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Relationship of a common *OXTR* gene variant to brain structure and default mode network function in healthy humans

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Abstract

A large body of research suggests that oxytocin receptor (*OXTR*) gene polymorphisms may influence both social behaviors and psychiatric conditions related to social deficits, such as autism spectrum disorders (ASDs), schizophrenia, and mood and anxiety disorders. However, the neural mechanism underlying these associations is still unclear. Relative to controls, patients with these psychiatric conditions show differences in brain structure, and in resting state fMRI (rs-fMRI) signal synchronicity among default mode network (DMN) regions (also known as functional connectivity). We used a stepwise imaging genetics approach in 328 healthy young adults to test the hypothesis that 10 SNPs in *OXTR* are associated with differences in DMN synchronicity and structure of some of the associated brain regions. As *OXTR* effects may be sex-dependent, we also tested whether our findings were modulated by sex. *OXTR* rs2254298 A allele carriers had significantly lower rsFC with PCC in a cluster extending from the right fronto-insular cortex to the putamen and globus pallidus, and in bilateral dorsal anterior cingulate cortex (dACC) compared to individuals with the GG genotype; all observed effects were found only in males. Moreover, compared to the male individuals with GG genotype ofrs2254298, the male A allele carriers demonstrated significantly thinner cortical gray matter in the bilateral dACC. Our findings suggest that there may be sexually dimorphic mechanisms by which a naturally occurring variation of the

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Conflict of Interest

The authors declare no competing financial interests.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuroimage.2016.12.062.

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OXTR gene may influence brain structure and function in DMN-related regions implicated in neuropsychiatric disorders.

Keywords

OXTR; Single nucleotide polymorphism; Functional magnetic resonance imaging; Resting-state functional connectivity; Default mode network

Introduction

Autism spectrum disorders (ASDs), schizophrenia, and mood and anxiety disorders are heritable, share a partially overlapping genetic etiology, and all involve impaired social behavior (Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013)). These disorders have all been associated with disruptions in the resting state functional connectivity (rsFC) of the functional magnetic resonance imaging (fMRI) signal among regions in the default mode network (DMN) (Assaf et al., 2010; Camchong et al., 2011; Liao et al., 2010; Liu et al., 2015). The DMN is a network of brain regions that exhibit higher metabolic activity at rest than when performing externally oriented cognitive tasks. rsFC is regarded as a means to measure functional organization of the brain. The rsFC of the DMN has been implicated in social cognition (Andrews-Hanna, 2012), so its disruption may be relevant to the manifestation of symptoms in these disorders. fMRI signal synchronicity among DMN regions is moderately heritable (Fu et al., 2015; Glahn et al., 2010), but so far, specific genetic variants that explain DMN synchronicity are unknown.

Here, we evaluate the relationship between variants in the oxytocin receptor (*OXTR*) gene previously associated with normal and abnormal social behavior (especially in ASDs, schizophrenia, and mood and anxiety disorders) to resting state fMRI (rs-fMRI) DMN synchronicity. Understanding how these variants relate to brain function may open new research directions for therapies in these disorders and may indicate an intermediate phenotype, rs-fMRI DMN synchronicity, by which effects of these therapies might be tested.

Oxytocin (OXT), an evolutionarily conserved neuropeptide, has a crucial role in regulating social perception and behavior in humans. It may play a key role in ASDs, schizophrenia, and mood and anxiety disorders (Meyer-Lindenberg et al., 2011). OXT exerts its effects by interacting with the OXTR (Yoshida et al., 2009). The human *OXTR* gene is located on chromosome 3p25.3, spans approximately 17 kilobases (kb) and contains four exons and three introns (Assaf et al., 2010). Common single nucleotide polymorphisms (SNPs) in the *OXTR* gene have been linked to differences in OXT-related social behavior and may influence risk for common neuropsychiatric disorders (Supplementary information, Table S1; for a review, please see Aspé Sánchez et al., 2015). Even so, the neural mechanisms underlying these associations are unclear. Researchers have just begun to investigate the influence of genetic variants in the *OXTR* gene on brain structure and function using imaging genetics techniques (for a review, please see Zink and Meyer-Lindenberg, 2012). The DMN, a coherent resting-state network, is thought to characterize basal neural activity. Accumulating evidence strongly suggests that default mode connectivity is influenced by genetic factors. In a pedigree study, the posterior cingulate/precuneus within the DMN

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showed the highest heritability in rsFC (Glahn et al., 2010). Aberrant rsFC has been reported in a host of neuropsychiatric diseases and in healthy individuals at genetic risk for such diseases, suggesting that this intrinsic network is sensitive to pathological alterations in brain structure and function (Baldwin et al., 2016; Connolly et al., 2013; Dodhia et al., 2014; Mikolas et al., 2016). But to date, no imaging genetics study has investigated how *OXTR* variants may link to rs-fMRI signal synchronicity in the DMN.

To address this question, we pursued a stepwise multimodal neuroimaging genetics approach, which first identified whether common genetic variants in *OXTR* SNPs were associated with voxel-wise rsFC in the DMN, in a large sample of healthy young adults (step 1). The next steps further investigated whether structural integrity of specific brain areas showing associations might partly explain differences in DMN rsFC by genotype (step 2) and whether our functional and structural findings were modulated by sex, as *OXTR* effects may vary by sex (Carter, 2007) (step 3).

Materials and methods

Subjects

3D T1-weighted (T1W) volumetric structural and rs-fMRI scans were performed, as part of the Queensland Twin Imaging (QTIM) study, on right-handed healthy young adults recruited to examine genetic influences on the brain. To reduce the possibility of spurious findings due to population stratification artifacts, we only selected subjects of European ancestry. We excluded ancestry outliers, identified by principal components analysis of genetic variants. Ancestry outliers were defined as participants at least 6 standard deviations from the mean along the axis of the first or second principal component of their genetic variants. All subjects were screened for significant medical, psychiatric or neurological conditions, including head injuries, and a current or past diagnosis of substance abuse. Additionally, no subjects had a first-degree relative with a neurological or psychiatric illness, substance abuse or dependence or reported a history of a psychiatric disorder. Full-scale intelligence quotient standardized scores were derived from subtest scores of the Multidimensional Aptitude Battery (Jackson, 1984), which is similar to the Wechsler Adult Intelligence Scale. All participants' intelligence quotient (IQ) is greater than 80. To avoid confounding effects of kinship, one subject per family was selected at random and included in the analysis. Our final sample comprised 328 right-handed genetically unrelated, healthy young adults (123 males / 205 females, mean age 23.2 ± 2.9 yo; range: 18–30 yo). After a complete explanation of the study, written informed consent was obtained from all participants. Our study was approved by the Queensland Institute of Medical Research (QIMR) Human Research Ethics Committee, and by the University of Southern California Institutional Review Board (IRB).

SNP selection and genotyping

Genome-wide genotyping was performed for all subjects, although we focused solely on SNPs in our candidate gene, *OXTR*. Genomic DNA samples were analyzed on the Human610-Quad BeadChip (Illumina) according to the manufacturer's protocols (Infinium HD Assay; Super Protocol Guide; Rev. A, May 2008).

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In this study, we chose 37 SNPs (Supplementary information, Table S2) in the *OXTR* gene region that have been associated with normal variations in social cognition and behavior as well as with neuropsychiatric disorders characterized by social dysfunction in at least one prior paper. We excluded 27 SNPs in high linkage disequilibrium (LD) with others in the sample (D'=1, we kept the one that was highlighted in the prior studies) or had a minor allele frequency (MAF) below 0.1. The MAFs of the final 10 SNPs in our study were similar to that previously identified for these same SNPs in the HapMap CEPH population (Utah Residents with Northern and Western European Ancestry) (1000 Genomes Project Consortium et al., 2010). The genotype distribution of each SNP in our sample did not deviate from Hardy-Weinberg equilibrium (HWE) using a standard threshold of $p > 0.01$. Genotype information for the 10 final SNPs is summarized in Table 1.

Image acquisition

Images were acquired on a 4 T Bruker Medspec whole-body scanner. For rs-fMRI scans, all subjects were instructed to lie still in the scanner, relax with their eyes closed and think of nothing in particular. All participants included confirmed that they remained awake and alert through the scanning session. The rs-fMRI scans lasted 5 min 19 sec with a total of 150 volumes, with the following parameters: repetition time (TR)=2100 ms, echo time (TE)=30 ms, flip angle (FA)=90°, field of view (FOV)=230 mm, 36 transverse 3 mmthick slices with 0.6 mm gap, yielding a voxel size of 3.6×3.6×3.0 mm^3. High-resolution T1W images were acquired with an inversion recovery rapid gradient echo sequence (TR/TE/TI = 1500/3.35/700 ms, FA=8°, FOV=240 mm, 256×256 acquisition matrix, 0.9×0.9×0.9 mm^3 voxels/0 mm gap).

fMRI preprocessing

The rs-fMRI data was preprocessed using FIX Version 1.06 (FMRIB's ICA-based Xnoiseifier) and FEAT Version 5.98 (fMRI Expert Analysis Tool), part of the FSL analysis package [fMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl; (Smith et al., 2004)] with the following standard procedures within FEAT. (1) The first 4 volumes from each subject were discarded to allow the signal to reach equilibrium; (2) The skull and other non-brain areas were extracted using FSL's script Brain Extraction Tool (BET); (3) Motion Correction was performed using FMRIB's Linear Image Registration Tool (FLIRT); (4) Slice timing correction; (5) Registration of fMRI images to structural (brain-extracted) images (boundary-based registration; BBR) and nonlinear registration to the Montreal Neurological Institute (MNI) template; (6) Spatial smoothing using a Gaussian kernel (FWHM=6 mm) and (7) A temporal filter (0.01–0.08 Hz) was performed to reduce the effect of low-frequency drifts and high-frequency noise.

T1W images preprocessing

T1W images were corrected for bias inhomogeneity with N4 from the Advanced Normalization Tools (ANTs) (Tustison et al., 2010) software package (http://stnava.github.io/ANTs/), and then run through FreeSurfer's (https://surfer.nmr.mgh.harvard.edu; version 5.3) recon-all pipeline. The quality control for FreeSurfer parcellation outputs was performed by using the following ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols/).

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rs-fMRI analysis

We conducted rs-fMRI analysis by applying a single seed region in the bilateral posterior cingulate cortex (PCC)/precuneus, which is commonly considered a central node of the DMN. The PCC region of interest (ROI) was a 4 mm radius sphere centered at MNI coordinates (0, −53, 26) reported in previous studies (Hedden et al., 2009), which was located in between the central portion of the precuneus and the ventral (lower) part of PCC (Bzdok et al., 2015; Margulies et al., 2009). For each subject, a representative time series for the PCC region was obtained by averaging the time series over all the voxels in the PCC mask. Pearson correlation coefficients between the mean time series of the seed PCC and that of each voxel of the whole brain were computed and converted to *z* values using Fisher's *r*-to-*z* transformation to improve the normality (Liu et al., 2016). We controlled for motion (translations and rotations in three directions each) and for the activity time courses in white matter, cerebrospinal fluid, and whole brain. We used FSL "FMRIB's Local Analysis of Mixed Effects" (FLAME) (Beckmann et al., 2003), to perform *t* tests to generate *z* statistic images across subjects. This step was to create individual subject-level maps of all positively- and negatively-predicted voxels correlated with the PCC seed. For each individual subject's scan, we used a *z* statistic threshold of 2.3 to define contiguous clusters. Gaussian Random Field theory was used to estimate each cluster's significance level and then that significance level was compared with the cluster probability threshold set at $p < 0.05$. Finally, these *z* statistic images evaluated the relationship between the *OXTR* SNPs and DMN rsFC.

In our study, the genotype effects of 7 of our *OXTR* SNPs were determined using an additive model, in which each genotype forms one group. However, as there were so few homozygotes of the minor allele of the remaining 3 SNPs (less than 10% of the total sample), they were collapsed with heterozygotes of the minor allele into a single group, defined by having at least one minor allele for statistical analyses in a dominant model, considering the common genotype (homozygotes of the major allele) as the reference group.

Group level analyses were performed using fMRIB's Local Analysis of Mixed Effects (FLAME) with age and sex as covariates of no interest to identify regions across the whole brain with significant rsFC differences to the PCC ROI between different genotype groups. We employed the widely-used false discovery rate (FDR) method with a threshold of 5% to control for multiple comparisons across all voxels considered (Benjamini and Hochberg, 1995). FDR controls the expected proportion of null results that are falsely identified as significant to a set rate (in our case this rate, q=5%, similar to the standard $p = 0.05$ frequently used to define significance). Considering several lines of evidence of sexual dimorphism for social effects of *OXTR* polymorphisms (Dumais et al., 2013; Dumais and Veenema, 2016), the significant rsFC correlation coefficients (*z* values) were extracted and we examined whether the results showed sex × genotype interactions using a *post-hoc* analysis of variance (ANOVA) *F* Test. If the interactions were significant, the *z* values were compared across genotypic groups in male and female subjects, respectively.

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T1W images analysis

We used FreeSurfer version 5.3 to examine whether the regions in which the two cluster ROIs with significant rsFC differences to the PCC ROI showed surface area, gray matter volume or cortical thickness differences between the two genotypic groups using a *post-hoc* ANOVA *F* Test, covarying for age and total intracranial volume, and testing for a sex-by-genotype interaction. For significant interactions, the structural index of each brain region was compared across genotypic groups in male and female participants, respectively.

Statistical analysis

All statistical analyses in this study, other than those included in the rsFC image analysis tools, were performed using Statistical Package for the Social Sciences version 18.0 (SPSS, Chicago, Ill). A Bonferroni correction was applied to control for type I error rate between our 2 ROIs in the T1W images analysis ($p < 0.05$, two-tailed).

Results

Differences in rsFC and structural alterations between genotypes

Compared to individuals with rs2254298 GG genotype (male/female=99/162, 23.3 ± 2.8 yo), A allele carriers (AA/AG genotypes, male/female=24/43, 23.1 ± 3.0 yo) had significantly lower rsFC with PCC in a cluster extending from the right fronto-insular cortex (FIC) to the subcortical structures including putamen and globus pallidus (peak MNI coordinates: x=30, y=4, z=−2), and in bilateral dorsal anterior cingulate cortex (dACC, peak MNI coordinates: x=0, y=10, z=40) (critical *p* value which controls FDR at q=0.05 is 0.00012; 409 voxels survive the FDR threshold; Fig. 1). No brain region showed higher rsFC with PCC in A allele carriers compared to individuals with the GG genotype. We found no significant associations between any other *OXTR* SNPs and rsFC.

To further investigate these significant results, we evaluated genotype-by-sex interactions. Consistent with past reports of sex-dependent *OXTR* effects (Stankova et al., 2012), we detected significant genotype-by-sex interactions on rsFC (F=3.6, p=0.000462, Bonferroni correction for rsFC between PCC and the right FIC, putamen and globus pallidus; F=3.3, p=0.00127, Bonferroni correction for rsFC between PCC and the bilateral dACC). These interactions manifested as relatively weaker rsFC in the male A allele carriers between PCC and the right FIC, putamen and globus pallidus (t=−3.50, p=0.000652, Bonferroni correction) and the bilateral dACC (t=−3.05, p=0.00281, Bonferroni correction) (Fig. 1) compared to the male individuals with GG genotype. Subsequent analysis of structural MRI data also demonstrated a genotype-by-sex interaction effect on cortical thickness of the bilateral dACC (F=3.01, p=0.00318, Bonferroni correction). Here, the male A allele carriers exhibited significantly thinner cortical gray matter in the bilateral dACC compared to male individuals with GG genotype (t=−3.20, p=0.00176, Bonferroni correction) (Fig. 2).

Post hoc correlation analysis between rsFC and cortical thickness of bilateral dACC

We found the male A allele carriers showed significantly weaker rsFC between the PCC seed and the bilateral dACC and showed significantly thinner cortical thickness in the bilateral dACC compared to the male individuals with GG genotype. To investigate whether

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rsFC changes of the bilateral dACC might be confounded by cortical thickness differences in the two male genotypic subgroups, we performed correlation analysis in the male group. For this purpose, we extracted rsFC correlation coefficients (*z* values) between PCC and bilateral dACC and cortical thickness of the bilateral dACC. We did not detect a significant correlation (r=0.025, n=328, p=0.652) between the cortical thickness of bilateral dACC and the rsFC of PCC and bilateral dACC, suggesting that genotypic difference in the rsFC of PCC and bilateral dACC was not driven by structural alterations in the bilateral dACC.

Discussion

In the current study, we identified neural mechanisms that may underlie the association between common genetic variants in *OXTR* and rsFC in the DMN of healthy young adults. Specifically, rs2254298 A allele carriers had significantly lower rsFC between the PCC ROI and a cluster extending from the right FIC to the putamen-globus pallidus and between the PCC ROI and the bilateral dACC compared to individuals with GG genotype, and notably, these effects were predominately driven by the males. Moreover, the male A-allele carriers demonstrated significantly thinner cortical gray matter in the bilateral dACC compared to the male individuals with the GG genotype. Brain regions showing associations partially overlap with the main regions of *OXTR* gene expression in the human brain, such as the anterior cingulate, medial insula, and globus pallidus (Gimpl and Fahrenholz, 2001).

A rich literature has suggested polymorphisms in the *OXTR* gene contribute to social behaviors in normal subjects and in people with impaired social cognition. The SNP rs2254298 has been studied considerably with regard to its impact on various psychopathological conditions. Variants in rs2254298 (G/A) have been reported to be associated with differential risk for certain psychiatric conditions including ASDs, schizophrenia, depression and anxiety disorders (Brüne, 2012; Thompson et al., 2011). For ASDs, the direction of association appears to strongly depend on ethnicity with the A allele in the Asian population (Liu et al., 2010; Wu et al., 2005); and the allele-G in Caucasians and in an Israeli sample (Jacob et al., 2007; Lerer et al., 2008). Schizophrenic patients carrying one or two A-alleles showed significantly more self-rated ‘empathic concern’ than those carrying two G-alleles (Montag et al., 2012). For depression and anxiety disorders, GG genotypes are positively associated with a higher risk of developing unipolar depression and with high levels of adult separation anxiety (Costa et al., 2009). Moreover, the rs2254298 A allele has been found to be associated with attachment security (Chen et al., 2011), less sensitive parenting (Feldman et al., 2013) and lower plasma OXT levels (Parker et al., 2014).

Several researchers have investigated the influence of rs2254298 normal variant on brain structure and function (Table 2). Most studies to date have assessed neural structural differences. Only one prior study investigated the functional effects of this SNP by measuring functional activity in limbic regulatory circuits (Tost et al., 2011). Functional and structural alterations in DMN-related brain regions are unexplored to date.

In our investigation, *OXTR* rs2254298 male A allele carriers showed lower rsFC in PCC with the dACC. This is partially consistent with a prior report that the male A allele carriers showed a significant decrease in medial ACC deactivation elicited while processing negative

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social emotional face stimuli (Tost et al., 2011). Our findings of significantly reduced dACC cortical thickness in the male A allele carriers are likewise partially supported by the findings of two past reports that AG Caucasians had lower gray matter volume in a region of the dorsomedial ACC than GG participants (Furman et al., 2011) and A allele load was associated with lower gray matter volume in dorsomedial ACC in a Japanese sample (Yamasue, 2011). Different rsFC in the DMN in the male A allele carriers compared to the male GG homozygotes may be one mechanism that may mediate previously reported effects on social cognition.

Structural and functional alterations of the dACC in our study are interesting for a number of reasons. First, convergent data show that the dACC is involved in a variety of cognitive processes, such as attention to behaviorally relevant stimuli (Silton et al., 2010), conflict monitoring (Kerns et al., 2004), error detection (Gehring and Knight, 2000; Menon et al., 2001), and decision-making (Turken and Swick, 1999). Second, abnormal structure or function in this region is noted in the common neuropsychiatric disorders, such as ASDs, schizophrenia, depression and anxiety disorders (Aizenstein et al., 2009; Camchong et al., 2011; Di Martino et al., 2009). More importantly, functional neuroimaging studies found abnormal rsFC between dACC and PCC in neurological and psychiatric disorders including ASDs, schizophrenia and depression (Kennedy and Courchesne, 2008; Pannekoek et al., 2014; Yan et al., 2012), even in subclinical depression (Kaiser et al., 2015), although some of the results were not consistent in direction with our results. The individuals with abnormal brain connectivity patterns between the two regions may be unable to shift away from internal thoughts and toward to the external world when emotionally salient information is detected.

We also found significantly lower rsFC between the PCC seed and a large area in the right hemisphere stretching from the fronto-insular cortex (FIC) to subcortical structures including the putamen and globus pallidus in the male A allele carriers. It is noteworthy that the right FIC, putamen and globus pallidus is not part of the DMN. The correlations among resting state networks (RSNs) have been extensively described, particularly for the DMN, which is the network containing hubs with the highest global functional connectivity. A recent fMRI study suggests that there are complex modulatory correlations among the DMN and other networks in the rs-fMRI (Di and Biswal, 2014).

Recent evidence highlights a crucial role for the insular cortex in social cognition and behaviors such as sharing other's sensation and emotions, and processing uncertainty (Singer and Lamm, 2009). The FIC is not usually connected with DMN regions, but several studies reported the rsFC between the DMN and the insula. Chronic pain patients showed greater DMN-insula connectivity than healthy controls (Napadow et al., 2010); even in healthy subjects, DMN-insula connectivity increased with state anxiety (Dennis et al., 2011). The right FIC is the core node of the salience network (SN) that serves to identify salient stimuli to guide behavior, which is reported to play a critical role in switching between the central executive network (CEN) and the DMN (Sridharan et al., 2008). The rsFC between the PCC and the right FIC was weaker in the male A allele carriers than in the male individuals with GG genotype, which may alter the capacity to switch between the CEN and DMN and may even lead to cognitive decline.

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Putamen and globus pallidus were originally viewed as motor structures, an emerging body of evidence supporting that the two basal ganglia nuclei mediate a full range of goal-directed behaviors, including emotions, motivation, and cognition (Haber and Knutson, 2010; Seger, 2006). Specifically, there is convergent evidence that the putamen nucleus is activated when presenting salient stimuli. Based on neurophysiology and anatomical data, the putamen and globus pallidus are functionally connected to widely distributed cortical regions (Di Martino et al., 2008) possibly supported by different white matter fibers (Leh et al., 2007; Lehericy et al., 2004). Reduced correlations between PCC and basal ganglia nuclei have been reported during healthy aging and in neurological and neuropsychiatric disorders (Manza et al., 2015; Schmidt et al., 2015; Wang et al., 2007; Zhang et al., 2009). Our results of significantly decreased rsFC between the PCC and the right putamen and globus pallidus in the male A allele carriers are in partly agreement with the previous studies, demonstrating altered rsFC between those two regions may result in a functional deficit in task switching and attention shifting.

Our rsFC findings using a bilateral PCC seed were more prominent in the right hemisphere (FIC, putamen and globus pallidus), but extended to many of the same brain regions in the left hemisphere using more lenient statistical thresholds (min $z > 2.3$; cluster significance: $p < 0.05$; Gaussian random field theory correction; Fig. S1). The apparent laterality of our partial rsFC findings is probably due to the sample size and our strict statistical correction in our voxel-wise analysis.

The impact of the *OXTR* rs2254298 polymorphism on the volume and rsFC of DMN-related brain regions varied by sex, and was detected only in males. Our distinct findings of sexual dimorphism are in line with our expectations. Prior work has shown that OXTR bonding are expressed in a sex-dependent manner, in which the binding capacity was higher in women than in men (Elands et al., 1990). It has also been reported in previous studies that certain genetic polymorphisms (including this SNP) in *OXTR* show a gender-specific effect on specific social behavior (Tost et al., 2010; Walum et al., 2012), but some of results were not consistent in direction with our results. Furthermore, the strong impact of intranasal oxytocin spray on male social behavior (Young and Wang, 2004), and the disproportionately high risk of men for social disorders (Baron-Cohen, 2002), suggest sex dependent effects at the neural systems level in male, but not female, rs2254298 A carriers are predictable. The cellular mechanism of this observed sex-by-genotype interaction is currently unknown, but gonadal steroids may affect both OXTR binding and expression (Gimpl and Fahrenholz, 2001). This may be the basis of sex differences in the effects of *OXTR* variants on the brain. Further work is necessary to verify this assumption.

The current findings may be important for understanding the mechanisms underlying the associations between *OXTR* gene variants and disorders of social cognition, however there are several limitations of this study that should be noted. First, we studied healthy young adults, who had not yet experienced the onset of a psychiatric disorder; as such, we cannot generalize the results to other age groups. Second, we had aimed to include the *OXTR* rs53576, one of the two particularly promising candidates (rs53576 and rs2254298) from prior studies, which may influence several behaviors associated with neuropsychiatric disorders; unfortunately, this SNP was not imputed in our genotyping assay. Third, because

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the molecular function of rs2254298 is unknown, our results cannot exclude the possibility that the observed effects may reflect the impact of *OXTR* variants (a not yet detected functional polymorphism) in LD with rs2254298. Fourth, we did not control for multiple comparisons across SNPs, but past work demonstrated empirically that when using FDR (as we did here) to control for voxel-wise multiple comparisons, the observed false positive rate was well below 5%, even when hundreds of SNPs not expected to have a significant effect on the fMRI data were examined (Meyer-Lindenberg et al., 2011). Here we examined only 10 SNPs, selected *a priori* to be likely to affect brain function. Therefore, it is likely that in our study, the type I error rate is still controlled below 0.05.

In summary, we provided evidence for a sex-dependent impact of *OXTR* rs2254298 (but none of the other SNPs) common variants on the structure and function related to DMN, suggesting a neural mechanism for genetically increased risk for social impairments in males. This is of potential relevance for neuropsychiatric disorders. Our results are preliminary and a larger sample is needed to verify this effect and understand any sex differences. Future studies are needed to probe the interactions between SNP-by-SNP and gene-by-environment to determine how the *OXTR* gene might modulate the neurobiology of circuits implicated in risk for human complex social behaviors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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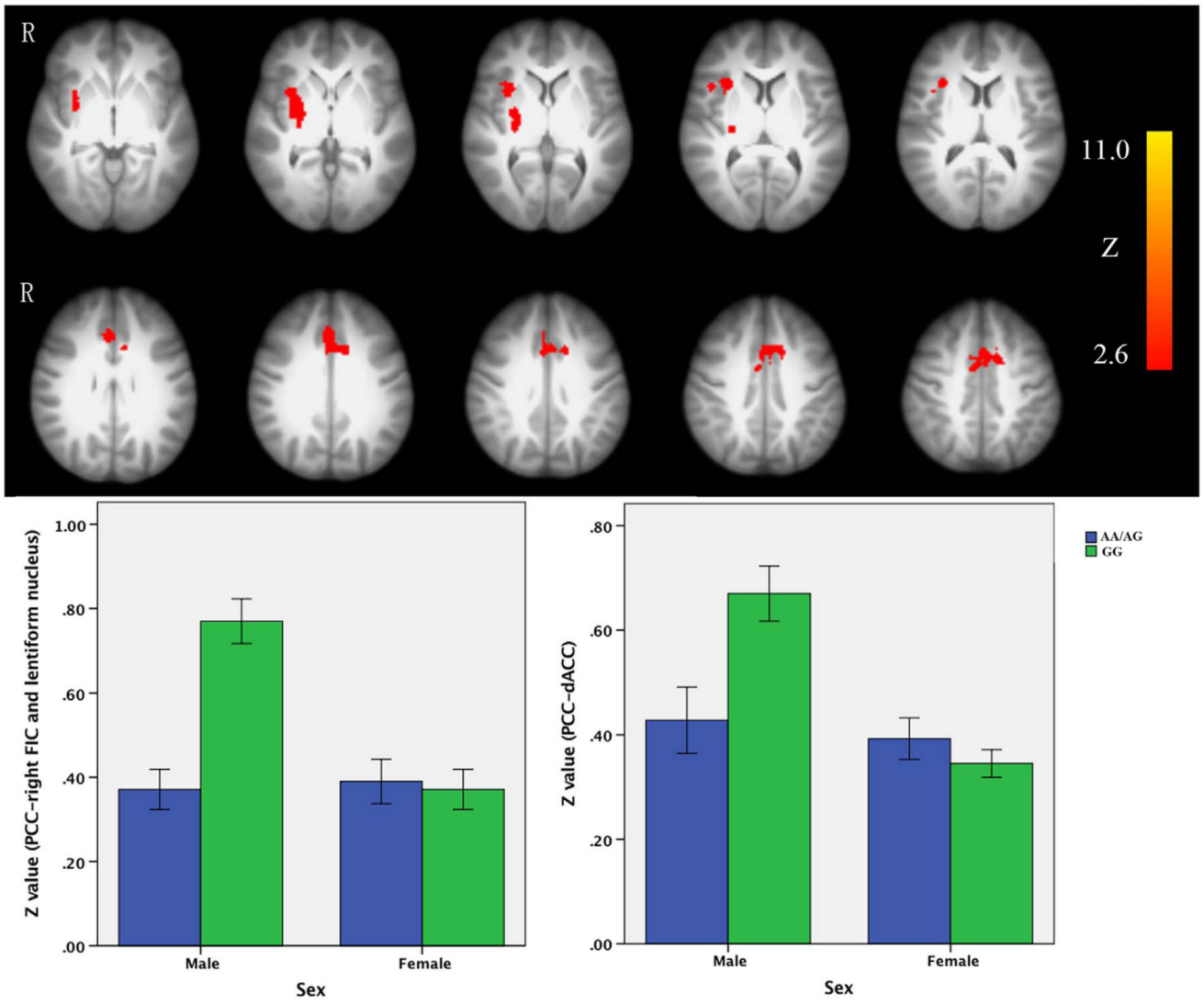

Fig. 1.

OXTR rs2254298 and DMN. A Allele carriers (AA/AG) of *OXTR* rs2254298 had significantly lower rsFC with PCC in a cluster extending from the right fronto-insular cortex to putamen and thalamus, and in bilateral dorsal anterior cingulate cortex (dACC) compared to individuals with GG genotype (FDR correction, $p < 0.05$). *Post-hoc* analysis demonstrated those effects were driven by males.

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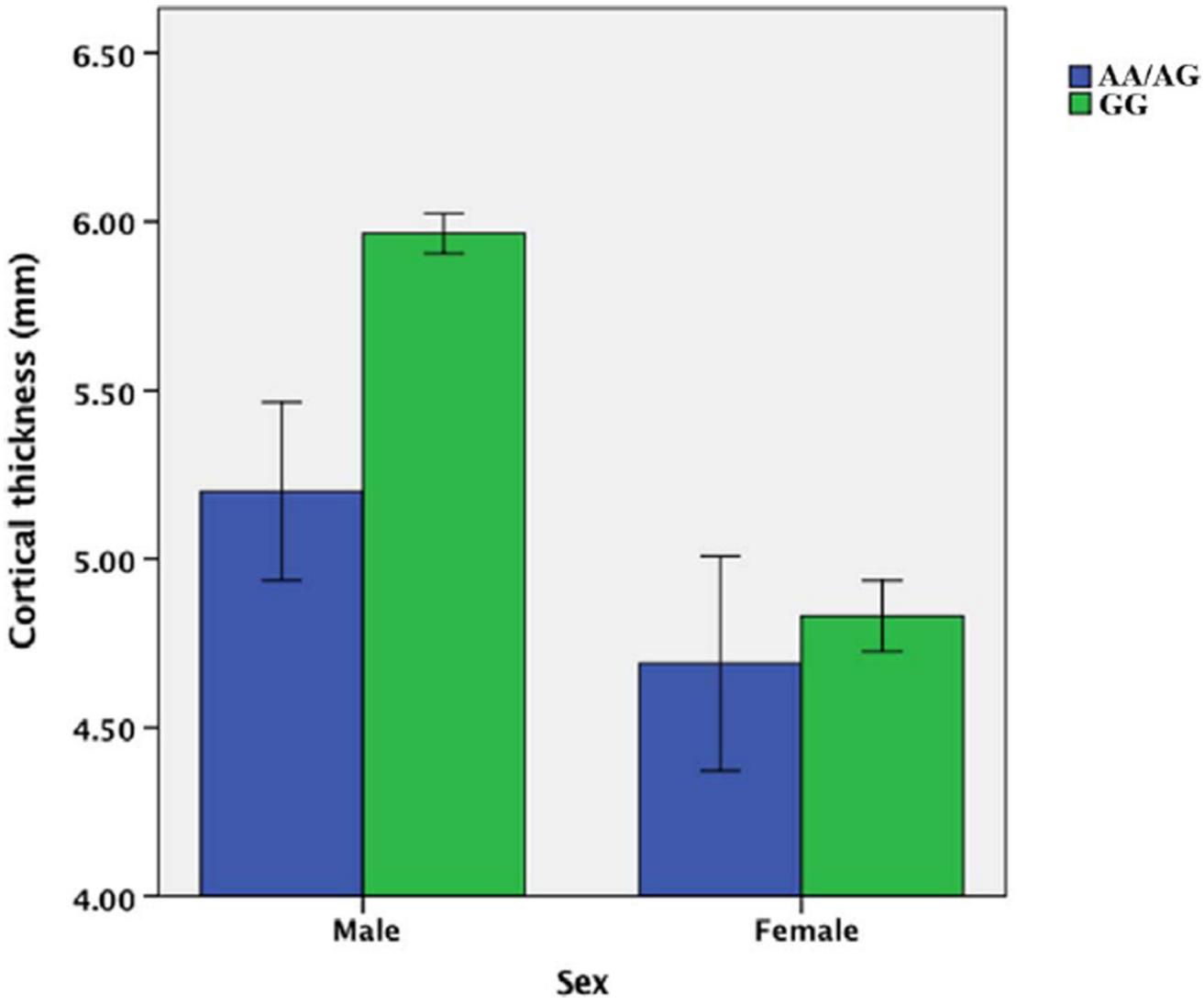

Fig. 2.

OXTR rs2254298 and cortical thickness. *Post-hoc* analysis showed *OXTR* rs2254298 male A allele carriers (AA/AG) had less cortical thickness of bilateral dACC compared to the male individuals with GG genotype (t=−3.203, p=0.002, Bonferroni correction). There was no significant genotypic difference in cortical thickness of bilateral dACC in female subjects (t=−0.69, p=0.505).

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Table 1

The further genotype information of 10 SNPs in the final analysis.

Marker	Major allele	Minor allele	Minor allele frequency (MAF)	Subjects with 0 minor alleles	Subjects with 1 minor alleles	Subjects with 2 minor alleles
rs7634632*	C	T	0.48	86	171	71
rs11914885	A	G	0.32	145	156	27
rs151462*	C	G	0.34	146	140	42
rs237875*	A	G	0.46	98	158	72
rs6791619*	C	T	0.47	90	168	70
rs2270465*	G	C	0.41	112	166	50
rs237888	T	C	0.14	237	87	4
rs2254298	G	A	0.10	264	61	3
rs237897*	G	A	0.38	116	175	37
rs237851*	G	A	0.48	86	171	71

* Indicates using an additive model.

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Table 2

The related imaging genetics studies of *OXTR* rs2254298 genetic variation.

Author (year)	Number of Subjects	Sex	Ethnicity	Measurements	Results (A-allele carriers/individuals with AA genotype)
Furman et al. (2011)	51	F	Caucasian	Gray matter volume	L/R amygdala↑
					L posterior brainstem↑
					L dorsomedial anterior cingulate cortex↓
Inoue et al. (2010)	208	M/F	Japanese	Gray matter volume	L/R amygdala↑
Tost et al. (2011)	212	M/F	Caucasian	Gray matter volume	R hypothalamus (male only)↓
	228			Task-dependent fMRI	Medial anterior cingulate cortex
				Brain activity	Deactivation↓
Yamasue et al. (2011)	206	M/F	Japanese	Gray matter volume	R dorsomedial anterior cingulate cortex↓
					R hypothalamus (female only)↓