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# The combined effects of the 5-HTTLPR and HTR1A rs6295 polymorphisms modulate decision making in schizophrenia patients

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**Decision making ability has been reported to be impaired in schizophrenia patients, but no research has examined the genetic bases of this impairment. This study investigated how decision making was affected by the genetic variants in the serotonin transporter gene (triallelic 5-HTTLPR) and serotonin receptor 1A gene (rs6295) and their interaction in 465 schizophrenia patients and 448 healthy controls. The Iowa Gambling Task (IGT) was used to evaluate decision making under ambiguity (the first 40 trials) and decision making under risk (the last 60 trials). Results showed that, among the patients, the main effects of 5-HTTLPR ( $F_{2,16} = 6.54$ ,  $P = 0.002$ ) and HTR1A rs6295 ( $F_{2,16} = 3.87$ ,  $P = 0.021$ ) polymorphisms and their interaction effect ( $F_{4,16} = 3.32$ ,  $P = 0.005$ ) were significant for the first 40 trials, with the GG genotype of HTR1A rs6295, the L'L' genotype of 5-HTTLPR and the GG-L'L' combination showing poorer IGT performance than their counterparts. Results for the healthy controls showed a similar pattern but did not reach statistical significance. No significant effects were found for the last 60 trials. These results are discussed in terms of their implications for our understanding of the genetic mechanisms of decision making in schizophrenia patients as well as healthy adults.**

Keywords: 5-HT1A, 5-HTTLPR, decision making, Iowa Gambling Task (IGT), polymorphism, schizophrenia

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Previous research has shown that impaired cognition is a core symptom of schizophrenia (Barch *et al.* 2009). Decision making is one of the severely impaired cognitive functions among schizophrenia patients. Researchers have made progress in understanding the genetic mechanisms of decision making among healthy adults (Cesarini *et al.* 2009; Kester *et al.* 2006; Ritter *et al.* 2004; Shurman *et al.* 2005), but few studies to our knowledge have examined genetic basis of decision making in schizophrenia (Kim *et al.* 2007).

One frequently studied polymorphism associated with decision making is 5-HTTLPR, a 44 bp insertion/deletion in the promoter region of the serotonin transporter gene (SERT, SLC6A4) (Crisan *et al.* 2009; Homberg *et al.* 2008; Kuhnen & Chiao, 2009; Van Den Bos *et al.* 2009; Zhong *et al.* 2009a). This biallelic polymorphism, either long (l) or short (s) allele, is reported to influence serotonin transporter gene expression and consequently serotonin concentration in the synaptic cleft (Heils *et al.* 1996; Lesch *et al.* 1996; Little *et al.* 1998). It is believed to play an important role in the decision-making process for at least two reasons. First, serotonin is linked to some processes considered important in decision making, such as negative emotions, impulsivity, attention to reward and working memory (Williams, 1994; Williams, 1998; Winstanley *et al.* 2005; Zhong *et al.* 2009b). Second, serotonin is distributed in the brain regions involved in making decisions, such as the prefrontal cortex, amygdala and insular cortex (Bechara *et al.* 2005; Hsu *et al.* 2005; Huettel *et al.* 2005).

In addition to the commonly studied biallelic polymorphism, Hu *et al.* (2006) found another single nucleotide polymorphism (SNP) rs25531 (an embedded A/G substitution) in the l allele (LA/LG), making 5-HTTLPR a triallelic polymorphism (Hu *et al.* 2006). Hu *et al.* (2006) showed that it was the triallelic, not the biallelic, 5-HTTLPR polymorphism that determined the serotonin transporter activity. The LALA genotype showed the highest serotonin transporter expression. A recent study genotyped this triallelic polymorphism in healthy Caucasians and reported that the LALA genotype was associated with poorer Iowa Gambling Task (IGT) performance (Miu *et al.* 2012).

Finally, the level of serotonin in the synaptic cleft is also affected by 5-HT1A receptors (Bayliss *et al.* 1997; Penington *et al.* 1993). In fact, previous studies have found a biological link between the receptors and the transporters. For example, animal studies showed a reduced density of 5-HT1A receptors in 5-HT transporter knock-out mice (Fabre *et al.* 2000; Li *et al.* 1999; Li *et al.* 2000) and a reduced density of 5-HT transporter-binding sites in 5-HT1A knock-out mice (Ase *et al.* 2001). The gene coding for 5-HT1A receptors (HTR1A) is located at chromosome 5 and the most commonly studied

polymorphism of this gene is rs6295 or C(−1019)G. This polymorphism has been linked to personality characteristics, especially affective traits and emotional reactions to stimuli (Koller *et al.* 2005; Lesch *et al.* 2003). Genetic studies in human involving both 5-HTTLPR and HTR1A rs6295 also indicated that they interact with each other (Zhang *et al.* 2009). However, to the best of our knowledge, no study has examined the effect of HTR1A rs6295 or the 5-HTTLPR by rs6295 interaction on decision making.

In this study, we investigated the effects of 5-HTTLPR triallelic polymorphism, HTR1A rs6295 polymorphism and their interaction on decision making in both schizophrenia patients and healthy controls. We used the IGT (Bechara *et al.* 1994) to assess decision making ability. The first two blocks (first 40 trials) of the IGT represent a 'decision under ambiguity' phase because subjects do not know the outcome probabilities yet. In this phase, the decision-making process is influenced more by emotion than by cognition because the situation would evoke an individual's previous emotion experience in similar situations (Bechara *et al.* 1997; Brand *et al.* 2006). The last three blocks (last 60 trials) reflect a 'decision under risk' phase as subjects learn more about the outcomes of their choices, and the decision-making process in this period is influenced more by executive functions than by emotion (Bechara *et al.* 1997; Brand *et al.* 2006; Brand *et al.* 2007). On the basis of the fact that the serotonin system is tightly related to emotion and plays a more important role in emotion than in executive functions (Cools *et al.* 2008; Dayan & Huys, 2008), our hypothesis was that the two serotonin-related polymorphisms – 5-HTTLPR and HTR1A rs6295 – would play a important role in decision making, especially decision making under ambiguity that was mainly driven by emotion.

## Materials and methods

### Subjects

Four hundred and sixty-five schizophrenia patients (307 males) and four hundred and forty-eight healthy controls (275 males) participated in this study. All subjects were Han Chinese. The patients were recruited from the Ankang Hospital in Shandong Province, a division of the Jining Medical College, from August 2008 to October 2010. All patients had been hospitalized for less than 1 month and fulfilled the ICD-10 criteria for schizophrenia based on the diagnostic consensus of two experienced psychiatrists using the Mini International Neuropsychiatric Interview (MINI). This scale has a Chinese version with high reliability and validity (Si *et al.* 2009). Patients were excluded if one of the psychiatrists was uncertain about their diagnosis. The general recruitment procedure was that a clinician first judged if the patient satisfied the inclusion and the exclusion criteria (see below). The clinician and the psychologist then together explained the study to the patient, including drawing of blood and cognitive tests, and answered all questions. Subjects then signed the informed consent document. Afterwards, a small volume of blood was drawn from the patient and the psychologist asked the patient to perform the cognitive tasks.

The Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) were used to assess each patient's positive and negative symptoms at the time of administration of the cognitive tests. The mean score of the patients' SAPS was  $19.1 \pm 6.6$  and the mean SANS score was

$17.4 \pm 7.3$ . The mean duration of illness was  $5.5 \pm 8.2$  years, and the mean number of previous hospitalizations was  $2.1 \pm 3.9$ . All patients underwent monotherapy for more than a week with atypical antipsychotics such as Risperidone, Olanzapine, Clozapine, Aripiprazole, Quetiapine, Ziprasidone and Sulpiride Aripiprazole. The chlorpromazine equivalent doses table was applied in this study to estimate the medication usage across different atypical antipsychotics (Woods, 2003) and the mean medication doses per day was  $578.1 \pm 419.0$  mg. Exclusion criteria for the patients included a history of other psychiatric disorders, a history of severe head injury (including any closed or open head injuries that may be related to current symptoms or impact cognitive functions), currently having acute psychotic episodes, current substance abuse and failure to cooperate during the cognitive tests. Subjects were deemed by the experimenter as 'fail to cooperate' when they abruptly stopped performing tasks in the middle of the experiment, when they pressed keys only when prompted by the experimenter, and when they failed to cooperate to complete the practice trials of a test to reach an acceptable threshold of accuracy after multiple attempts.

The healthy controls were from the same geographical region as the patients and were interviewed by experienced psychiatrists to screen for any personal or family history of psychiatric disorders. Additional demographic information for both patients and healthy controls is shown in Table 2. This study was approved by the Institutional Review Board of the Institute of Cognitive Neuroscience and Learning at Beijing Normal University, and all subjects gave written informed consent for this study.

### Iowa Gambling Task (IGT)

Three hundred and fifty-one patients with schizophrenia (233 males) and 344 healthy controls (208 males) completed the IGT. In this study, a computerized version of the IGT was used. Subjects were asked to select one card at a time from one of the four decks (labeled A, B, C, D) and try to make as much money as they could. Cards from decks A and B are associated with a large average gains (¥100), whereas cards from decks C and D are associated with relatively small average gains (¥50). However, for every 10 cards from decks A and B, there is a ¥1000 gain and ¥1250 loss; for every 10 cards from decks C and D, there is a ¥500 gain and ¥250 loss. Therefore, decks A and B were disadvantageous as they yielded high immediate gain but a greater loss in the long run, whereas decks C and D were advantageous because they yielded lower immediate gain but a smaller loss in the long run. The number of choices from the advantageous decks minus the number from the disadvantageous decks [(C + D) − (A + B)] was used as the main score to evaluate the participants' IGT performance (Bechara *et al.* 1994; Bechara *et al.* 1997; Bechara *et al.* 2000; Bechara *et al.* 2005). This test had 100 trials and most previous studies divided them into five blocks with 20 trials in each. Participants in this study achieved increasing IGT scores as the task went on. As mentioned in previous studies, subjects dramatically improved their performance after 40 trials, with participants choosing more disadvantageous cards in the first 40 trials and beginning to choose more advantageous cards afterwards (Bechara *et al.* 1994; Bechara *et al.* 1997; Homberg *et al.* 2008; Van Den Bos *et al.* 2009, 2006). Similar to those researches, we also found this pattern in both patients and controls. Accordingly, we also divided all the 100 trials into two parts: first 40 trials and the last 60 trials, and considered the first 40 trials (first two blocks) as 'decision under ambiguity' and the last three blocks (last 60 trials) as 'decision under risk'.

### Genotype analysis

Genomic DNA was extracted from a 200 µl ethylenediaminetetraacetic acid venous blood sample from each subject using the QuickGene-Mini80 equipment and QuickGene DNA whole blood kit S (Fujifilm, Tokyo, Japan). The triallelic 5-HTTLPR polymorphism and SNP rs6295 were genotyped following the procedures detailed in previous studies (Beste *et al.* 2010; Wendland *et al.* 2006). Each sample was genotyped twice and all the final digestion products were read by two researchers, and the samples that failed to show consistent

results were excluded from this study. In this study, we grouped the LG allele together with s allele as they functioned similarly in the expression of serotonin transporters (Hu *et al.* 2006). Besides the three commonly reported alleles s (70.98%), LA (14.00%) and LG (10.21%), an extra long (XL) (4.81%) allele that is approximately 81 bp longer than the l allele was also observed. This allele had been reported previously in samples of African, Japanese and Chinese populations (Delbruck *et al.* 1997; Gelernter *et al.* 1999). Since no previous studies of triallelic 5-HTTLPR offered a clear grouping strategy for the XL allele, 40 XL carriers in this study were excluded from the analysis. Therefore, in this study, we used L' to stand for the LA allele and S' to stand for the s and the LG alleles.

**Data analysis**

The PLINK program was used to perform the Hardy–Weinberg test for each SNP. SPSS 17.0 was used to perform one-way ANOVA or the chi-square test to investigate whether demographic factors (including age, IQ and years of education) showed significant differences between genotypes or between patients and controls. Those demographic factors that showed significant associations were used as covariates in the subsequent analyses. ANOVA was conducted in this study using 5-HTTLPR, HTR1A rs6295 and group (patients vs. controls) as independent variables and IGT scores for the first 40 trials and the last 60 trials as dependent variables. Significant interaction effects or the main effect of genotype were further explored in patients and controls separately by ANOVA (5-HTTLPR and HTR1A rs6295 as independent variables). Because two polymorphisms were included in this study, the

significance level was set as 0.025 (0.05/2) after the Bonferroni correction.

**Results**

The allele frequencies for each SNP in the total sample did not show any deviation from Hardy–Weinberg equilibrium ( $P_{rs6295} = 0.71$ ;  $P_{5-HTTLPR} = 0.261$ ). HTR1A rs6295 genotypes showed an association with schizophrenia ( $\chi^2 = 6.45$ ,  $P = 0.040$ ). 5-HTTLPR showed no significant difference in allele frequencies between patients and controls ( $\chi^2 = 2.51$ ,  $P = 0.284$ ) (Table 1). One-way ANOVA and  $\chi^2$  tests showed significant differences between the patients and controls in age, years of education and total IQ (all  $P$  values  $< 0.05$ ) (Table 2).

In terms of genetic effects, for the first 40 trials, there was a significant main effect of HTR1A rs6295 on the IGT performance ( $F_{2,16} = 3.87$ ,  $P = 0.021$ ). Post-hoc analysis showed that subjects with the GG genotype had significantly lower IGT scores than subjects with the GC and CC genotypes. 5-HTTLPR was also significantly associated with the IGT scores ( $F_{2,16} = 6.54$ ,  $P = 0.002$ ): Individuals with the L'L' genotype those with a significantly lower mean IGT score than had the S'L' and S'S' genotypes. Analysis also

**Table 1:** Genotype and allele frequencies

	Genotype N (%)					Allele N (%)			
	1	2	3	$\chi^2$	$P$	Minor	Major	$\chi^2$	$P$
5HTR1ARs6295	GG	GC	CC	6.45	0.040*	G	C	1.06	0.302
Case	31 (6.7)	182 (39.5)	248 (53.8)			244 (26.5)	678 (73.5)		
Control	21 (4.9)	203 (47.3)	205 (47.8)			245 (28.6)	613 (71.4)		
5-HTTLPR	L'L'	S'L'	S'S'	2.51	0.284	L'	S'	1.82	0.177
Case	14 (3.5)	101 (24.8)	289 (71.7)			129 (16.0)	679 (84.0)		
Control	7 (1.8)	90 (23.4)	288 (74.8)			104 (13.5)	666 (86.5)		

\* $P < 0.05$ .

**Table 2:** Clinical and demographic data (mean  $\pm$  SD) for schizophrenia and control groups

	Schizophrenia patients (351)	Healthy controls (344)	$F$ (or $\chi^2$ )	$P$ value
Age (years)	28.1 $\pm$ 8.0	22.4 $\pm$ 6.6	108.6	$< 0.001^*$
Gender (F/M)	118/233	136/208	2.625	0.106
Education (years)	9.9 $\pm$ 2.9	10.6 $\pm$ 2.7	10.1	0.002*
IQ	99.1 $\pm$ 13.4	108 $\pm$ 12.0	107.6	$< 0.001^*$
Medication (mg)	578.1 $\pm$ 419.0	NA	NA	NA
Illness duration (years)	5.5 $\pm$ 8.2	NA	NA	NA
Previous hospitalization (times)	2.1 $\pm$ 3.9	NA	NA	NA
PANSS <sup>†</sup>	71.1 $\pm$ 18.8	NA	NA	NA
SANS <sup>‡</sup>	17.4 $\pm$ 7.3	NA	NA	NA
SAPS <sup>§</sup>	19.1 $\pm$ 6.6	NA	NA	NA

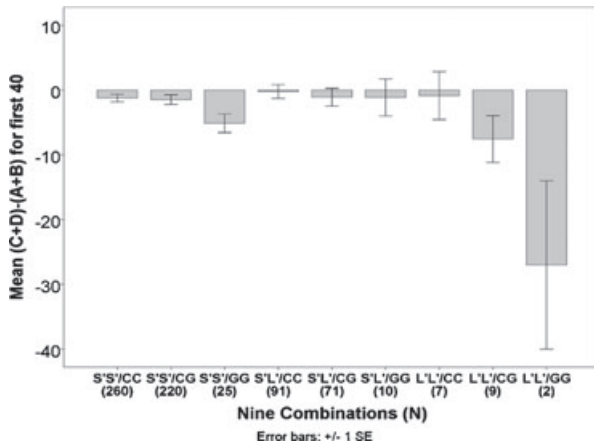
NA, not applicable.

\* $P < 0.05$ .

<sup>†</sup>The positive and negative syndrome scale.

<sup>‡</sup>Scale for the assessment of negative symptoms.

<sup>§</sup>Scale for the assessment of positive symptoms.



**Figure 1: Mean number of cards taken from advantageous decks C and D minus the number of cards taken from disadvantageous decks A and B in the first 40 trials across the nine combinations of the two polymorphisms –5-HTTLPR and rs6295 for total sample.**

showed a significant interaction between 5-HTTLPR and HTR1A rs6295 on the first 40 trials ( $F_{4,16} = 3.32, P = 0.005$ ) (Fig. 1). It should be mentioned that there were only two cases for the combination of the L'L' and GG genotype. The two cases showed the lowest scores (–14 and –40, which were –1.22 and –3.75 SD, respectively, away from the grand mean).

To strengthen the statistical power, two strategies were applied in this study. First, when the two cases were excluded, the omnibus  $F$  statistic for the interaction term in ANOVA was marginally significant ( $F_{3,15} = 2.95, P = 0.032$ ). Second, when we grouped the GG and GC genotypes of HTR1A rs6295 together, the interaction effect was still marginally significant ( $F_{2,11} = 2.903, P = 0.056$ ) (Supporting Information, Fig. S2). There were no significant interaction effects involving subject group (rs6296 × groups, 5-HTTLPR × groups and rs6295 × 5-HTTLPR × groups) (all  $P$  values >0.05). As for the last 60 trials, no significant association was found (Table 3).

An additional analysis was performed to determine whether the overall effect of genotype was comparable when cases and controls were considered separately. No demographic characteristics showed differences among genotypes in either of the two groups (Supporting information, Table S1), so they were not used as covariates in subsequent analyses. It seems that the findings reported above for the total sample were mainly driven by the patient sample. There were significant effects of both 5-HTTLPR ( $F_{2,8} = 5.68, P = 0.004$ ) and HTR1A rs6295 ( $F_{2,8} = 3.68, P = 0.025$ ) and their interaction ( $F_{4,8} = 3.32, P = 0.011$ ) for the patient sample. For the healthy controls, which had a sample size comparable to that of schizophrenia patients, we only found a significant interaction effect ( $F_{3,7} = 2.64, P = 0.067$ ) that did not withstand the multiple-comparison correction (Table 3).

**Table 3: Means (SD) of ICT score for different genotypes and groups**

	Rs6295 Mean ± SD(N)				5-HTTLPR Mean ± SD(N)				$F_{rs6295 \times 5-HTTLPR} (P)$	$F_{rs6295} (P)$	$F_{5-HTTLPR} (P)$	$F_{rs6295 \times 5-HTTLPR} (P)$	
	GG	GC	CC	L'L'	S'L'	S'S'	S'L'	S'S'					
First 40													
Total (695) <sup>†</sup>	–5.7 ± 2.1 (37)	–3.2 ± 1.2 (300)	0.218 ± 1.5 (358)	–7.4 ± 2.6 (18)	1.3 ± 1.2 (172)	–2.8 ± 0.7 (505)	3.87 (0.021)*	6.54 (0.002)*	3.75 (0.005)*				
Case (351)	–10.3 ± 2.7 (21)	–2.8 ± 1.6 (136)	–2.1 ± 1.5 (194)	–11.5 ± 3.0 (11)	–0.4 ± 1.4 (93)	–3.5 ± 1.0 (247)	3.68 (0.025)*	5.68 (0.004)*	3.32 (0.011)*				
Control (344)	1.3 ± 3.1 (16)	–3.6 ± 1.8 (164)	2.6 ± 2.7 (164)	–1.3 ± 4.6 (7)	2.9 ± 2.0 (79)	–2.2 ± 1.1 (258)	2.12 (0.122)	2.02 (0.135)	2.41 (0.067)				
Total (695) <sup>†</sup>	10.1 ± 4.7 (37)	3.5 ± 2.7 (300)	11.3 ± 3.3 (358)	4.4 ± 5.8 (18)	11.1 ± 2.7 (172)	8.4 ± 1.6 (505)	1.73 (0.177)	0.70 (0.499)	1.75 (0.117)				
Case (351)	13.2 ± 6.2 (21)	1.4 ± 3.8 (136)	3.4 ± 3.4 (194)	2.5 ± 7.1 (11)	9.5 ± 3.3 (93)	6.2 ± 2.2 (247)	1.35 (0.260)	0.56 (0.570)	2.26 (0.062)				
Control (344)	5.4 ± 6.7 (16)	5.5 ± 3.8 (164)	19.1 ± 5.7 (164)	7.4 ± 9.8 (7)	12.7 ± 4.3 (79)	10.6 ± 2.4 (258)	2.89 (0.057)	0.351 (0.704)	1.13 (0.338)				

\*  $P < 0.025$ .

<sup>†</sup>IQ, education and age were included as covariates.



## Discussion

Consistent with our hypothesis, the main effects of both 5-HTTLPR and HTR1A rs6295 polymorphisms and their interaction effect on IGT scores were significant for the first 40 trials but not for the last 60 trials of the IGT. For both polymorphisms, it was the genotypes associated with low synaptic serotonin levels (L'L' of 5-HTTLPR and GG of HTR1A rs6295) that showed impaired IGT performance. The pattern was similar in both schizophrenia patients and healthy controls as reflected by the non-significant interaction effects (rs6295 × group, 5-HTTLPR × group and rs6295 × 5-HTTLPR × group), although separate analyses showed that the results were significant for patients, but not for controls.

Most previous studies of 5-HTTLPR and IGT did not genotype rs25531, and many of them had Caucasians as subjects and found the *l* allele to be related to improved IGT performance (Homberg *et al.* 2008; Jollant *et al.* 2007; Must *et al.* 2007; Van Den Bos *et al.* 2009). However, by considering rs25531, not only the allele frequencies changed but the allele function also changed consequently. For example, in Caucasians, previous biallelic studies indicated the *s/s* genotype was highly associated with post-traumatic stress disorder (PTSD) (Kilpatrick *et al.* 2007; Lee *et al.* 2005), but with the consideration of rs25531, the L'L' genotype became the risk genotype for developing this disorder (Grabe *et al.* 2009). Consistently, our study in Han Chinese population also considered rs25531, and indicated the L'L' genotype showed poorer IGT performance, which is in line with Miu *et al.* (2012) studies in Caucasians.

Although 5-HTTLPR has been intensively studied, no study has examined the effect of HTR1A rs6295 on decision making. Previous studies indicated that the G allele was the risk allele for many mental disorders such as major depression, suicide, anxiety, panic disorder and schizophrenia (Huang *et al.* 2004; Lemonde *et al.* 2003; Lemonde *et al.* 2004; Serretti *et al.* 2004; Strobel *et al.* 2003). According to Wang *et al.* (2008) study, this risk allele was also associated with less sensitive response to atypical antipsychotic treatment for improving the negative symptom, a symptom that has been reported to relate with impaired IGT performance (Shurman *et al.* 2005), with Chinese schizophrenia patients. Moreover, similar to the function of the *l*' allele of 5-HTTLPR, the GG genotype was accompanied by a decreased synaptic serotonin density through up-regulating the 5-HT1A pre-receptor expression (David *et al.* 2005; Lemonde *et al.* 2003; Parsey *et al.* 2006). Consistent with its functions in the serotonin system, the GG genotype also seemed to show the same regulation direction as the L'L' genotype as reflected by its lower IGT scores in the first 40 trials than those of the GC and CC genotypes.

Besides the main effect of the two polymorphisms, our data suggested a possible 5-HTTLPR by rs6295 interaction effect on IGT performance in the first 40 trials as well. Previous publications have already reported a biological link between the two polymorphisms (David *et al.* 2005; Parsey *et al.* 2006), but none of them involved rs25531.

Our study was the first to include rs25531 and to report a significant combined effect of these two polymorphisms. Although particular combinations of the 5-HTTLPR by rs6295 genotypes had a small sample size, the interaction effect appeared robust because it was marginally significant even when we excluded the informative but extreme cases of L'L'-GG combination and grouped the GG and GC genotypes. These encouraging results should inspire further replications with larger samples.

In this study, the individual differences of IGT scores were not affected by the 5-HTTLPR and HTR1A rs6295 polymorphisms when examining the two genes in isolation. However, when the two polymorphisms were considered together, both the main effect and the interaction effect became significant. Similar to our study, some other studies also found that IGT performance were not affected by 5-HTTLPR polymorphism until other factors were introduced into consideration (Ha *et al.* 2009; He *et al.* 2010). All these suggest that the effect of 5-HTTLPR on IGT could be influenced by many other factors, which might contribute to the controversial results of previous association studies of 5-HTTLPR and IGT.

When interpreting the results of this study, some limitations of the study should be considered. First, this was a case-control study of the two polymorphisms – 5-HTTLPR and rs6295 – in schizophrenia. We found that the HTR1A rs6295 polymorphism showed a significant association with schizophrenia, which is in line with one previous study (Huang *et al.* 2004) but inconsistent with two Japanese studies that reported no associations between HTR1A rs6295 and schizophrenia (Kawanishi *et al.* 1998; Kishi *et al.* 2011). As for 5-HTTLPR, although many previous studies investigated this polymorphism in schizophrenia and showed mixed results, only one of them involved rs25531 and found no association (Sullivan *et al.* 2010). Consistent with this study, our results did not show a significant association between this triallelic polymorphism and schizophrenia.

Second, the mean IQ scores of the patient group and healthy controls were relatively high. This pattern has been found in our previous studies and as we argued in those researches, the old version of IQ test and the relative high failure rate for samples with low IQ to finish our computerized cognitive task may contribute significantly to this high IQ problem (Zhang *et al.* 2011).

In conclusion, our study provided evidence for the effects of 5-HTTLPR and HTR1A rs6295 on decision making under ambiguity in schizophrenia patients. These findings help us better understand the relationship between the two polymorphisms and schizophrenia and provide further evidence for the underlying genetic mechanisms of the decision-making process.

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## Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

**Figure S1:** Mean number of cards taken from advantageous decks C and D minus the number of cards taken from disadvantageous decks A and B in the first 40 trials across the six combinations of the two polymorphisms-5-HTTLPR and rs6295 for the total sample.

**Table S1:** Demographic differences among genotypic groups in schizophrenia patients and healthy controls.