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ORIGINAL RESEARCH

Oxytocin-Receptor Gene Modulates Reward-Network Connection and Relationship with Empathy Performance

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Introduction: Empathy traits are highly heritable and linked with reward processing. It is implicated that common variations of the oxytocin-receptor gene (*OXTR*) play a modulatory effect on empathic performance. However, it is unclear about the neural substrates underlying the modulatory effect of the *OXTR* genotype on empathic performance. This study aimed to characterize the modulatory effect of common *OXTR* variations on reward-circuitry function and its relationship with empathy.

Methods: Based on the seed of the nucleus accumbens (NAcc; a key hub of reward circuitry), we examined differences in spontaneous local activity and functional connectivity between *OXTR* rs2268493 genotype groups and their relationship with empathic performance among 402 high-homogeneity participants.

Results: Comparing with C carriers (CC/CT) group, the individuals with the rs2268493 TT genotype exhibited lower functional connectivity of the right NAcc with the medial prefrontal cortex (mPFC) and inferior frontal gyrus. Similarly lower functional connectivity was found between the left NAcc and mPFC. Consequently, no significant difference was found in the spontaneous local activity of NAcc.

Discussion: Our findings suggested that common *OXTR* variations have a modulatory effect on the connection of the NAcc with the hub of empathic networks (mPFC and IFG), which may provide insight on the neural substrate underlying the modulatory effect of *OXTR* on empathic behavior.

Keywords: empathy, oxytocin-receptor gene, reward network, RS-fMRI, rs2268493

Introduction

Empathy is the ability to resonate with others' intentions and thoughts, which is crucial for facilitating prosocial behavior and driving mental health.[1–3] Current health professional evidence suggests that higher levels of empathy are correlated strongly with better life satisfaction, interpersonal skills, and mental state,[4] but also associated with core features of several mental diseases, such as autism spectrum disorder (ASD) and schizophrenia.[5–8] According to the dual nature of empathy, it could be categorized into two components — cognitive and emotional.[9–11] Cognitive empathy is the ability to assess the reasons behind emotional states of oneself and other people.[12] Emotional empathy refers to sharing the emotional state of another, which is closely related to emotional contagion or empathic arousal.[9,12]

It is widely believed that the empathy is a heritable trait in humans, confirmed by strong evidence from studies of twins and offspring.[13–15] These genetic studies provided convincing evidence of a link between gene variations and risk with aberrant affective and empathic responses.[16,17] The oxytocin-receptor gene (*OXTR*) is the significant empathic gene,

and exerts its effects by oxytocin (OXT).[18–20] OXT, a neurotransmitter, has a crucial role in social trust/altruism and emotional empathy.[21,22] Oxytocin in combination with *OXTR* then modulates social behavior.[23] Common variations of *OXTR* have demonstrated the impact on social performance.[24] Risk alleles of *OXTR* single-nucleotide polymorphisms (SNPs) for ASD, a social dysfunction disorder, have been linked with poor social interaction.[25–27] For example, compared with individuals homozygous for the C allele of 2268493 (CT/CC), individuals with the rs2268493 TT allele (risk allele) present low perceived ability in maternal care and dispositional empathy via modulation of OXT.[28] *OXTR* polymorphisms exhibit individual differences in empathic communication.[29] They are distributed in social–empathic brain circuits, which implicate the key role of the brain network in the modulation of OXTR on empathic performance.[22,30]

The social–affective network, especially the inferior frontal gyrus (IFG), fusiform gyrus, and medial prefrontal cortex (mPFC), are thought to be critical for the empathy processing.[17,31–33] For example, increased activity in the IFG has been demonstrated during the condition of emotional empathy, but not cognitive empathy.[9] Conversely, individuals with impaired cognitive empathy have reduced hemodynamic responses in the mPFC.[34] Recently, besides social–affective processing, reward processing has also been linked with empathy.[35,36] During social interactions, stimuli are often predictors of rewards for us and others. Effective social interaction and empathy need the ability to compute the value of stimuli that predict rewards for others.[37] Deficits in reward processing may relate to empathic disturbance.[36]

Decades of neuroimaging research have identified regions involved in different reward processes, including the nucleus accumbens (NAcc), ventral striatum, and orbitofrontal cortex.[38–41] NAcc is considered a hub of the reward circuit,[42] receiving 5-hydroxytryptamine and further reinforcing properties of social interaction. Evidence suggests that oxytocin mediates 5-hydroxytryptamine release in the NAcc and thereby regulates social reward.[43] Also, the *OXTR* risk alleles are closely associated with impaired reward-circuitry function, including the NAcc and PFC, in response to reward anticipation.[28,44]

Importantly, the OXTR risk allele rs2268493 TT has confirmed decreased activation in the reward circuitry.[45] Intriguingly, the local function of NAcc during empathy tasks can be modulated by *OXTR* polymorphisms.[46] These studies support the key role of reward process in empathy.[33] However, recent theories have emphasized that reward is not attributable to single brain regions, but critically depends on interconnected brain networks.[47] Resting-state functional magnetic resonance imaging (RS-fMRI), which enables the identification of spontaneous neural activity and provides an available tool to depict interconnected brain networks.[47] Taken together, the exploration of core seed target (especially NAcc) functional connections is associated with clarifying the relationship between *OXTR* genetic variation and brain empathy processing.

In the present study, we aimed to examine the modulatory effect of common *OXTR* variations on reward-circuitry function and their relationship with empathy. Considering the key role of the NAcc in reward, functional connectivity with the seed of the NAcc was used to depict the reward network. Based on the aforementioned findings, we hypothesized that carriers with the *OXTR* risk genotype rs2268493 TT may show lower empathy performance, as well as reduced reward-circuitry function. The reward-network function may be positively associated with empathy performance.

Methods

Participants

Initially, 641 healthy young college students in the same year at Anhui Medical University were recruited. The average age of the participants was 20.7 years, and their ages ranged from 19 to 23 years. Exclusion criteria were head trauma, metal implants, history of neurological or psychiatric disorders, drug or alcohol abuse, and having first-degree relatives with psychiatric disorders.

Procedures

This experiment was approved by the Ethics Committee at Anhui Medical University. Participants provided written informed consent prior to the experiment, in accordance with the Declaration of Helsinki. A total of 641 eligible participants completed the Chinese version of the Interpersonal Reactivity Index (IRI-C) questionnaire, which is frequently used in measuring empathy. Of these participants, rs2268493 genotype data were available for 530. With

available behavior (IRI-C) and genotype data for the participants, 446 completed MRI scanning. After excluding poor MRI data (resulting from artifacts or excessive head motion), 402 participants were included in the final analysis of functional connectivity (Figure 1). Considering the strong impact of singular values on correlation analyses, we excluded singular data defined as greater than three standard deviations from the mean. Ten participants (three participants in the CT/CC group in and seven participants in the TT group) were excluded when performing correlation analysis because of singular data for mean connectivity. Finally, there were 392 participants (102 in the CT/CC group and 290 in the TT group) included in the correlation analysis for the subscales of the IRI-C.

Measures

All participants completed the IRI-C questionnaire, which is a 28-item instrument to measure multiple dimensions of trait empathy. Items are measured on a five-point Likert scale (scores 0–4). The IRI-C includes cognitive and affective subscales, both scored on four seven-item subscales: cognitive aspects (perspective taking [PT] and fantasy [FS]) and affective processes (empathic concern [EC] and personal distress [PD]).

Oxytocin-Receptor Genotyping

Participants had blood taken to obtain DNA using standard procedures. The genotyping of all participants was determined in comparison with control DNA and confirmed by sequencing in the SNP pattern. The genotype of *OXTR* rs2268493 is TT, CT, and CC. According to previous studies' grouping,[28,48] we classified the genotypes of *OXTR* rs2268493 into TT and C carrier (CT/CC) groups. Finally, there were 297 participants in the TT group and 105 in the CT/CC group.

Image-Data Acquisition

Image scanning was performed with a 3 T scanner (Discovery GE750w) at the University of Science and Technology of China. During fMRI scanning, participants were told to remain awake with their eyes relaxed and closed and not to think
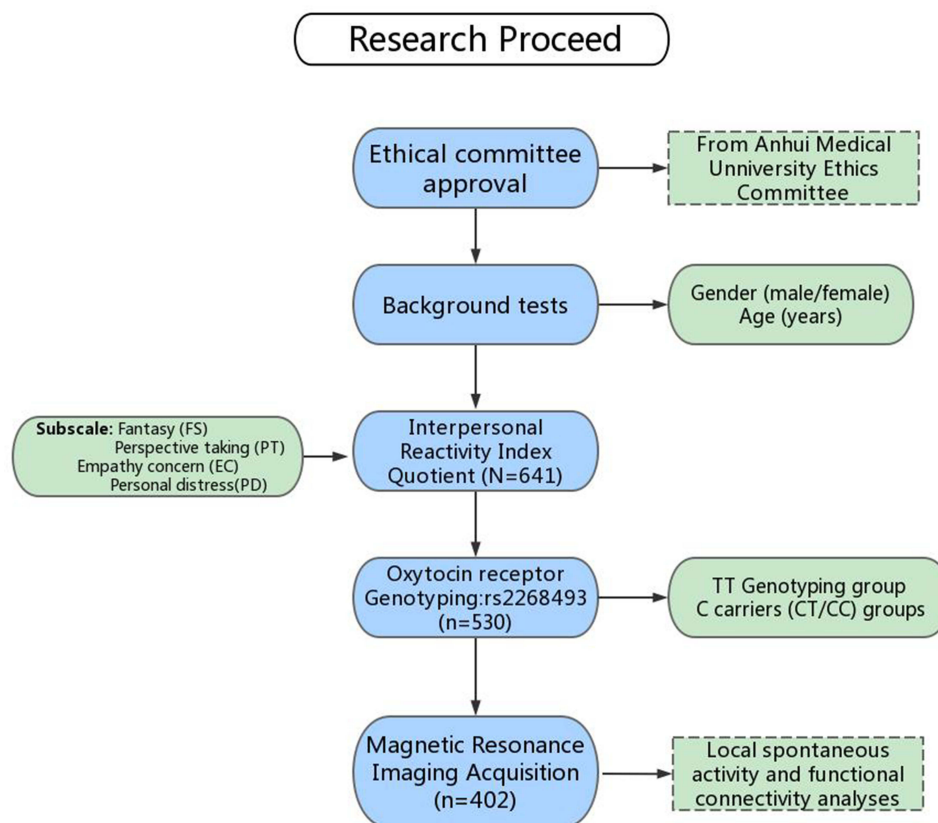

Figure 1 Study flowchart.

of anything. Functional images were acquired composed of 217 echo-planar imaging volumes with parameters of repetition time 2400 ms, echo time 30 ms, flip angle 90°, matrix size 64×64, field of view 192×192 mm^2, slice thickness 3 mm, and 46 continuous slices (one voxel, 3×3×3 mm^3). High spatial resolution T_1-weighted anatomic images with 188 slices were also acquired in sagittal orientation (TR 8.16 ms, TE 3.18 ms, flip angle 12°, field of view 256×256 mm^2, slice thickness 1 mm, and voxel size 1×1×1 mm^3).

Functional Data Preprocessing

We preprocessed functional neuroimaging data using the Data Processing Assistant for Resting-State Functional MR Imaging (DPARSF) toolkit.[49] Data were preprocessed in the following steps: removing first five volumes, slice-timing correction, realignment, spatial normalizing based on the unified segmentation of structural images, regressing out 24 Friston motion parameters, high white-matter signal, cerebrospinal fluid signal and global signals, spatial smoothing (Gaussian kernel 4×4×4 mm), and filtering with a temporal band-pass of 0.01–0.1 Hz.

Local Spontaneous Activity and Functional Connectivity Analyses

After preprocessing, the filtered time series was converted to a frequency domain using fast Fourier transform. The square root of the power for each frequency was calculated to obtain amplitude values. The amplitude of low-frequency fluctuation (ALFF) was calculated as the sum of the amplitude values in the 0.01–0.1 Hz low-frequency power range. To reduce the global effects of variability across participants, the ALFF was normalized by the mean within-brain ALFF value for each participant. In the present study, we focused on the ALFF within the NAcc region. The NAcc was defined with the human Brainnetome atlas,[50] a new brain atlas built upon connectional architecture. Functional connectivity based on the seed of the NAcc was calculated using DPARSF software. For each individual, Pearson's correlation coefficients were computed between the mean time series of seed and time series of each voxel for the rest of the whole brain. To improve the normality, the correlation coefficients were converted to z values using Fisher's $r–z$ transformation and the results displayed as connectivity maps for each participant.

Statistical Analysis

We used SPSS 26.0 for statistical analysis of the data. The χ^2 and t tests were used to compare demographic data and cognitive performance, such as sex, age, IRI-C subscale scores, and local spontaneous activity (ALFF) between the two genotype groups (TT vs CT/CC). Voxel-wise two-sample t tests were used to quantitatively compare differences in NAcc functional connectivity between the two genotype groups within the gray-matter mask with sex as covariate. Statistical maps were corrected using the Gaussian random-field method at the threshold for voxel $P\leq0.001$ and cluster $P\leq0.05$. Pearson's correlation analyses were applied to explore the associations between NAcc connectivity and IRI-C subscale scores. Significance was set at $P\leq0.05$ (two-tailed), with no correction.

Results

Genotype Effects on Behavior Performance

The demographics and range of scores on the IRI-C subscales are listed in Table 1. Genotype distributions of *OXTR* rs2268493 were divided into CT/CC and TT groups in the current study. There were differences between the two genotype groups ($P\leq0.05$). There was no significant difference in cognitive IRI-C and its subdomain scores (FS, PT) between the CT/CC and TT groups ($P>0.05$). There was a significant difference in affective IRI-C between the groups ($P=0.046$). This difference was mainly derived from the subdomain of PD ($P=0.004$).

Genotype Effects on ALFF and Functional Connectivity in NAcc

There were 402 participants in the final RS-fMRI analysis (CT/CC group 105, TT group 297). No significant difference was found between the genotype groups for head motion indexed by frame-wise displacement (Table 1).[51] There was no significant difference between the groups in ALLF of the bilateral NAcc (Figure 2 and Table 1). Participants in the TT group exhibited lower functional connectivity of the right NAcc with the medial mPFC (peak voxel MNI coordinates x=9, y=60, z=−6, t=−4.44, cluster size 37) and higher functional connectivity of the right NAcc with the

Table 1 Demographic and behavioral information for participants with available IRI data grouped by rs2268493 genotype (mean ± SD)

	TT genotype	CC/CT genotype	t/χ^2	P
Number of participants	297	105	/	/
Sex (male/female)	101/196	105/0	135.22	<0.001***
Age (years)	20.91 ± 1.03	20.65 ±1.01	2.228	0.026*
Fantasy (FS)	17.78±4.23	17.95±4.39	0.341	0.733
Perspective taking (PT)	17.42±3.72	17.86±3.84	0.1039	0.299
Empathy concern (EC)	17.90±3.54	18.04±4.22	0.302	0.763
Personal distress (PD)	15.89±3.59	17.15±3.94	2.890	0.004**
Cognitive IRI	35.20±6.08	35.81±6.33	0.869	0.385
Emotional IRI	33.79±5.54	35.19±6.38	2.000	0.046*
ALFF — LNAcc	0.78±0.14	0.78±0.12	0.490	0.624
ALFF — RNAcc	0.80±0.13	0.84±0.22	1.624	0.105

Notes: *P<0.05; **P<0.01; ***P<0.001. Cognitive IRI, FS+PT; emotional IRI: EC+PD.
Abbreviations: IRI, Interpersonal Reactivity Index; FS, including fantasy; PT, perspective taking; EC, empathy concern; PD, personal distress; SD, standard deviation; ALFF, amplitude of low-frequency fluctuation; LNAcc, left nucleus accumbens; RNAcc, right nucleus accumbens.

IFG (peak voxel MNI coordinates x=51, y=15, z=21; t=4.18, cluster size 26) than the CT/CC group (Figure 3A and B). Participants in the TT group also exhibited lower functional connectivity of the left NAcc with the mPFC (peak voxel MNI coordinates x=9, y=60, z=−3; t=−4.45, cluster size 48; Figure 4A and B).

Correlation Analyses

Functional connectivity for the right NAcc with the IFG was significantly correlated with emotional IRI-C score (R=−0.205, P<0.05, low power), especially the empathic concern subscore (R=−0.301, P<0.01, medium power; Figure 3C). Functional connectivity between the left NAcc and mPFC was significantly correlated with cognitive IRI score (R=0.151, P=0.01, low power) and Fantasy subscore(R=0.134, P<0.05, low power; Figure 4C).

Discussion

The current investigation aimed to examine the modulatory effect of common *OXTR* variations on reward-circuitry function and its relationship with empathy using resting-state functional connectivity within healthy individuals. Our results demonstrated that individuals with the rs2268493 TT genotype exhibited lower functional connectivity for right NAcc–mPFC, right NAcc–IFG, and left NAcc–mPFC than the rs2268493 CT/CC genotype. Associations were
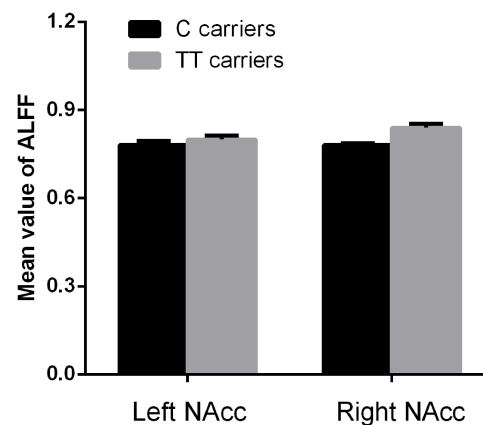

Figure 2 Genotype effects on ALFF in the NAcc. There was no significant difference in ALLF of the bilateral NAcc between C carriers and TT groups in rs2268493 (P>0.05 for both).
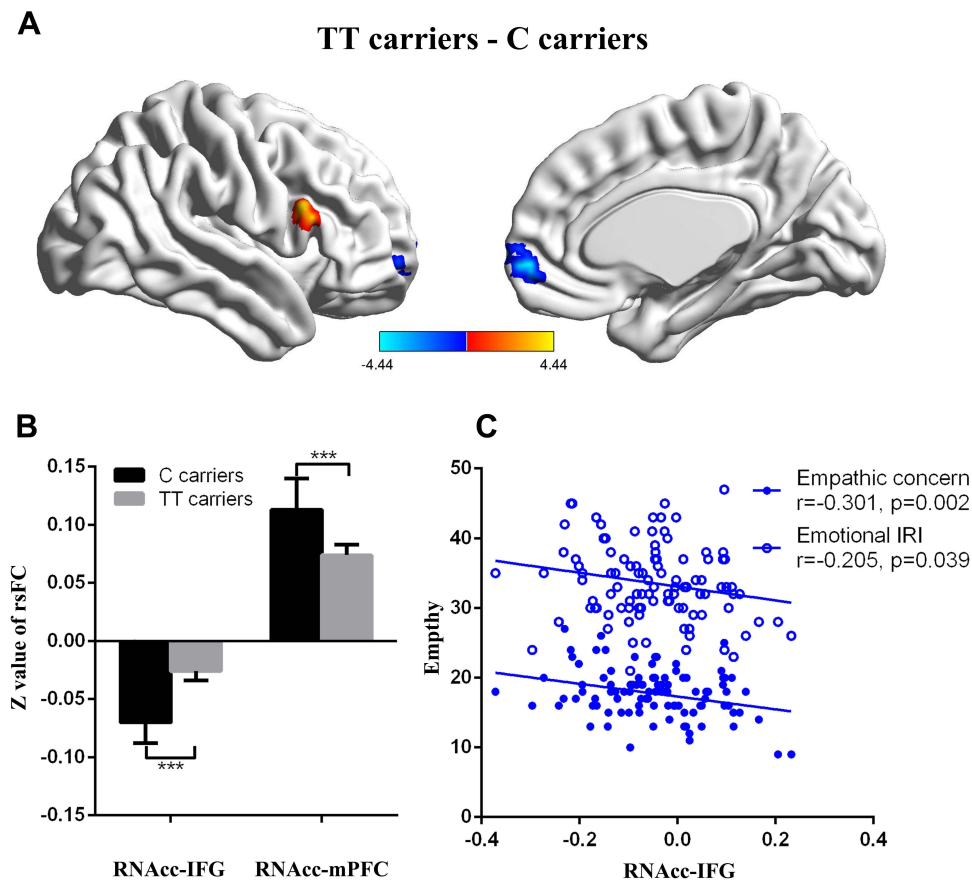
Figure 3 Genotype effects on functional connectivity in the RNAcc. Participants in the TT group exhibited lower functional connectivity of the RNAcc with the medial prefrontal cortex (mPFC) and higher functional connectivity of the RNAcc with the inferior frontal gyrus (IFG) than the CC/CT group ($P<0.05$: Figure 3A and B). Functional connectivity for the RNAcc with the IFG was significantly correlated with emotional IRI score ($R=-0.205$, $P<0.05$), especially the subscore of empathic concern ($R=-0.301$, $P<0.01$; Figure 3C).

demonstrated between performance on the emotional/cognitive IRI-C and reward-network function, suggesting that the *OXTR* gene (rs2268493) modulated empathy performance through functional reward-network connections between the NAcc and mPFC regions.

Consistently with previous findings, allelic variations in rs2268493 were associated with social cognition, including reward and emotional processing.[28,52] Damiano et al (2014) found decreased activation in reward circuitry during reward tasks among carriers of the rs2268493 TT allele. Similarly, a previous study also reported an interaction between the rs2268493 T allele and perceived maternal care during emotion processing.[28] Importantly, both social–affective and reward processing contribute to normal empathy, hence it is predictable that carriers of the rs2268493 TT allele may have empathic impairments.[53] Indeed, the rs2268493 TT allele is frequently reported in patients with empathic dysfunction, such as thos with ASD and schizophrenia.[26] Our study further confirmed the *OXTR* polymorphism is associated with reward-network connection and related to empathy performance.

Our results suggested abnormal NAcc-mPFC and NAcc-IFG resting-state functional connectivity in individuals with the rs2268493 TT genotype. The mPFC and IFG are recognized as integral parts of empathic neural activity.[54] The mPFC has frequently been confirmed to have aberrant structure and function in patients with empathic impairment.[31] Evidence from structural studies suggests that bilateral mPFC damage abolishes empathic response and insight.[33,47] Functionally, mPFC activity shows increased functional connectivity with affective pain regions during emotional empathy.[55] In addition, IFG is another region involved in empathy processing. Significant activation of the right IFG is associated with performance on the IRI-C empathy questionnaire.[9] Interestingly, the IFG plays a preferential role in emotional empathy, but not cognitive empathy.[31] It should be noted that our findings have similar connections between emotional empathy
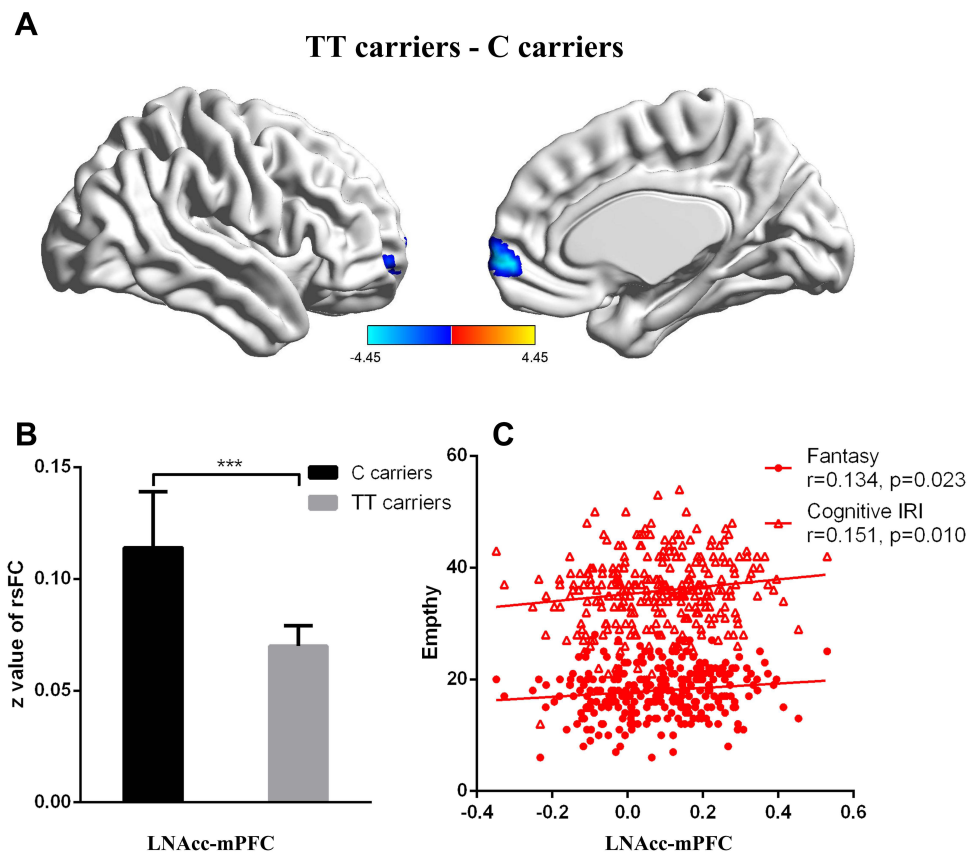
A

TT carriers - C carriers

B

C

Figure 4 Genotype effects on functional connectivity in the LNAcc. Participants in the TT group exhibited lower functional connectivity of the LNAcc with the medial prefrontal cortex (mPFC, *P*<0.05; Figure 4A and B). The functional connectivity between the LNAcc and mPFC were significantly correlated with the cognitive IRI score (*R*=0.151, *P*=0.01) and Fantasy subscore (*R*=0.134, *P*<0.05; Figure 4C).

andthe IFG, mainly due to the functional connectivity for the right IFG correlating with emotional IRI-C score, but not cognitive ones.

Although empathy is intimately related to the reward network, we did not find gene-regulating empathy function in the rs2268493 genotype. There was no ALFF difference in the bilateral NAcc among the rs2268493 subgroups. On the contrary, our results indicated that the NAcc had a modulatory effect on empathic activities by connections with the empathic-related region.[8,56] This result underscored an interaction between *OXTR* variation and empathy by means of modulating intranetwork connections of the reward network, independently of the effects of local activity.

Our findings showed that right-connection NAcc–IFG was significantly correlated with emotional IRI-C scores and left-connection (NAcc-mPFC) linked with cognitive IRI-C. The nature of hemisphere lateralization may be behind this discrepancy. Substantial evidence support cognitive and emotional activity preferentially depending on the left and right hemispheres, respectively. This is very similar to the neural mechanisms underlying the two types of empathy (cognitive and emotional).[46] Hemisphere lateralization for the two types has been implicated in previous studies.[16] The involvement of the left mPFC, left amygdala, and left anterior insula are related to cognitive empathy, and affective empathy is mediated by the right TPJ and right IFG.[54,57,58] It is notable that this assumption is based on the left-hemisphere dominance of participants. Research on a large scale has shown 87.7%–94.8% right-sided domination in China's population; therefore, most of the participants enrolled were left hemisphere–dominant. The left NAcc-mPFC may preferentially be involved in cognitive empathy processing.

We observed a curious phenomenon whereby all the C-carriers were male, which has never been seen in other related studies,[28,44,45,59] most likely due to ethnicity differences. The rs2268493 gene polymorphisms were first reported among Han Chinese. Although we compared the differences in NAcc functional connectivity between the two genotype groups with sex as

a covariate, we still need to admit that the sex imbalance had some impact on our results, and follow-up research should be conducted to fully understand rs2268493 gene specificity and comprehensively across different ethnic groups.

We also admit to several additional limitations in this study. Based on the behavioral and imaging research findings, we chose only *OXTR* rs2268493. Multiple polymorphisms in the *OXTR* gene have demonstrated relationships with reward–empathy processing. However, examination based on one SNP may not provide a comprehensive understanding of the variance in behavioral and neuroimaging phenotypes, hence inevitably attenuating the generalizability of our results. Moreover, the correlation between the neural features of right NAcc–IFG and left NAcc-vmPFC functional connectivity and IRI-C subscores achieved statistical significance (at the 0.05 level) without correction in our study. This low effect size may have been caused by the high homogeneity of the enrolled students (same race, similar educational backgrounds and ages). Future studies should verify gene–brain interactions of reward networks contributing to the effect of empathy in patients with typical disorders, especially ASD.

Conclusion

The current study provided evidence of the modulatory effect in common *OXTR* variations on reward-circuitry function and its relationship with empathy in a highly homogeneous population. Our results suggest that *OXTR* rs2268493 has a modulatory effect on the connection of NAcc with hubs of empathic networks (mPFC and IFG), which was closely related with empathic performance. Those with the rs2268493 TT genotype exhibited lower functional connectivity of the right NAcc with the mPFC and IFG, and similarly lower functional connectivity between the left NAcc and mPFC. These findings may provide insight into the neural substrates underlying the modulatory effect of *OXTR* on empathic behavior.

Ethics Statement

The subjects were recruited from Anhui Medical University, Anhui Province, China. This study was approved by the Research Ethics Committee of Anhui Medical University. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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