regions showed *OXTR* expression that was significantly above 0 and critically, was also significantly stronger than expression in a tissue we would expect to show little expression (i.e. skin) (Table 1). Cortical regions from the BrainSpan dataset also exhibit significant *OXTR* expression (above 0 and when compared to skin; Table 1), albeit at much more modest levels than some subcortical regions. This modest degree of *OXTR* expression may be particularly relevant given studies that show broad oxytocin-related effects on complex human social behavior, social communication, and social cognition that affects distributed cortical regions (e.g., superior temporal gyrus, medial prefrontal cortex (MFC)). However, there is a lack of specificity apparent in *OXTR* expression in cortex, as most regions show similar levels of expression. As a whole, these data indicate that oxytocin could have potent direct effects on *OXTR* within subcortical circuitry, particular areas of the striatum and midbrain, but may also have similar *OXTR*-driven effects to a lesser extent across most cortical areas where *OXTR* expression is modest. Given the lack of specificity within cortex, these data also support an approach for examining oxytocin-related effects on intrinsic functional connectivity that examines all between-networks connections, as all may be susceptible to plausible effects. However, given the enrichment particularly in striatal and midbrain regions, it is likely that oxytocin-related effects on connectivity may particularly affect connections between cortex and the densely *OXTR*-populated striatum and midbrain.

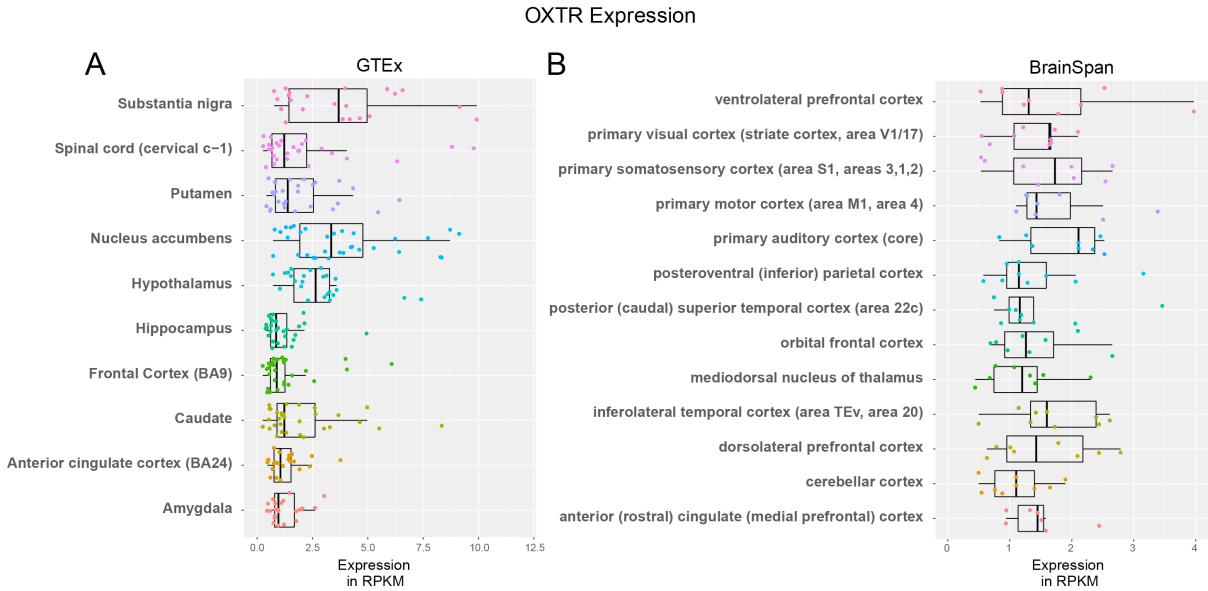

Figure 1: Oxytocin receptor (*OXTR*) gene expression in the female human brain. This figure illustrates *OXTR* gene expression measured via RNAseq in BrainSpan (http://www.brainspan.org) and GTEx (http://www.gtexportal.org/home/) datasets. Panel A shows expression for all subcortical regions available in the GTEx dataset in women. All brain regions show significant expression of *OXTR* above 0 and compared to expression in non-brain (skin) tissue. On-average, *OXTR* expression is particularly enriched in ventral striatum (Nucleus Accumbens), substantia nigra, and hypothalamus. Panel B shows expression for all cortical areas and the thalamus available in the BrainSpan atlas in women. All areas also show significant, albeit modest, levels of *OXTR* expression compared to 0 and non-brain (skin) tissue.

Table 1: Descriptive statistics for *OXTR* expression in females

Descriptive statistics for all female data from the GTEx and BrainSpan datasets. RNAseq data was summarized to RPKM and all descriptives and inferential statistics are based on these RPKM values. Two different one-sample t-tests were performed to compare OXTR expression to 0 and to non-brain (skin) tissue. These tests were performed within a permutation test (1000 permutations) to derive p-values.

	Expression Descriptives				Compared to 0		Compared to skin tissue expression		
Region	n	mean	sd	median	T	P	T	P	Mean Difference
Caudate (basal ganglia)	32	2.51	3.27	1.27	4.33	1.43E-04	4.12	3.64E-04	2.38
Nucleus accumbens (basal ganglia)	34	4.52	3.58	3.60	7.37	1.81E-08	7.17	4.56E-08	4.40
Frontal Cortex (BA9)	31	1.32	1.27	0.88	5.76	2.70E-06	5.23	1.74E-05	1.19
Putamen (basal ganglia)	28	1.98	1.56	1.38	6.73	3.13E-07	6.32	1.20E-06	1.86
Hypothalamus	25	3.23	2.77	2.88	5.82	5.26E-06	5.60	1.14E-05	3.10
Spinal cord (cervical c-1)	28	2.11	2.43	1.22	4.61	8.68E-05	4.34	2.37E-04	1.99
Anterior cingulate cortex (BA24)	23	1.29	0.78	1.05	7.96	6.36E-08	7.21	3.48E-07	1.17
Substantia nigra	24	6.65	10.84	3.92	3.01	6.29E-03	2.95	8.36E-03	6.53
Hippocampus	29	1.12	0.90	0.86	6.69	2.91E-07	5.96	2.75E-06	1.00
Amygdala	22	1.23	0.69	0.96	8.39	3.83E-08	7.55	2.13E-07	1.11
primary motor cortex (area M1, area 4)	8	1.78	0.79	1.43	6.39	3.72E-04	2.83	1.81E-02	1.65
dorsolateral prefrontal cortex	8	1.57	0.81	1.43	5.48	9.28E-04	2.83	1.81E-02	1.45
posterior (caudal) superior temporal cortex (area 22c)	9	1.44	0.85	1.16	5.08	9.49E-04	2.36	3.58E-02	1.32
primary visual cortex (striate cortex, area V1/17)	9	1.37	0.52	1.64	7.85	4.99E-05	2.36	3.58E-02	1.24
anterior (rostral) cingulate (medial prefrontal) cortex	7	1.46	0.51	1.45	7.60	2.70E-04	3.37	9.29E-03	1.33
orbital frontal cortex	8	1.41	0.68	1.26	5.88	6.11E-04	2.83	1.81E-02	1.29
inferolateral temporal cortex (area TEv, area 20)	9	1.69	0.69	1.60	7.29	8.44E-05	2.36	3.58E-02	1.56
primary somatosensory cortex (area S1, areas 3,1,2)	8	1.63	0.82	1.73	5.66	7.70E-04	2.83	1.81E-02	1.51
ventrolateral prefrontal cortex	9	1.69	1.07	1.30	4.75	1.44E-03	2.36	3.58E-02	1.57
cerebellar cortex	9	1.09	0.48	1.10	6.78	1.40E-04	2.36	3.58E-02	0.97
primary auditory cortex (core)	8	1.88	0.63	2.11	8.36	6.89E-05	2.83	1.81E-02	1.75
mediodorsal nucleus of thalamus	8	1.19	0.59	1.20	5.70	7.35E-04	2.83	1.81E-02	1.07
posteroventral (inferior) parietal cortex	9	1.42	0.78	1.15	5.47	5.93E-04	2.36	3.58E-02	1.30

Oxytocin-Related Between-Component Connectivity Differences

Analyses of all pairwise comparisons of between-component connectivity differences as a function of oxytocin administration revealed only one pair of components, IC11 and IC21 (Figure 2, panels A and B), whose connectivity was substantially affected by oxytocin ($t(24)$ = 6.99, p = 3.10e-7, effect size d = 1.39) and survived after Bonferroni correction (FWE $p<0.05$) for multiple comparisons. As shown in Fig 2E, all but 2 participants (92%; 23/25) showed evidence of a non-zero oxytocin-related boost in connectivity over the placebo condition (Figure 2, panel E). Within the placebo condition alone, connectivity was not different from 0 ($t(24)$ = -0.86, p = 0.39). However, within the oxytocin condition, connectivity was substantially elevated above 0 ($t(24)$ = 6.22, p = 1.95e-6).

The IC11 component comprised regions in primary auditory cortex, middle and posterior divisions of the insula, superior temporal gyrus, posterior superior temporal sulcus, middle and posterior cingulate cortex, ventromedial prefrontal cortex, amygdala, and superior parietal lobe. These brain regions overlap with areas typically considered important in processes such as language, social-communication, self-referential and social cognition, pain, and emotion (Amodio and Frith, 2006; Hickok and Poeppel, 2007; Friederici, 2012; Wager et al., 2013; Yang et al., 2015). A formal reverse inference was obtained using the decoder function within NeuroSynth, which computes the correlation between the component map and all meta-analytic maps within the NeuroSynth database. Here we found that most of the terms with the highest correlation with IC11 were predominantly terms referring to pain-related, motor-related, or language/speech-related processes (Figure 2, panel C). The IC21 component was comprised entirely of subcortical regions such as the striatum, basal ganglia, amygdala, thalamus, midbrain, and brainstem. These regions, particularly the striatum, midbrain, and amygdala, are typically considered highly involved in reward and emotion-related processes (Kober et al., 2008; Haber and Knutson, 2010; Lindquist et al., 2012). This was confirmed with NeuroSynth decoding showing a predominance of reward, motivation, and affective terms (Figure 2, panel D).

Next, we examined whether individual differences in autistic traits account for variability in oxytocin-related effects on connectivity between these networks. Given prior work suggesting that oxytocin may have its largest effect on individuals who show the most atypical social behavior (Auyeung et al., 2015), we hypothesized that oxytocin may have the largest effects on connectivity in individuals with the highest degree of autistic traits. Here we found evidence confirming this hypothesis, as oxytocin's effect on between-component connectivity appeared to increase with increased degree of autistic traits: r = 0.41, one-tailed $p = 0.0351$ (Figure 2, panel F).

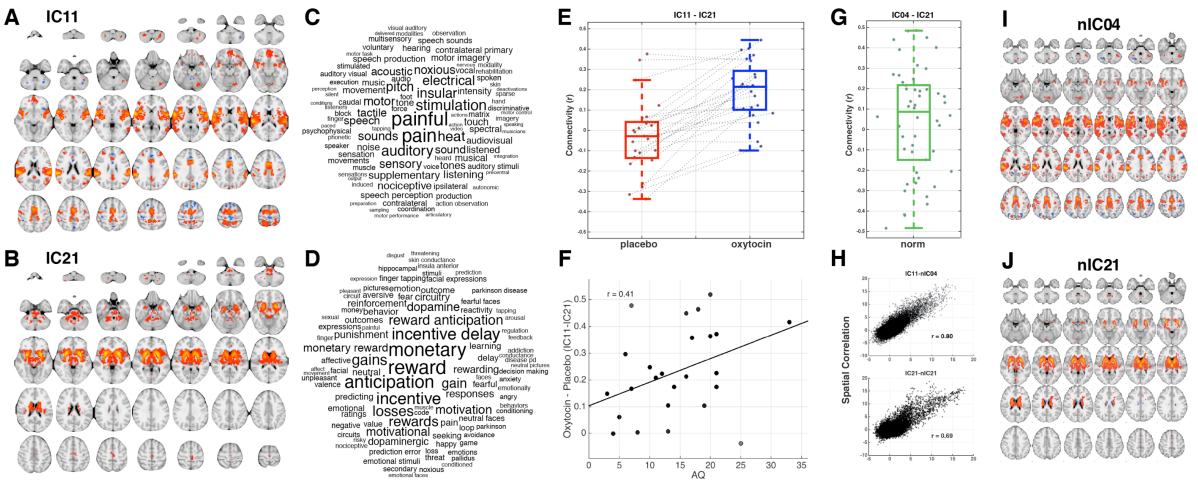

Figure 2: Oxytocin-related enhancement of intrinsic functional connectivity.
Panel A shows the spatial map of component IC11. Voxels are colored by Z-statistics indicating how well each voxel's time series fits the component's time series. **Panel B** shows the same information for component IC21. **Panel C** shows the top 100 terms associated with component IC11 based on NeuroSynth decoding and font size represents relative correlation strength of that term to the component. **Panel D** shows the same information for component IC21. **Panel E** shows connectivity between IC11 and IC21 for each subject during placebo or oxytocin administration. Dots represent individual subjects and the lines connect each individual's data under placebo and oxytocin, with the positive slopes indicating an enhancement of connectivity after oxytocin administration. Underneath the individual-level data are boxplots that indicate the median, interquartile range, and outer fences. Interestingly, the two individuals who would be considered outliers in the placebo condition are the minority of individuals showing no enhancement of connectivity as a function of oxytocin. **Panel F** shows the relationship between oxytocin-related effects on connectivity and continuous variation in autistic traits as measured by the AQ. **Panel G** shows the between component connectivity of between comparable components of the normative dataset. **Panel H** shows the spatial correlation between the oxytocin data components and the two normative components that were selected. **Panels I and J** show the normative components spatial maps.

Finally, we ran further analyses to aid the interpretation of such an effect. One interpretation could be that oxytocin is the primary driver of enhanced connectivity between these components. However, the alternative could be that oxytocin has no effect on connectivity, and that the placebo might somehow induce a decrease in connectivity between these components. To tease apart these different interpretations, we looked to an independent dataset of rsfMRI to ascertain what the normative connectivity strength is between these two components. If oxytocin was truly enhancing connectivity between these components, we would predict that connectivity between these components under normative conditions would be similar to those seen under placebo. That is, normative connectivity effects between these components should manifest similarly to placebo and on average show no difference from 0. We identified two components that spatially appeared nearly identical to the component pair we observed an oxytocin effect in; nIC4 and nIC21 (Figure 2I & 2J). Quantitatively confirming this similarity, we find very large correlations between the spatial component maps of the normative and oxytocin/placebo datasets (nIC4-IC11, $r = 0.80$; nIC21-IC21, $r = 0.69$, see Figure 2H). No other components showed anywhere near such strong correlations (all $r < 0.2$). Similar to our placebo condition, this component-pair showed connectivity that was not significantly different from zero: $t(49) = 1.23$, $p = 0.22$ (Figure 2G). Furthermore,

comparison between normative connectivity and connectivity during placebo revealed no statistical difference (t-test with unequal variance assumed and degrees of freedom estimated using Satterthwaite's approximation; $t(64.6) = -1.507$, $p = 0.1370$). This further clarifies our interpretation that it is indeed the oxytocin condition that drives enhancements in connectivity between these components and that the placebo condition is a good approximation of normative functional connectivity effects within this corticostriatal circuit.

Discussion

This is the first study to investigate how oxytocin affects intrinsic functional organization of the human brain at the level of between-network interactions. We discovered a specific corticostriatal network implicated in social-communicative, motivational, and affective processes that is heavily affected by oxytocin. Under oxytocin the connectivity between these two components was substantially elevated on-average and an oxytocin-related boost was observed in almost all participants. The fact that these corticostriatal connections are not particularly strong under normative conditions and with the administration of placebo, but become increasingly coordinated under oxytocin may be important for understanding how oxytocin influences cognition and behavior. Future work is needed to examine oxytocin-related strengthening of connectivity between these circuits and its effect on specific cognitive and behavioral processes. For example, these corticostriatal connections under pain or social-communication processes may illuminate important brain-behavior links that are affected by oxytocin. These results also illustrate how oxytocin is likely to extend beyond certain brain regions traditionally thought to be important (Meyer-Lindenberg et al., 2011). For example, previous neuroimaging studies in humans have largely focused on amygdala-related effects and to a lesser extent on striatal regions. The current study suggests oxytocin's effects may extend well beyond the amygdala and striatum, and most importantly, may incorporate interactions between subcortical striatal regions with cortical areas.

The degree to which oxytocin enhanced connectivity was also associated with continuous variation in autistic traits, such that those with the highest levels of autistic traits showed the largest oxytocin-related effect on connectivity. These results may point towards the idea that oxytocin may have varying impact on different subsets of individuals. Individuals with the highest levels of autistic traits seem to show the largest oxytocin-related connectivity boost. It will be important to extend these ideas into neuropsychiatric conditions such as autism spectrum conditions (ASC). Oxytocin is hypothesized to be of some potential value therapeutically for autism (Meyer-Lindenberg et al., 2011). However, given the large degree of heterogeneity in ASC (Lai et al., 2013) and the knowledge that therapies may work well for some individuals and not others, it will be of the utmost importance to examine how oxytocin may or may not work well on specific subsets of affected individuals.

Supporting the plausibility of oxytocin-related effects on connectivity between these circuits, we also showed evidence supporting the idea that many of the brain regions involved in both IC11 and IC21 maps show some degree of *OXTR* expression. For instance, it is well known from non-human animal work that the striatum and regions within the midbrain are highly populated with oxytocin receptors (Insel and Shapiro, 1992; King et al., 2015). Here we confirmed such finding with evidence from *OXTR* expression in the brain in human females and furthered a proof-of-concept evidence that oxytocin may leverage this enrichment in *OXTR* to influence neural circuits connected to the striatum. We also discovered that there are modest levels of *OXTR* expression throughout many cortical areas. Given the lack of cortical specificity for *OXTR* enrichment, it remains possible that the

observed connectivity effects with rsfMRI may not necessarily be mediated by direct action of oxytocin on *OXTR* in specific cortical regions. Rather, oxytocin could exert such effects via other indirect routes, perhaps originating in striatal circuitry where there is highly enrichment in *OXTR* or via other mechanisms of action (Bethlehem et al., 2013). Although expression patterns of *OXTR* were not specific to cortical regions it may be that more fine-grained spatial maps of *OXTR* might provide a clearer picture. For example, the development of a PET ligand could certainly further advance our understanding of *OXTR* distribution in-vivo in the human brain.

This study has several novel elements that need to be highlighted. Specifically, this is one of the first studies to focus specifically on oxytocin-related effects in women. There are notable male biases throughout neuroscience and medical research and this bias may explain why studies looking at the effects of drugs tend to miss many adverse effects or show a lack of efficacy when applied to females (Beery and Zucker, 2011; McCarthy et al., 2012). This bias can be observed in much of the prior work on oxytocin in humans as well, with some neuroimaging studies indicating potential differences in the oxytocin system between sexes (Domes et al., 2010; Riem et al., 2012; Rilling et al., 2013; Ebner et al., 2016; Gao et al., 2016). For example, previous studies examining functional connectivity during tasks show enhanced connectivity in women but decreased connectivity in men (Riem et al., 2012; Wittfoth-Schardt et al., 2012). Although our study was not explicitly set to examine sex differences in the effects of oxytocin, future research should focus on how oxytocin may have different effects across males and females.

Second, surpassing much of the existing neuroimaging work on oxytocin, our study is the first to take a whole-brain, unsupervised approach to examine connectivity between neural networks. The small number of studies examining in-vivo oxytocin-related changes to functional connectivity in humans utilized a seed-based connectivity approach. This approach elucidates effects of oxytocin on connectivity with the pre-selected seed region, but is limited by the a priori selection. As we have shown with the modest, albeit lack of specificity of *OXTR* expression across the cortex, much of the prior work is not necessarily informed by this expression pattern. Rather, prior work tends to be heavily directed to regions that are justified based on their role in psychological processes that are linked to oxytocin (e.g., amygdala). In our work, we have taken an unbiased approach to provide insight into oxytocin's effect on corticostriatal connectivity. These circuits might not have been identified with an approach constrained by task-based activation or seed-based connectivity based on this task-related activation.

The highlighted effect places emphasis on striatal interactions with cortical areas that are associated with pain processing. These results are interesting in light of work showing that oxytocin can not only act as an anxiolytic (Churchland and Winkielman, 2012), but can also act as a painkiller (Rash et al., 2013). To our knowledge, there is little neuroimaging work in females focusing on oxytocin and its influence on neural systems for pain processing, as most published work is exclusively on males and/or is focused on empathy for pain (Singer et al., 2008; Bos et al., 2015; Zunhammer et al., 2015; Paloyelis et al., 2016). Similar to oxytocin research, research on pain has traditionally been heavily male biased (Zagni et al., 2016), while women tend to suffer more from acute and chronic pain (Mogil, 2012). Our results suggest that future work is needed in this area, particularly on oxytocin's effect on pain and how such corticostriatal networks may be involved.

There are some caveats and limitations to keep in mind. First, the sample size is moderate and potentially provides low power to detect small effects. However, our multi-echo fMRI approach is a strength that could help counteract issues associated with statistical power. Multi-echo EPI acquisition and the ME-ICA denoising technique employed here is known to greatly enhance temporal signal-to-noise ratio (tSNR) and allow for enhanced ability to reduce false positives (Kundu et al., 2013). These enhancements tied to principled elimination of non-BOLD noise in rsfMRI could be beneficial for power because reduction in noise potentially increases observable effect sizes (Lombardo et al., 2016), and reduce effect size estimates for false positive effects. Future work collecting larger samples to replicate and extend these findings would be facilitated by characterizing individuals in continuous variation in autistic traits. Our study indicates that oxytocin-related effects tend to be stronger in individuals with more autistic traits. As noted in the points about sex and gender, future work should also examine whether similar or different effects are present in males. It would also be important to further extend this work in clinically diagnosed individuals with autism. The correlation with autistic traits may suggest that oxytocin could facilitate corticostriatal connectivity in clinically diagnosed patients. If such a relationship extends into the clinically diagnosed population of the autism spectrum, we may expect to see that oxytocin provides the largest enhancements to the most affected individuals (Auyeung et al., 2015).

In conclusion, we have discovered that oxytocin enhances corticostriatal connectivity in women. These corticostriatal networks play roles in social-communicative, motivational, and affective processes and the results may be particularly important for understanding how oxytocin changes neurodynamics that may be relevant for many neuropsychiatric conditions with deficits in those domains and neural circuits. Future work examining these effects in males as well as clinically diagnosed samples will be important, as will be the examination of what subsets of individuals may benefit most from oxytocin-related changes in between-network connectivity.

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Conflict of Interest

All authors declare no conflict of interest.

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