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Serotonin receptor gene (*HTR2A*) T102C polymorphism modulates individuals' perspective taking ability and autistic-like traits

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Previous studies have indicated that empathic traits, such as perspective taking, are associated with the levels of serotonin in the brain and with autism spectrum conditions. Inspired by the finding that the serotonin receptor 2A gene (*HTR2A*) modulates the availability of serotonin, this study investigated to what extent *HTR2A* modulates individuals' perspective taking ability and autistic-like traits. To examine the associations of the functional *HTR2A* polymorphism T102C (rs6313) with individuals' perspective taking abilities and autistic-like traits, we differentiated individuals according to this polymorphism and measured empathic and autistic-like traits with Interpersonal Reactivity Index (IRI) and Autism-Spectrum Quotient (AQ) scale in 523 Chinese people. The results indicated that this polymorphism was significantly associated with the scores on Perspective Taking and Personal Distress subscales of IRI, and Communication subscale of AQ. Individuals with a greater number of the C alleles were less likely to spontaneously adopt the point of view of others, more likely to be anxious when observing the pain endured by others, and more likely to have communication problems. Moreover, the genotype effect on communication problems was mediated by individuals' perspective taking ability. These findings provide evidence that the *HTR2A* T102C polymorphism is a predictor of individual differences in empathic and autistic-like traits and highlight the role of the gene in the connection between perspective taking and autistic-like traits.

Keywords: empathy, perspective taking, autistic-like traits, serotonin, *HTR2A*

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INTRODUCTION

Empathy, in the broadest sense, is the lens through which we understand, experience, and respond to the internal states of others (Davis, 1983). It is composed of a variety of skills or components, such as perspective taking (the understanding of another person's beliefs and thoughts, also termed "theory of mind") and empathic response (the emotional response to others' affective states) (Baron-Cohen and Wheelwright, 2004; Batson, 2009; Shamay-Tsoory, 2009). These skills allow

us to understand and predict others' motives, intentions, thoughts, and emotions, so as to foster and maintain social relationships (Davis and Oathout, 1987). Deficit in empathic ability is a central feature of social behavioral abnormalities. For example, individuals with autism, which is a developmental disorder characterized by restricted interests, stereotyped and repetitive behaviors, as well as deficits in social interaction and communication (Gmitrowicz and Kucharska, 1994), show severe impairment in perspective taking (Baron-Cohen et al., 1985).

Empathic traits are strikingly variable among individuals. Twin studies showed that empathic traits are highly heritable,

downstream primer, 5′-GTATGTTTCCAGCAAT-3′. The PCR reaction was performed with an initial 5 min denaturation at 94°C, followed by 35 cycles of 94°C for 30 s, 60°C for 30 s, 72°C for 1 min, and a final extension period at 72°C for 5 min. The PCR product was incubated with the restriction enzyme MspI (Fermentas) at 37°C overnight in a 5 μL digestion system, containing 1.0 μL PCR products, 0.40 μL (10U/μL) MspI, 0.40 μL Tango buffer and 3.2 μL H_2O. The incubated mixture was analyzed by using 8% polyacrylamide gel electrophoresis in 220 V for 2.5 h. The gels were stained with 1.0% silver nitrate solution, and the genotypes bands in gels were identified by the Bio-imaging Systems software. In the current sample of 523 individuals, the distribution of genotypes (CC = 105, CT = 271, TT = 147) did not deviate from Hardy-Weinberg Equilibrium ($\chi^2 = 0.970$, $p = 0.325$). The genotype frequencies were similar to those found in other Chinese Han samples (Zhang et al., 2008; Chen et al., 2009).

Interpersonal Reactivity Index (IRI)

Empathic traits were measured with the Chinese version (Rong et al., 2010) of the 28-item IRI (Davis, 1983), which is the most commonly used self-report instrument assessing empathy and which is based on a multidimensional approach. The scale consists of four 7-item subscales including Perspective Taking, Fantasy, Empathic Concern, and Personal Distress. Perspective Taking subscale evaluates an individual' s cognitive propensity to spontaneously adopt the point of view of others; Fantasy subscale assesses the extent to which people immerse themselves into the feelings and actions of characters in fictional situations; Empathic Concern subscale measures the feeling of warmth, compassion, and concern in response to the misfortune of others; Personal Distress subscale taps "self-oriented" feelings of personal anxiety and discomfort when observing the pain endured by others. For each item, the respondent selected on a 5-point Likert scale the degree to which the description applied to him/herself, with 0 indicating "does not describe me well" and 4 indicating "describes me very well." The internal consistencies for Perspective Taking, Fantasy, Empathic Concern, and Personal Distress were 0.601, 0.605, 0.642, and 0.684, respectively. They were comparable to what were reported in a previous study ($0.59 \leq \alpha \leq 0.78$) (Rong et al., 2010). The total score of each subscale was calculated according to the scoring procedure suggested by Davis (1983). Of note, 178 participants (out of 523) completed the IRI in a previous study (Gong et al., 2014) and they completed the IRI again for this study.

Autism-Spectrum Quotient (AQ)

Autistic-like traits were measured with the Chinese version (Liu, 2008) of the 50-item AQ (Baron-Cohen et al., 2001), a self-administered questionnaire for adults of normal intelligence that identifies to what extent the respondent might have features of the core autistic phenotypes. It consists of five 10-item subscales: Social Skill, Attention Switching, Attention to Detail, Communication, and Imagination. Social Skill subscale measures the unwillingness and inability to develop social relationships; Attention Switching subscale assesses the preference to focus on and the inability to shift attention away from stereotyped, repetitive patterns of activities; Attention to Detail subscale evaluates the willingness and ability to notice or remember detail, such as dates and numbers; Communication subscale assesses the unwillingness and inability to initiate or sustain a conversation with others; Imagination subscale measures the unwillingness and inability to engage in symbolic, imaginative activities, including reading fiction, watching dramas, and playing games involving pretending. For each item, the respondent answered 'definitely agree,' 'slightly agree,' 'slightly disagree,' or 'definitely disagree' according to the extent to which the description applied to him/herself. Each item scores one point if the respondent agreed with the description of autistic-like behavior, i.e., poor social skill, poor communication, poor imagination, exceptional attention to detail, poor attention switching/strong focus of attention. The internal consistency for the Chinese version of AQ was 0.578 in the present sample, which is slightly lower than the score (0.670) in a previous study with a large healthy sample (Hurst et al., 2007). The total score of each subscale was calculated according to the scoring procedure suggested by Baron-Cohen et al. (2001). For the total score on AQ, eight participants scored from 32 to 34, at or above the cutoff for distinguishing autistic populations versus non-autistic populations (Baron-Cohen et al., 2001). This is to be expected, as autistic traits are reported to a greater extent in the general populations of Eastern cultures than Western cultures (Liu, 2008; Freeth et al., 2013), which strongly suggests that these individuals would not be diagnosed with autism. In addition, the percentage of autistic-like individuals in the current study was consistent with what has been reported in a previous study (Liu, 2008), so we decided to include these participants in the data analysis.

Statistical Analysis

To test the effects of the *HTR2A* T102C polymorphism on empathic and autistic-like traits, we conducted univariate linear regression analyses with the genotypes (0 = CC, 1 = CT, 2 = TT) as a single predictor (for the outcome variables, see **Table 1**). Because of multiple testing (n tests = 10), to control for the rate of false-positive findings by chance, we adjusted p values using Bonferroni correction. To estimate the probability of correctly rejecting the null hypothesis when it is false (1 – β), *post hoc* power analyses were carried out using the program G*power 3.0 (Faul et al., 2007) with the two-tailed alpha level set at 0.05 (uncorrected) or 0.005 (Bonferroni corrected). The power analysis was also used to calculate the minimal detectable effect. Results indicated that the minimum regression coefficient of 0.122 (i.e., the coefficient of determination $R^2 > 1.48\%$) was required for a sample of 523 (two-tailed $\alpha = 0.05$, $1 - \beta = 0.8$).

To test the robustness of the results in the regression analyses, we randomly selected a subsample with a given size (e.g., $N = 400$) from the total sample 20,000 times and estimated the regression coefficient in each simulated subsample. Then we calculated the probability of the estimated regression coefficients reaching significance in the 20,000 subsamples. The size of the subsample was set at 200, 300, 400, or 500 (**Table 1**).

To test for the mediating role of perspective taking in the association between the *HTR2A* T102C polymorphism and communication problems, we bootstrapped the indirect effectffi

of the polymorphism on Communication through Perspective Taking 20,000 times using the SPSS version of INDIRECT macro (http://www.afhayes.com/; Preacher and Hayes, 2008) and obtained the bias-corrected 95% confidence interval of the indirect effect. The indirect effect is considered statistically significant at $p < 0.05$ when the 95% confidence interval does not include zero.

In our previous study, we found an association between a variant (−1021C/T) in the *DBH* gene and empathic traits, with the CC carriers showing higher scores on the Empathic Concern subscale than the CT/TT carriers (Gong et al., 2014). To examine whether the effects of the T102C polymorphism on empathic and autistic-like traits continued to hold after controlling for the scores on Empathic Concern subscale and/or the −1021C/T polymorphism in the *DBH* gene, we conducted hierarchical regression analysis: step 1, entering control variables; step 2, entering both control variables and the T102C polymorphism.

Results

Direct Effect

As shown in **Table 1**, regression analyses revealed that the polymorphism was significantly associated with the total scores on the Perspective Taking subscale and Personal Distress subscale of IRI, and the Communication subscale of AQ both before and after Bonferroni correction. Individuals with a greater number of the C alleles, which is associated with lower activity of HTR2A, were less likely to spontaneously adopt the point of view of others, were more likely to be anxious when observing the pain endured by others, and were more likely to have communication problems (**Figure 1**). Additionally, results also showed that the polymorphism seemed to be associated with scores on the Attention to Detail subscale of AQ, with a greater number of the C alleles significantly associating with a decreased ability to notice or remember details; however, this result did not survive Bonferroni correction (**Table 1**).

Mediation Analysis

Considering that previous studies have demonstrated the causal link between individuals' perspective taking ability and communication problems (Saxton et al., 2013; Wardlow et al., 2014), we conducted a mediation analysis to examine whether the genotype effect on communication would be mediated by individuals' perspective taking abilities. Compared with a regression in which genotype was included as the only predictor of Communication (the genotype effect: $\beta = -0.125$, $t = -2.880$, $p = 0.004$), when both genotype and Perspective Taking were included as predictors, the effect of genotype on Communication decreased, $\beta = -0.098$, $t = -2.285$, $p = 0.023$ (**Figure 2**). The total indirect effect accounted for 21.6% (1-0.098/0.125) of the genotype effect on Communication. Mediation analysis indicated a significant mediating effect of perspective taking ability on the relationship between *HTR2A* T102C polymorphism and communication problems, indirect effect estimate = −0.0075, *SE* = 0.0031, bias-corrected 95% confidence interval is [−0.0150, −0.0026].

TABLE 1 | Results of descriptive statistics and regression analysis examining the effects of *HTR2A* T102C on empathic and autistic-like traits.

Outcome variable	Mean ± (*SD*)	Range	R^2	β	t	Uncorrected *p*	Power	Bonferroni corrected *p*	Power after Bonferroni correction	The probability of reaching significance when the subsample size is			
										200 (%)	300 (%)	400 (%)	500 (%)
IRI													
Perspective Taking	17.7 ± 3.9	5–28	0.017	0.130	3.002	0.003	0.849	0.028	0.571	44	67	91	100
Fantasy	17.9 ± 4.2	6–28	<0.001	−0.006	−0.147	0.883	0.052	1.000	0.005	1	0	0	0
Empathic Concern	21.2 ± 3.6	4–28	<0.001	0.016	0.354	0.723	0.065	1.000	0.008	2	1	0	0
Personal Distress	14.6 ± 4.6	0–26	0.015	−0.123	−2.829	0.005	0.808	0.049	0.507	39	60	84	100
AQ													
Social Skill	4.2 ± 2.4	0–10	0.004	−0.064	−1.458	0.146	0.310	1.000	0.089	9	9	8	1
Attention Switching	5.0 ± 1.8	0–10	0.007	−0.081	−1.860	0.063	0.458	0.635	0.170	15	20	25	24
Attention to Detail	4.4 ± 2.1	0–10	0.013	0.114	2.616	0.009	0.745	0.092	0.424	34	51	73	100
Communication	3.1 ± 1.9	0–9	0.016	−0.125	−2.880	0.004	0.820	0.041	0.525	41	62	86	100
Imagination	4.0 ± 1.6	0–9	<0.001	0.002	0.046	0.963	0.050	1.000	0.005	1	0	0	0
Total Score	20.8 ± 5.0	8–34	0.003	−0.059	−1.343	0.180	0.271	1.000	0.072	7	7	5	0

We conducted regression analysis with the genotypes (0 = CC, 1 = CT, 2 = TT) as a single predictor of each outcome variable. β refers to the regression coefficient of the genotypes; t refers to the t-statistic of β; uncorrected p refers to the significance of β before Bonferroni correction; Bonferroni corrected p refers to the significance of β after Bonferroni correction. The probability of reaching significance refers to the probability of the estimated regression coefficients reaching significance in the 20,000 subsamples. The size of the subsample was set at 200, 300, 400, or 500.

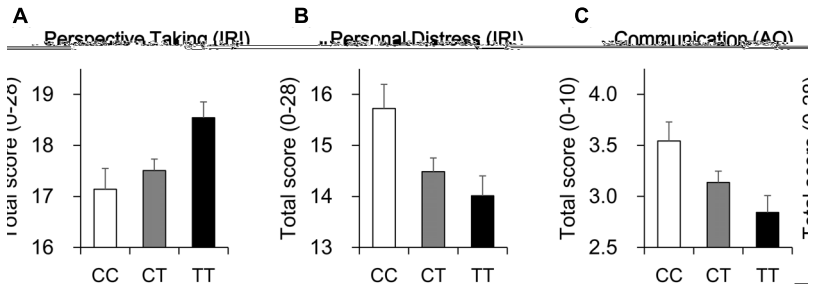

FIGURE 1 | Effects of *HTR2A* T102C polymorphism on perspective taking and autistic-like traits. (A) Individuals with a greater number of the C alleles, which is associated with lower activity of HTR2A, were less likely to spontaneously adopt the point of view of others. **(B)** Individuals with a greater number of the C alleles were more likely to be anxious when observing the pain endured by others. **(C)** Individuals with a greater number of the C alleles were more likely to have communication problems.

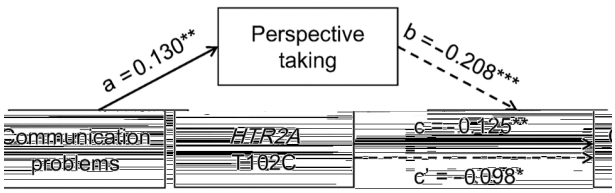

FIGURE 2 | The mediating role of perspective taking ability in the association between *HTR2A* T102C polymorphism (0 = CC, 1 = CT, 2 = TT) and communication problems. All estimates are standardized, *$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Supplementary Analysis

Given the association between a variant (−

TABLE 3 | Results of mediation analysis after controlling for the scores on Empathic Concern subscale and/or the −1021C/T polymorphism in the *DBH* gene.

Control variable(s)	Indirect effect estimate	*SE*	Bias-corrected 95% confidence interval
IRI Empathic Concern	−0.0071	0.0030	[−0.0145, −0.0024]
−1021C/T polymorphism	−0.0083	0.0032	[−0.0161, −0.0032]
IRI Empathic Concern and the −1021C/T polymorphism	−0.0077	0.0031	[−0.0154, −0.0029]

adopt the point of view of others and more likely to be anxious when observing the pain endured by others. We also found that individuals with a greater number of the C alleles were more likely to have communication problems, an autistic-like trait. Further analysis showed that the genotype effect on communication is mediated by individuals' perspective taking abilities.

Previous studies have demonstrated that the reduced availability of HTR2A impairs empathy-related behaviors, such as social communication (Murphy et al., 2006) and prosocial and affiliated orientations (Gerretsen et al., 2010). The present study extended these findings by suggesting that the serotonin receptor gene, *HTR2A*, which regulates the serotonin levels in the brain, to a certain extent, is associated with individual differences in empathic traits.

to misunderstand the intentions and behaviors of others and more likely to have difficulties in communicating with others. Our findings suggest a possible psychobiological mechanism underlying the genotype effect on deficits in social interactions.

Several limitations of this study should be noted. First, we demonstrated small effects of a single polymorphism on empathic and autistic traits while these traits are likely to be influenced by multiple polymorphisms (Rodrigues et al., 2009; Wu et al., 2012; Gong et al., 2014) and by a variety of non-genetic factors (O'Reilly and Peterson, 2014). More systematic studies are needed to simultaneously take into consideration genetic and environmental factors underscoring individual differences in empathic and autistic traits. Second, the present study relied on self-report questionnaires which require the participants to be introspective to provide accurate response to the items. The lack of introspective ability and the influence of social desirability may add noises to the measurement, thereby leading to over- or under-estimation of the contribution of the *HTR2A* T102C polymorphism to individuals' empathic and autistic traits. Third, our power analyses suggested that a genotype effect accounting for less than 1.48% of the phenotypic variance would not be detected because of the medium sample size ($N = 523$) in the present study. As the effect size of a single polymorphism for a complex trait is relatively small (Lander, 2011; Hewitt, 2012), this study might suffer from the low statistical power to distinguish some small but true effects from random chance. Finally, the findings do not have a direct replication in a second sample, a recommended procedure for screening false findings in candidate gene association studies (Hewitt, 2012). To substantiate our claims, we randomly selected subsamples from the total sample and calculated the probability of obtaining significant effects in these samples. We found that our findings have a high probability to be replicated in subsamples of enough size. We have also applied Bonferroni correction to control for false positives in multiple testing.

CONCLUSION

By differentiating individuals according to the polymorphism of *HTR2A* T102C and by measuring empathic and autistic-like traits with IRI and AQ scale, we demonstrated the impact of *HTR2A* gene on individuals' empathic traits and social communication in a general population. Our findings highlight the role of the *HTR2A* gene in social functioning and the connection between perspective taking and autistic-like traits.

AUTHOR CONTRIBUTIONS

PG and JL contributed equally to this work. PG, JL, and XZ designed the study. PG, JL, PB, and XZ wrote the manuscript. PG, JL, and SL performed the experiment and analyzed the data.

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