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Sex Differences in Associations of Arginine Vasopressin and Oxytocin With Resting-State Functional Brain Connectivity

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Oxytocin (OT) and arginine vasopressin (AVP) exert robust and sexually dimorphic influences on cognition and emotion. How these hormones regulate relevant functional brain systems is not well understood. OT and AVP serum concentrations were assayed in 60 healthy individuals (36 women). Brain functional networks assessed with resting-state functional magnetic resonance imaging (rs-fMRI) were constructed with graph theory–based approaches that characterize brain networks as connected nodes. Sex differences were demonstrated in rs-fMRI. Men showed higher nodal degree (connectedness) and efficiency (information propagation capacity) in left inferior

SIGNIFICANCE:

Oxytocin and arginine vasopressin are hormones that contribute to sex differences in brain systems supporting emotion and cognition. We examined sex differences in the association between these hormones and functional brain connectivity. Findings suggest that different hormones modulate brain systems supporting emotion processing in men and women and may account for well-established sex differences in verbal and visuospatial abilities.

L.H. Rubin and L. Yao contributed equally to this work.

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frontal gyrus (IFG) and bilateral superior temporal gyrus (STG) and higher nodal degree in left rolandic operculum. Women showed higher nodal betweenness (being part of paths between nodes) in right putamen and left inferior parietal gyrus (IPG). Higher hormone levels were associated with less intrinsic connectivity. In men, higher AVP was associated with lower nodal degree and efficiency in left IFG (pars orbitalis) and left STG and less efficiency in left IFG (pars triangularis). In women, higher AVP was associated with lower betweenness in left IPG, and higher OT was associated with lower nodal degree in left IFG (pars orbitalis). Hormones differentially correlate with brain networks that are important for emotion processing and cognition in men and women. AVP in men and OT in women may regulate orbital frontal cortex connectivity, which is important in emotion processing. Hormone associations with STG and pars triangularis in men and parietal cortex in women may account for well-established sex differences in verbal and visuospatial abilities, respectively.

Key words: sex differences; oxytocin; vasopressin; resting state; brain function

Sex differences in emotion processing and cognitive functioning are well documented. For instance, women are more emotionally perceptive and reactive to emotional stimuli and show enhanced emotional memory compared with men (Gur and Gur, 2002; Cahill, 2003; Whittle et al., 2011; Stevens and Hamann, 2012). Additionally, women excel at verbal abilities, whereas men excel at visuospatial abilities (Voyer et al., 1995; Kimura, 1999; de Frias et al., 2006; Andreano and Cahill, 2009; Gur and Gur, 2013). Meta-analyses show that structural and functional neuroimaging data parallel these behavioral sex differences. Sex differences in human brain morphology (Ruigrok et al., 2014) and in activation during behavioral tasks are apparent in networks related to emotion processing, language, and visuospatial abilities. Sex differences in emotion processing typically include differential activation of prefrontal, temporal, and limbic brain regions (Stevens and Hamann, 2012; Sacher et al., 2013). With respect to language, the most common areas showing sex differences are in the prefrontal (inferior frontal gyrus) and temporal (superior temporal gyrus) regions, whereas, for visuospatial abilities, differences are most often demonstrated in posterior parietal cortex (Costafreda et al., 2006; Wagner et al., 2014; Tomasino and Gremese, 2015). These sex differences may, in part, reflect the effects of sex steroid hormones on brain function.

Two sexually dimorphic neurohormones, oxytocin (OT) and arginine vasopressin (AVP), are believed to contribute to sex differences in brain functioning, particularly in regions supporting emotion and cognition. OT, including measurements of basal hormones in plasma, is associated with better emotion processing and worse cognition, whereas AVP is associated with increased emotional reactivity and better cognitive function (Carter et al., 2008; Heinrichs and Domes, 2008; Meyer-Lindenberg et al., 2011; Rubin et al., 2011, 2014). Effects of OT and AVP are impacted by biological sex (Carter, 2007; Carter et al., 2009) because endogenous peptides activate their receptors with cascading downstream effects. In men, OT reduces amygdala activation in response to emotional face processing and perception of threatening situations (Kirsch et al., 2005; Domes et al., 2007; Petrovic et al., 2008; Singer et al., 2008), whereas the converse is seen in women (Domes et al., 2010; Lischke et al., 2012). OT administration also influences intrinsic brain connectivity in men, with unknown effects in women. For men, OT is reported to reduce amygdala–precuneus connectivity (Kumar et al., 2015) or to enhance amygdala–prefrontal connectivity (Sripada et al., 2013). AVP administration effects are also sex dependent, with AVP having opposite effects on temporal-limbic and insular activity during cooperative interactions, with increased activation in men (Lee et al., 2013; Rilling et al., 2014) and decreased activation in women (Rilling et al., 2014). It is important to note that previous studies have focused on the consequences of exogenous peptide administration on regional brain activity and behavior rather than examining relations between resting-state physiological levels of these hormones and their relation to brain physiology.

OT and AVP may have sex-dependent associations with cognitive and emotion brain networks, particularly in those showing sex differences (Sacher et al., 2013; Hjelmervik et al., 2014). To the best of our knowledge, no study has examined associations between these peripheral hormones and functional brain connectivity. Therefore, we examine sex differences in functional brain networks and then assess the relationships of functional connectivity in sex-dependent brain regions with peripheral levels of OT and AVP. Functional brain networks are characterized with graph theory methods (Rubinov and Sporns, 2010), which consider brain networks as connected nodes. We predict that basal levels of OT and AVP are associated with functional connectivity of sex-dependent brain networks important for cognition and emotion processing.

MATERIALS AND METHODS

Participants

The current study was approved by the University of Illinois at Chicago Institutional Review Board, and all participants provided written informed consent. Participants included 60 healthy individuals (24 men and 36 women) between the ages of 16 and 60 years (Table I). Seven of the 36 women reported using oral contraceptives. All participants were screened with the Structured Clinical Interviews for DSM-IV (Nonpatient Edition) to rule out current or past psychiatric illness. Exclusion criteria included history of head injury, pregnant or lactating (for women), positive urine toxicology screen for common drugs of abuse on the day of scanning, diagnosis of substance abuse in the past 30 days or substance dependence in the past 6 months, history of systemic medical or neurological disorder

TABLE I. Demographic Characteristics, Hormone Levels, and Cognitive Data as a Function of Sex

Variable	Men (n = 24)	Women (n = 36)	*P* value
Demographics; mean (SD)			
Age in years	36.96 (12.03)	34.67 (12.11)	0.47
Education in years	14.38 (2.75)	15.47 (2.65)	0.13
WRAT* reading	103.48 (9.71)	107.74 (13.00)	0.18
Race (%)			0.38
Caucasian	12 (50)	22 (61)	
African-American	10 (42)	9 (25)	
Other	2 (8)	5 (14)	
Handedness (%)	20 (83)	33 (92)	0.33
Blood drawn before noon (%)	23 (95)	36 (100)	0.20
Hormone levels in pg/ml (SD)			
Mean log OT	6.10 (0.66)	6.15 (0.89)	0.83
Mean log AVP	4.36 (0.65)	4.53 (0.51)	0.29
Emotion and cognitive outcomes; mean (SD)			
Emotion recognition	80.88 (8.93)	84.99 (5.54)	0.03
Verbal learning	42.27 (8.36)	50.30 (8.63)	0.001
Verbal fluency	51.73 (13.51)	55.86 (11.41)	0.21
Processing speed	56.64 (13.88)	62.11 (10.88)	0.10

*Wide Range Achievement Test-IV, reading subtest.

affecting mood or cognition, and age-corrected Wide-Range Achievement Test reading test standard score ≥65. Anatomic images were inspected by an experienced neuroradiologist, and no gross abnormalities were observed for any subject.

Serum Hormone Assays

Blood samples were drawn in the morning when possible (98% blood draws before noon). Samples were stored in plain tubes, spun at 4 °C, divided into 300-μl aliquots, and stored at –80 °C. Samples were batched, diluted in an assay buffer to give reliable results within the linear portion of the standard curve (OT 1:4, AVP 1:2), and completed in duplicate with unextracted plasma. OT and AVP were quantified with an EIA kit (Enzo Life Sciences/Assay Designs; Carter et al., 2007). These ELISA immunoassays are highly sensitive (minimal detection levels < 12 pg/ml OT, 4 pg/ml AVP) and specific, with cross-reactivity between OT and AVP <0.04%. Samples were batched and assayed simultaneously, blind to subject information. The laboratory selected OT values >2,000 pg/ml and AVP values >400 pg/ml to be rerun to confirm sample accuracy. This was the case for only one participant's OT levels. There were no participants with AVP values >400 pg/ml. Intra-assay coefficients of variation were less than 10.3% for both assays. Hormone values were log transformed for statistical analysis. Age was not associated with hormone levels ($r < 0.20$).

Emotion Processing and Cognition

From the Brief Assessment of Cognition in Schizophrenia neuropsychological test battery, we selected three subtests, verbal learning (total words recalled across five trials), verbal fluency (total words generated across categories [animals] and letters [F, S]), and processing speed (symbol coding). The Penn Emotion Recognition Test assessed the ability to recognize facial emotions accurately (Gur et al., 2002). The tests were selected based on previous research indicating that the tests demonstrate sex differences among the general population (Kramer et al., 1988, 1997; Mann et al., 1990; Weiss et al., 2003, 2006; Williams et al., 2009) or whether tests (verbal learning, processing speed) showed a sex difference in favor of women ($P < 0.01$) in the large sample of healthy controls from the Bipolar and Schizophrenia Network on Intermediate Phenotypes study (n = 304, 55% women), from which the current sample was recruited (subjects from the Chicago site).

Resting-State Data Acquisition

Participants underwent 5 min of scanning with a GE Signa EXCITE 3.0-T MR imaging system and an eight-channel phased-array head coil. Participants fixed on a central crosshair for the duration of the scan. Video monitoring of participants eyes confirmed adherence to this instruction. Soft ear plugs were used to reduce scan noise, and head motion was minimized with head cushions. Echo-planar imaging sensitive to changes in blood oxygen level–dependent signals (repetition time 1,775 msec, echo time 27 msec, flip angle 60°) were obtained. The slice thickness was 4 mm (1-mm gap) with a matrix size of 64 × 64 and a field of view of 220 × 220 mm^2, resulting in a voxel size of 3.44 × 3.44 × 5 mm^3. Each brain volume comprised 29 axial slices, and each functional run contained 210 image volumes.

Data Processing and Network Construction

Image processing and connectivity network construction for each subject followed those of our prior work (see Zhang et al., 2011). Briefly, the resting-state image time series preprocessing was carried out in statistical parametric mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm), including slice-time correction, realignment, unwrapping, normalization to Montreal Neurological Institute space, resampling to 3 × 3 × 3 mm^3, and bandpass filtering (0.01–0.08 Hz). Head motion artifacts were reduced with a 24-parameter autoregressive model (Friston et al., 1996; Satterthwaite et al., 2013; Yan et al., 2013), and white matter and cerebrospinal fluid signals were regressed out. Head Movement was < 2.2 mm translation and <2° rotation. No significant sex differences were found with respect to head translation or rotation (both $P > 0.05$).

Brain functional networks consisting of nodes connected by edges (defined below) were constructed from each participant's preprocessed time series. This was performed with graph theoretical approaches in the Brain Connectivity Toolbox (http://www.brain-connectivity-toolbox.net; Rubinov and Sporns, 2010), an approach that is well established and reliable (Power et al., 2010; Wig et al., 2011; Welton et al., 2015). Nodes were defined as the 90 noncerebellar regions of the automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002). For each subject, the time series of voxels in each node was averaged and then correlated with each other node's average time series, creating a 90 × 90 correlation matrix for each subject that reflects interregional functional connectivity strength. These node-to-node correlations represent the initial edges in the network. Networks were then pruned by dropping any edge (correlation) that did not meet statistical significance ($P < 0.05$, uncorrected).

To estimate network connectivity properties for group analyses, we applied a range of cost thresholds to the pruned networks (Watts and Strogatz, 1998). Cost was defined as the total number of edges divided by the maximum possible number of edges. Instead of selecting a single threshold, we selected a wide range of cost thresholds for the 90 nodes according to the following criteria: 1) the averaged degree (number of edges linked to the node) over all nodes of each thresholded network was greater than $2 \times \log(N)$, where $N = 90$ (number of maximum possible nodes); 2) the largest size of each individual network was greater than 80 nodes; and 3) the small worldness of the thresholded networks was greater than 1.1; e.g., clustering properties of nodes (connectedness among them) were greater than those of a randomly generated network (Watts and Strogatz, 1998). From the criteria discussed above, the network analysis was performed against random network models generated in the small-world interval of $0.12 \leq \text{cost} \leq 0.49$, with step = 0.01.

We calculated nodal network measurements at each cost threshold for each subject and then calculated the area under the curve (AUC) as the value for that network measure for each subject in group comparisons and correlations with hormone levels. AUC of network metrics over a cost threshold range has been found to be sensitive to group differences (Onnela et al., 2005; Achard and Bullmore, 2007). Regional measures per node were nodal degree (number of edges a node has connected to it), nodal efficiency (how quickly information flows between it and other nodes), and nodal betweenness (importance of a node via how many short paths between nodes of which it is part). Mathematical descriptions of network measures are the following.

Nodal degree. The nodal degree quantifies the extent to which a node is relevant to the graph (Rubinov and Sporns, 2010). In a network, G, the nodal weighed degree, S_i^w, is measured as the sum of the weights of all the connections of node *i*; that is

$$S_i^w = \sum_{j \in N} w_{ij}$$

Nodal efficiency. The nodal weighed efficiency of a given node, $i(i(E_i^w))$, is defined as the inverse of the mean harmonic shortest path length between this node and all other nodes in network G (Achard and Bullmore, 2007) according to the formula

$$E_i^w = \frac{1}{N-1} \sum_{i - \neq j \in N} \frac{1}{L_{ij}}.$$

Nodal efficiency measures the information propagation ability of a node within the network; the node *i* is more important if the value of E_i^w is higher.

Nodal betweenness. The betweenness centrality B_i^w of a node, *I*, considers the fraction of all shortest paths in the network that pass through the node (Freeman, 1977).

Statistical Analysis

We examined sex differences in network metrics using nonparametric permutation tests (Bullmore et al., 1999). Statistical significance was set at $P < 0.01$, Bonferroni corrected. Brain regions showing significant sex differences in nodal metrics were then correlated with peripheral hormone levels for each sex to assess both brain connectivity–hormone associations and brain connectivity–behavioral performance associations. Although age has been shown to be associated with functional brain network connectivity in previous studies (Biswal et al., 2010), age was not correlated with our extracted resting-state metrics in our study of primarily midlife adults ($r < 0.17$) and, thus, was not used as a covariate in our hormone–resting state correlations. Given that this is the first exploratory study to examine these associations, statistical significance was set at $P < 0.05$, uncorrected.

RESULTS

Sex Differences in Network Metrics

Compared with women, men showed higher nodal degree and nodal efficiency in left inferior frontal gyrus (IFG; pars orbitalis and pars triangularis) and bilateral superior temporal gyrus (STG) as well as higher nodal degree in left rolandic operculum. In comparison, women showed higher nodal betweenness in right putamen and left inferior parietal gyrus (IPG; $P < 0.01$, Bonferroni corrected; Fig. 1, Table II). Notably, pars triangularis and STG are important for verbal/language processes, pars orbitalis is important for emotion processing, and IPG is important for spatial processing.

Relationships Between Hormones and Network Measures

Nodal network indices showing significant sex differences in a brain region were correlated with peripheral hormone measures stratified by sex. In men, higher AVP was associated with lower nodal degree and lower nodal efficiency in left IFG (pars orbitalis) and left STG and lower nodal efficiency in left IFG (pars triangularis; $P < 0.05$; Fig. 1). In women, higher AVP was associated with lower betweenness in left IPG, and higher OT was associated with lower nodal degree in left IFG (pars orbitalis; $P < 0.05$; Fig. 1). No significant associations were found between AVP and nodal degree and efficiency in frontal or temporal regions for women. Similarly, for men, there was no association between OT and betweenness in parietal or frontal areas.

Next, we explored associations between hormone levels and nodal metrics stratified by sex in regions not showing sex differences in regional nodal metrics. In men, higher AVP was associated with lower nodal degree and efficiency in widespread brain regions, including regions in frontal (e.g., IFG, superior and middle frontal gyri), temporal (e.g., hippocampus, middle and superior temporal gyri), and occipital (e.g., superior, middle, and inferior occipital gyri) cortices. In women, fewer correlations between AVP and nodal metrics were observed,

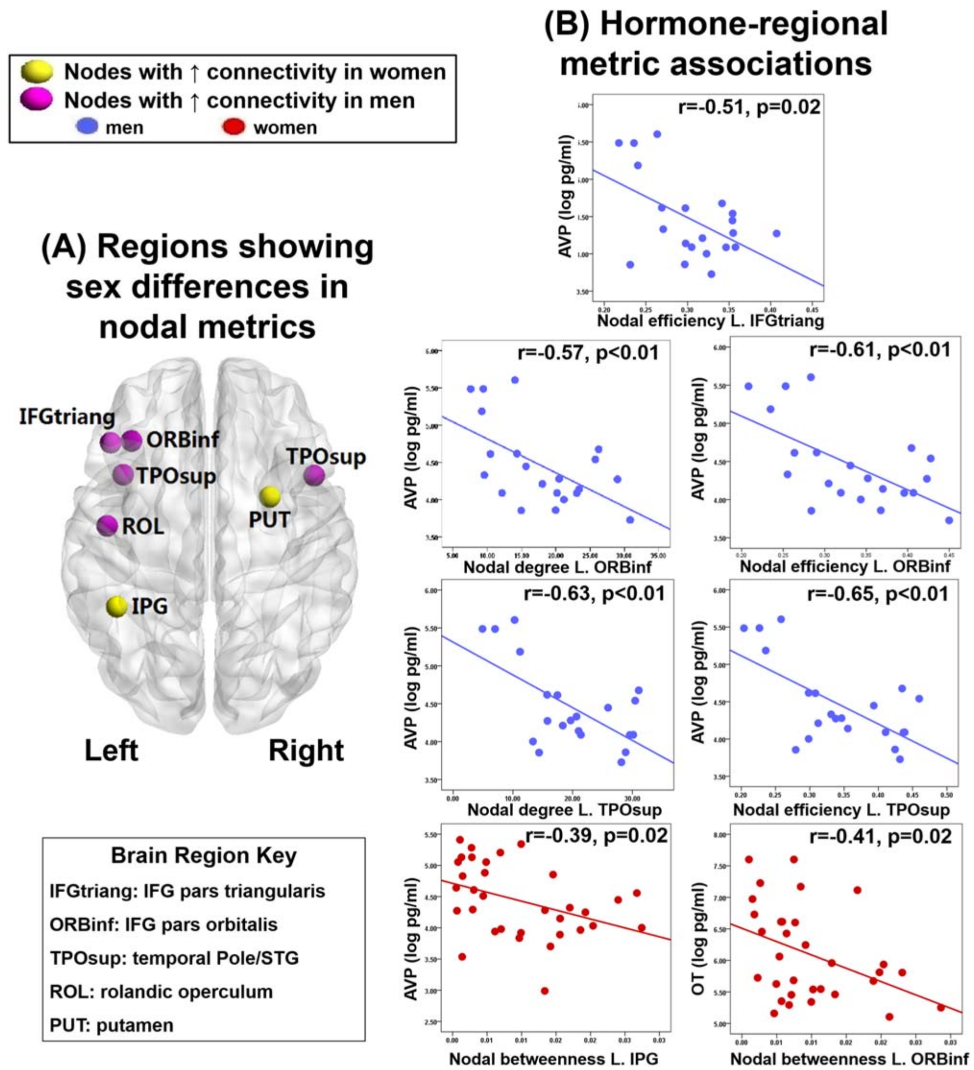

Fig. 1. **A**: Differences in nodal metrics between men and women. **B**: Significant correlations of the metrics in those brain regions shown in A with AVP and OT. Red and blue scatterplots represent men and women, respectively. Brain image is a ventral view.

TABLE II. Comparison of Nodal Network Metrics Between Men and Women

	P value		
Brain region	Nodal degree	Nodal efficiency	Nodal betweenness
Men > women			
L* inferior frontal gyrus (pars orbitalis)	0.001‡	0.004‡	0.050
R† temporal pole: superior temporal gyrus	0.004‡	0.009‡	0.043
L temporal pole: superior temporal gyrus	0.004‡	0.009‡	0.097
L inferior frontal gyrus (pars triangularis)	0.008‡	0.006‡	0.050
L rolandic operculum	0.008‡	0.017	0.321
Women > men			
L inferior parietal gyrus	0.455	0.304	0.005‡
R putamen	0.065	0.084	0.002‡

*Left.
†Right.
‡Regions showing significant differences between healthy men and women ($P < 0.01$, Bonferroni corrected) in at least one of the three nodal centralities.

TABLE III. Brain Regions Correlating With Peripheral AVP Levels in Men and Women

	Men *r* value				Women *r* value		
Brain region	Nodal degree	Nodal efficiency	Nodal betweenness	Brain region	Nodal degree	Nodal efficiency	Nodal betweenness
L⋆ precentral gyrus	−0.48‡	−0.55‡		L lingual gyrus	0.37‡		
R† middle frontal gyrus, orbital part	−0.46‡			R middle occipital gyrus		0.38‡	
L inferior frontal gyrus, pars orbitalis	0.57⋆‡	−0.61§		R postcentral gyrus		0.36‡	
L anterior cingulate gyri	−0.47‡	−0.67§		R pallidum		0.40‡	
L median cingulate gyri	−0.46‡	−0.50‡		R thalamus		0.38‡	
R median cingulate gyri	−0.47‡	−0.51‡		L median cingulate gyri			0.51§
L superior temporal gyrus	−0.54‡	−0.55‡		R median cingulate gyri			0.36‡
R superior temporal gyrus	−0.45‡	−0.49‡		L fusiform gyrus			0.51§
L superior temporal gyrus, temporal pole	0.63§	−0.65§		L inferior parietal gyrus			−0.39‡
L middle temporal gyrus	0.64§	−0.65§		L inferior temporal gyrus			−0.36‡
R middle temporal gyrus	−0.44‡	−0.52‡					
R inferior temporal gyrus	−0.44‡	−0.53‡					
R precentral gyrus		−0.48‡					
L superior frontal gyrus, dorsolateral		−0.47‡					
L inferior frontal gyrus, pars opercularis		−0.47‡					
L inferior frontal gyrus, pars triangularis		−0.51‡					
R inferior frontal gyrus, pars orbitalis		−0.51‡					
L rolandic operculum		−0.49‡					
L supplementary motor area		−0.47‡					
R supplementary motor area		−0.50‡					
L superior frontal gyrus, medial		−0.44‡					
L insula		−0.52‡					
R anterior cingulate gyri		−0.56§					
R hippocampus		−0.49‡					
L calarine fissure		−0.49‡					
R calarine fissure		−0.54‡					
L cuneus		−0.44‡					
R cuneus		−0.51‡					
L lingual		−0.51‡					
R lingual		−0.51‡					
L superior occipital gyrus		−0.53‡					
R superior occipital gyrus		−0.57§					
L middle occipital gyrus		−0.48‡					
R middle occipital gyrus		−0.55‡					
L inferior occipital gyrus		−0.51‡					
R inferior occipital gyrus		−0.52‡					
L fusiform gyrus		−0.45‡					
R postcentral gyrus		−0.49‡					
L superior parietal gyrus		−0.52‡					
R superior parietal gyrus		−0.53‡					
L Heschl's gyrus		−0.52‡					
L middle temporal gyrus, temporal pole		−0.52‡					
L inferior temporal gyrus		−0.50‡					

⋆Left.
†Right.
‡$P < 0.05$.
§$P < 0.01$

especially in nodal efficiency (Table III). To supplement this result of a high number of nodal metrics in men correlating with AVP, we evaluated AVP correlations with global efficiency, a summary network efficiency measure across the brain. Efficiency is a relevant metric to describe the brain networks from the perspective of information flow across nodes (Latora and Marchiori, 2001). For a network G with N nodes, the global efficiency can be computed as

$$E_{glob} = \frac{1}{N(N-1)} \sum_{i-\neq j \in G} \frac{1}{L_{ij}},$$

where L_{ij} is the shortest weighed path length between nodes i and j in network G. As expected, higher AVP was associated with lower global efficiency only in men ($r = -0.50$, $P = 0.01$). OT was associated with activity in few brain nodes, and sex differences in OT-related nodal metrics were not as evident as the AVP-related nodal metrics (Table IV).

Relationships Between Network Measures and Behavioral Performance

In men, higher nodal degree and higher nodal efficiency in left IFG (pars orbitalis) and higher nodal efficiency in left IFG (pars triangularis) were associated with better verbal fluency ($r = 0.47$, $P = 0.02$; $r = 0.43$, $P = 0.04$; $r = 0.44$, $P = 0.03$, respectively). In women, higher nodal efficiency in left IFG (pars orbitalis) was associated with better verbal learning ($r = 0.54$, $P = 0.001$) and verbal fluency ($r = 0.38$, $P = 0.02$). However, higher betweenness in left IPG was associated with worse emotion recognition ($r = -0.40$, $P = 0.02$).

Relationships Between Hormones and Behavioral Performance

In women, OT was significantly associated with emotion recognition ($r = 0.42$, $P = 0.02$). There were no other significant or near-significant hormone–behavior associations in men or women. However, we note that associations between OT and emotion recognition ($r = 0.37$, $P = 0.12$), OT and verbal learning ($r = 0.36$, $P = 0.14$), AVP and processing speed ($r = -0.38$, $P = 0.10$), and AVP and verbal fluency ($r = -0.34$, $P = 0.15$) in men were observed.

DISCUSSION

In this investigation, using a graph theory analytic approach to investigate hormonal associations with resting-state brain function, we found sex differences in functional brain networks important for emotion and cognitive processing. Our findings suggest a differential role of OT and AVP in these complex brain networks important in emotion processing and cognition between men and women.

Sex Differences in Regional Functional Brain Networks

In the present study, left orbital cortex and bilateral superior temporal cortex, neocortical regions central in emotion and language processing, were more connected and efficient in men than in women. Right putamen and left inferior parietal cortex, central to visuospatial abilities, had higher betweenness values for women compared with men, indicating greater network integration of these regions. The regional brain network differences found here are in line with findings from previous structural and functional neuroimaging studies (Frederikse et al., 1999; Goldstein et al., 2001; Biswal et al., 2010; Stevens and Hamann, 2012; Sacher et al., 2013; Ruigrok et al., 2014; Wagner et al., 2014; Tomasino and Gremese, 2015). However, we did not find sex differences in connectivity of corticolimbic circuitry, including amygdala, insula, anterior and posterior cingulate, and dorsolateral and medial prefrontal cortices, which are also important for emotion and cognitive processing (Bluhm et al., 2008; Liu et al., 2009; Biswal et al., 2010; Kong et al., 2010; Zuo et al., 2010; Allen et al., 2011; Filippi et al., 2013). Although the directionality of our findings in the superior temporal and parietal cortex is in line with previous studies (Biswal et al., 2010; Filippi et al., 2013; Hjelmervik et al., 2014), there is less consistency with respect to the orbital cortex. Whereas we and others report greater connectivity in men compared with women (Allen et al., 2011; Kong et al., 2010), still others report the converse (Bluhm et al., 2008; Biswal et al., 2010; Hjelmervik et al., 2014) or no differences (Weissman-Fogel et al., 2010).

Sex Differences in Hormone Associations With Regional Functional Brain Networks

The correlations between hormones and network metrics indicate that higher levels of both OT and AVP were associated with reductions in network connectivity. This is noteworthy because hormone-related connectivity reductions in each sex were in areas in which that sex had overall *higher* connectivity. Thus, AVP and OT may function by dampening connectivity of regions in which connectivity was elevated in each sex, with different hormones serving that function in men and women. Higher levels of AVP were generally associated with decreased connectedness and efficiency of connections across the brain for men; this pattern was not seen overall for women's network metrics and AVP levels. OT associations were fewer but more frequently observed in women. These findings are in line with previous neuroendocrine studies in animal models, suggesting that males are more sensitive to AVP than females (Carter, 2007; Carter et al., 2009).

Sex Differences in Hormonal Associations With Emotion Processing

Our findings in the left IFG (pars orbitalis) highlight different profiles of hormone associations with functional brain connectivity in men and women. This region exerts prominent top-down regulation of limbic regions, including the amygdala (Ochsner et al., 2004), and, thus, the hormonal–neural activity may play a role in sex differences in emotion processing and reactivity. Whereas AVP was negatively associated with functional connectivity of left orbital cortex in men, OT was negatively associated in women. With respect to AVP, our findings are, in

TABLE IV. Brain Regions Correlating With Peripheral OT Levels in Men and Women

	Men *r* value				Women *r* value		
Brain region	Nodal degree	Nodal efficiency	Nodal betweenness	Brain region	Nodal degree	Nodal efficiency	Nodal betweenness
R* superior frontal gyrus, orbital part	$0.47^{\ddagger}$			L middle temporal gyrus	$-0.41^{\ddagger}$	$-0.37^{\ddagger}$	
R Heschl's gyrus	$0.49^{\ddagger}$			temporal pole			
L† inferior frontal gyrus, pars opercularis			$-0.47^{\ddagger}$	L precentral gyrus			$0.39^{\ddagger}$
L insula			$-0.52^{\ddagger}$	L inferior frontal gyrus			$-0.41^{\ddagger}$
R anterior cingulate gyri			$-0.46^{\ddagger}$	pars orbitalis			
R superior occipital gyrus			$-0.46^{\ddagger}$				
R angular gyrus			$-0.56^{\S}$				
L caudate nucleus			$0.48^{\ddagger}$				
R thalamus			$-0.51^{\ddagger}$				

*Right.
†Left.
$^{\ddagger}P < 0.05$.
$^{\S}P < 0.01$.

part, in line with previous functional imaging studies. Previous studies have shown sex-specific associations between plasma AVP levels and neural activity during the processing of negative emotions; however, associations are with the amygdala and not with the prefrontal cortex (Motoki et al., 2016). Additionally, exogenous AVP increases amygdala–prefrontal connectivity during emotion processing in men (Zink et al., 2010). Although the exact underlying factors driving these differences are unknown, one possibility for the findings in men is that higher AVP, which is in part androgen dependent (De Vries and Panzica, 2006), may modulate activity in orbital frontal cortex and thereby influence emotional reactivity and activity in limbic regions. Consistent with this hypothesis, male rodents show higher AVPR1a receptor density in the medial prefrontal cortex compared with females (Smeltzer et al., 2006). Males have more androgen receptors than females in the paraventricular nucleus of the hypothalamus (Fernandez-Guasti et al., 2000), which is the major site of synthesis of AVP. In humans, androgen relationships with AVP could contribute to greater emotional reactivity in men because AVP is associated with amplifying reactivity to stressors and increasing behavioral or emotional reactivity (Carter et al., 2008; Heinrichs and Domes, 2008; Meyer-Lindenberg et al., 2011).

In contrast to men, higher levels of OT in women were associated with decreased connectivity in the IFG and better emotion recognition. These findings are in line with some previous neuroimaging studies. Whereas plasma levels of OT were not found to be associated with brain activation during the processing of negative emotions in men or women (Motoki et al., 2016), there are sex-dependent associations between exogenous OT and amygdala–prefrontal connectivity (Ebner et al., 2016). In particular, exogenous OT has robust effects on amygdala–prefrontal connectivity among young women, with no effects in young men. OT receptor binding can be comparatively sparse in socially monogamous primates (Freeman et al., 2014), and females have higher densities of OT receptors than males in the medial prefrontal cortex (Smeltzer et al., 2006). Such findings may in part explain the capacity of chronic exposure to OT to dampen emotional reactivity and suggest that the mechanism for this effect may be its impact on reducing functional connectivity among targeted brain regions with sharing circuit-level integration.

Sex Differences in Brain Substrates of Cognition

Our findings, particularly with the left IFG (pars triangularis), STG, and IPG, suggest that OT and AVP may modify brain physiology in ways that contribute to sex differences in cognitive abilities, given that these regions support verbal and visuospatial abilities, respectively. In men, higher AVP was associated with less connectedness and efficiency in left IFG (pars triangularis) and left STG, two important regions for verbal abilities (Costafreda et al., 2006; Wagner et al., 2014; Wang et al., 2014). In line with this, higher connectedness and efficiency in left pars triangularis was associated with better verbal fluency in men. Thus, AVP levels may in part explain why on average men perform worse than women on verbal abilities, particularly verbal fluency. Although not significant, higher AVP was trending toward relating to worse performance on verbal abilities in men. However, in women, higher AVP was associated with lower efficiency in the left parietal cortex, which is important for visuospatial abilities (Tomasino and Gremese, 2015). Consequently, AVP levels may, in part, explain why women, on average, perform worse than men on visuospatial abilities. However, it is important to note that, because higher levels of hormones were associated with lowered connectivity, which overall was increased in men or women, it remains to be determined in future experimental studies whether hormones were partially compensating for heightened functional connectivity to enhance adaptive neural function.

Limitations

The present study has limitations, beginning with the cross-sectional study design and a single measurement of hormone levels. Second, we measured peripheral hormone levels of OT and AVP. However, animal data indicate that central and peripheral hormone levels are correlated (Landgraf and Neumann, 2004), and peripheral measures of OT are strongly associated with neural activation in response to animacy in humans (Lancaster et al., 2015). Third, choices in methodology of network construction, including anatomical parsing scheme and network construction and pruning, may have impacted our findings. The choices made were similar to those in prior work, but there is a range of approaches for assessing neural connectivity. Fourth, we did not control for parity, menopausal stage, endogenous hormone cycling (menstrual cycle), or exogenous hormone administration (e.g., oral contraceptive pills). Some (Petersen et al., 2014) but not all (Hjelmervik et al., 2014) studies have demonstrated the effects of sex steroid hormones on brain connectivity. However, in the present study, only a small proportion of women was on oral contraceptives. Finally, a more thorough behavioral association of emotional reactivity and sexually dimorphic cognitive abilities, particularly tasks typically showing a male advantage (visuospatial abilities), may enhance the detection of associations among network measures, hormones, and behavior.

CONCLUSIONS

Understanding the interplay among biological sex, hormones, and neural networks serves as a foundation on which to model the mechanisms of behavioral and cognitive differences between males and females. This is fundamentally important, and it has applied implications, given that alterations in hormones and neural systems may underlie differences between males and females in psychological manifestations of psychiatric disorders (Ross and Pearlson, 1996; Goldstein, 2002). There are sex differences in intrinsic brain activity, particularly in regions important in emotion processing and cognition, including prefrontal, temporal, and parietal regions. Our data suggest that OT and AVP may modify brain physiology in these regions to contribute to or to diminish these differences rather than to increase them. Notably, our findings suggest a differential role of OT and AVP in these complex brain networks that are important in emotion processing and cognition in men and women.

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CONFLICT OF INTEREST STATEMENT

J.R.B. has served as an advisory board member for Physician Choice Laboratory Services. J.A.S. has consulted for Eli Lilly, Roche, and Takeda. The other authors have nothing to disclose.

ROLE OF AUTHORS

LHR and JAS conceived the neuroendocrine study idea. JAS coordinated the Chicago B-SNIP study, and the sample presented here was ascertained as part of the B-SNIP study at the Chicago site. LHR, LY, SL, CSC, LLD, JAS, and SKK wrote the first draft of the manuscript. LHR and LY take responsibility for the integrity of the hormone data and the MRI data analyses, respectively. LY, SL, WL, and G-JJ planned and conducted the graph theory-based connectivity analyses. JAS provided oversight as principle investigator of the study. CSC developed the methodology to examine oxytocin and vasopressin, and assays were performed in her laboratory by HP-N and LLD. JRB collected and managed the biological samples. All authors contributed to the writing of the manuscript and approved the final version of the article.

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