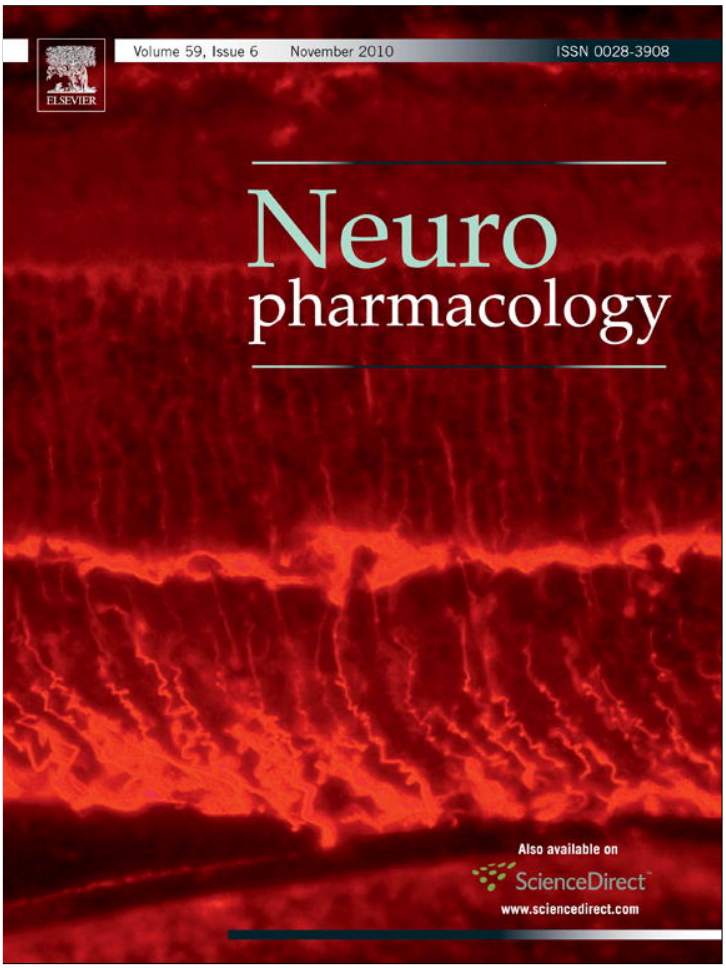

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Serotonin transporter gene-linked polymorphic region (5-HTTLPR) influences decision making under ambiguity and risk in a large Chinese sample

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ABSTRACT

Risky decision making is a complex process that involves weighing the probabilities of alternative options that can be desirable, undesirable, or neutral. Individuals vary greatly in how they make decisions either under ambiguity and/or under risk. Such individual differences may have genetic bases. Based on previous studies on the genetic basis of decision making, two decision making tasks [i.e., the Iowa Gambling Task (IGT) and Loss Aversion Task (LAT)] were used to test the effect of 5-HTTLPR polymorphism on decision making under ambiguity and under risk in a large Han Chinese sample (572 college students, 312 females). Basic intelligence and memory tests were also included to control for the influence of basic cognitive abilities on decision making. We found that 5-HTTLPR polymorphism significantly influenced performance in both IGT and LAT. After controlling for intelligence and memory abilities, subjects homozygous for *s* allele had lower IGT scores than *l* carriers in the first 40 trials of the IGT task. They also exhibited higher loss aversion than *l* carriers in the LAT task. Moreover, the effects of 5-HTTLPR were stronger for males than for females. These results extend the literature on the important role of emotion in decision making under ambiguity and risk, and shed additional lights on how decision making is influenced by culture as well as sex differences. Combining our results with existing literature, we propose that these effects might be mediated by a neural circuitry that comprises the amygdala, ventromedial prefrontal cortex, and insular cortex. Understanding the genetic factors affecting decision making in healthy subjects may allow us to better identify at-risk individuals, and better target the development of new potential treatments for specific disorders such as schizophrenia, addiction, and depression.

1. Introduction

Making economic decisions under uncertainty, such as whether or not to invest in stocks or buy insurance, is common and essential in everyday life. It is a complex process that involves weighing alternative outcomes' desirability and their probabilities (Fox and Poldrack, 2009; Xue et al., 2010, 2009). There are two main types of economic decisions, decisions under ambiguity and decisions under risk, distinguished by the degree of uncertainty about the outcome probability. For decisions under ambiguity, the decision maker lacks the knowledge of the precise probability distribution of the possible outcomes. On the other hand, decisions under risk are those with known outcome probabilities (Fox and Poldrack, 2009; Stoltenberg and Vandever, 2010).

Individuals vary greatly in how they make decisions under uncertainty. Such individual differences may have genetic bases. Twin studies have estimated that genetic effect accounts for about 20% of the variance in risk taking behavior (Cesarini et al., 2009). It is important to explore the genetic factors affecting decision making in both healthy subjects (van den Bos et al., 2009) and patients with certain psychiatric disorders (such as addiction, schizophrenia, or depression) who are known to have deficits in decision making (e.g., Jollant et al., 2007; Lenze et al., 2005; Roiser et al., 2006; Tremeau et al., 2008, 2007). In this study, we investigated the influence of serotonin transporter gene-linked polymorphic region (5-HTTLPR) on decision making under uncertainty, using a large healthy sample.

Serotonin modulates the synaptic activities of neurons in brain regions that have been shown to be functionally important when making economic decisions (e.g., the prefrontal cortex, see Bechara

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and Damasio, 2005). The serotonin neuronal cell bodies, which reside in the brainstem, project their axons into many brain regions related to decision making, including the prefrontal cortex (orbital, ventromedial and dorsolateral), amygdala, striatum and insular cortex (Baumgarten and Grozdanovic, 1999; Wai et al., 2008). The most often studied genetic polymorphism in the serotonin system is the serotonin transporter gene-linked polymorphic region (5-HTTLPR). The 5-HTTLPR consists of a 44-bp insertion/deletion, resulting in either a long (*l*) or short (*s*) allele. The *s* allele is reported to be associated with reduced serotonin transporter expression as compared to the *l* allele (Heils et al., 1996; Lesch et al., 1996). Polymorphism of the 5-HTTLPR is associated with activation in the amygdala (e.g., Hariri et al., 2005, 2002a, 2002b; Hariri and Holmes, 2006; Labus et al., 2008; see Munafo et al., 2008 for a review), ventromedial prefrontal cortex (e.g., Heinz et al., 2005; Labus et al., 2008), and insular cortex (e.g., Labus et al., 2008).

Recent studies using behavioral and neuroimaging techniques have examined the effect of 5-HTTLPR on economic decision making in both healthy subjects (Crisan et al., 2009; Homberg et al., 2008; Kuhnen and Chiao, 2009; Roiser et al., 2009; Stoltenberg and Vandever, 2010; van den Bos et al., 2009; Zhong et al., 2009) and patients (Jollant et al., 2007; Must et al., 2007). The results are mixed (see Table 1 for a summary of these studies). Five studies (including 2 patient studies) focused on the Iowa Gambling Task (IGT), which is a widely used task with mixed gambles (Bechara et al., 1994, 2000). Three of them showed that *s* allele homozygotes performed worse than those with *l* allele in the overall IGT score (Homberg et al., 2008; Must et al., 2007; van den Bos et al., 2009). Such difference was also present when dividing the IGT into the first 40 (decisions under ambiguity) and the last 60 trials (decisions under risk) (Homberg et al., 2008; van den Bos et al., 2009). Although the other two studies failed to show a significant main effect of genotype, one did suggest that *l* carriers (but not *s*/*s*) showed significant performance improvement from the early to the late stage of the IGT (Jollant et al., 2007), and the other one suggested a significant gender by genotype interaction in the first 20 trials (Stoltenberg and Vandever, 2010). Using a different task (Balloon Analogue Risk Task, BART) aimed to test decision making under ambiguity, it has been shown that the *s* allele was associated with fewer pumps (i.e., taking less risk under ambiguity) in BART (Crisan et al., 2009). In addition, researchers have also examined decision making under risk, using the investment task (Kuhnen and Chiao, 2009), framing design (Crisan et al., 2009; Roiser et al., 2009), and multiple price list design (Zhong et al., 2009). These studies revealed that the *s* allele was associated with more risk aversion, such as less investment in risky asset (Kuhnen and Chiao, 2009) and a larger framing effect (Crisan et al., 2009; Roiser et al., 2009). However, Zhong et al. (2009) only showed a trend (non-significant) that *s* allele was associated with more risk aversion.

A number of factors may have contributed to the inconsistencies in the literature on the influence of 5-HTTLPR on decision making. First and most importantly, previous studies used different tasks. Different tasks not only involve different cognitive and emotional processing, but also target different brain areas that may involve different neurotransmitter systems with different genetic architectures (Stoltenberg and Vandever, 2010). It is thus important to choose tasks whose cognitive and neural mechanisms have been well understood. Second, the sample sizes of most previous studies are relatively small (the largest sample is the study by Zhong et al., $N = 325$). Small sample size has low statistical power and is difficult to yield stable results (Munafo et al., 2008). Third, some of these studies only included female subjects (Homberg et al., 2008; van den Bos et al., 2009), which prevented them from examining gender differences in decision making (e.g., Bolla et al., 2004; Overman et al., 2006; Reavis and Overman, 2001), as well as the interaction between gender and 5-HTTLPR polymorphism (Stoltenberg and Vandever, 2010). Finally, most previous studies did not control other individual differences such as intelligence and memory abilities that play important roles in decision making (e.g., Gupta et al., 2009; Morsanyi and Handley, 2008; Yechiam and Busemeyer, 2005; Yechiam et al., 2008).

The present study tested the effect of 5-HTTLPR polymorphism on decision making under ambiguity and under risk, using two widely used tasks: the Iowa Gambling Task (Bechara et al., 1994) and the Loss Aversion Task (Tom et al., 2007). The initial stage of the IGT (typically the first 40 trials) is usually recognized as decision making under ambiguity because subjects do not yet know the outcome probabilities. And as the task progresses, subjects may acquire some subjective sense of what the outcome probabilities associated with different decisions might be, hence rendering at least the later trials of the IGT as a test of decision making under risk (usually the last 60 trials, see Bechara et al., 1997). The Loss Aversion Task (LAT) tests a specific type of decision making under risk (loss aversion in the prospect theory). A large Han Chinese sample (572 college students, 312 females) was included in the present study. Basic intelligence and memory tests were also included to control for the influence of cognitive abilities on decision making.

Table 1
Summary of previous studies investigating the 5-HTTLPR effect on economic decision making.

Study	*N*	Race	Genotypes			Task	Results
			s/*s*	*s*/*l*	*l*/*l*		
Crisan et al., 2009	32 (23F)	NA[a]	9	9	14	BART and Framing Design	BART numbers of pumps: *s*/*s* < *l* carriers, Gamble in loss frame: *s* carriers > *l*/*l*
Homberg et al., 2008	88 (88F)	NA	22	49	17	IGT	IGT score: *s*/*s* < *l* carriers (larger in trials 41–100)
Jollant et al., 2007[b]	162 (66.1% F)	Caucasian	32	69	61	IGT	No genotype main effect, but significant performance improvement in *l* carriers but not *s*/*s*
Kuhnen and Chiao, 2009	65 (26F)	NA*	21	10	34	Investment Task	Amount invest in risky asset: *s*/*s* < *l* carriers
Must et al., 2007[c]	124 (83F)	NA	35	58	31	IGT	IGT score: *s*/*s* < *l*/*l* with *l*/*s* in the middle
Roiser et al., 2009	30 (13F)	Caucasian	15	0	15	Framing Design	Framing effect: *s*/*s* > *l*/*l*; frontal-amygdala coupling: *s*/*s* < *l*/*l*
Stoltenberg and Vandever, 2010	188 (117F)	Caucasian	39	86	62	IGT	No genotype effect, but a significant gender by genotype interaction in first 20 trials. IGT score for males: *s* carriers > *l*/*l*; IGT score for females: *s* carriers < *l*/*l*
van den Bos et al., 2009	70 (70F)	NA	18	39	13	IGT	IGT score: *s*/*s* < *l* carriers (larger in trials 41–100)
Zhong et al., 2009	325 (53.7% F)	Chinese	168	118	39	Multiple Price List Design	No genotype effect, but a trend of higher risk aversion in subjects with *s* allele

F: females; NA: not available; IGT: Iowa Gambling Task; BART: Balloon Analogue Risk Task.
[a] Subjects were recruited from university campus.
[b] Subjects were all suicide attempters.
[c] Subjects were all diagnosed as unipolar major depressive disorder according to DSM-IV.

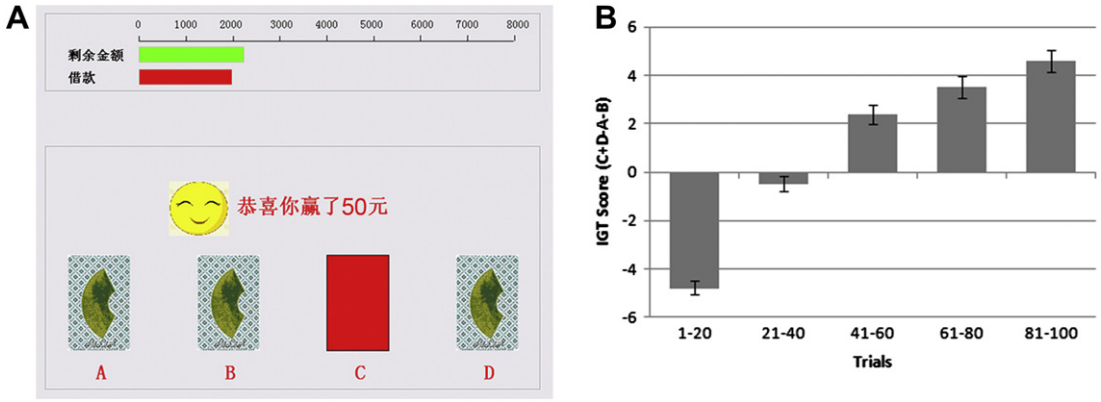

Fig. 1. A) Illustration of the Iowa Gambling Task. Subjects were instructed to choose one card at a time from 4 decks of cards (labeled A, B, C and D). Green bar (the lighter one) on the top represents money in his/her wallet which changed in length as he/she "wins" or "loses". Red bar (the darker one) represents his/her loan (2000 *yuan*). B) IGT score (number of choices from "good" decks minus choices from "bad" decks) showed a linear improvement over 5 blocks (20 cards each). Error bars indicate standard errors. Please note that to protect the validity of the IGT test, the payoffs on the cards are just for illustration purpose, and were not the actual ones subjects received in the task.

2. Materials and methods

2.1. Subjects

Five hundred and seventy-two (312 females) undergraduate students (Han Chinese, aged from 17 to 27 years old, with a mean of 20.47 years, SD = 1.01) were recruited from Beijing Normal University (Beijing, China) to participate in a large-scale gene–brain–behavior project. All subjects had normal or corrected-to-normal vision. According to a modified version of Edinburgh Handedness Inventory (Xue et al., 2004), only a few subjects are left-handers ($N = 35$, 6.12%).[1] Two questionnaires were used to measure drinking (the Alcohol Use Disorders Identification Test, Saunders et al., 1993) and smoking (the Fagerström Test for Nicotine Dependence, Heatherton et al., 1991) behavior separately.

Only 4 subjects[2] were identified to have high levels of alcohol problems (scored 16 or higher on the AUDIT, Saunders et al., 1993); and no subject was found to show high (6–7 on the FTND) or very high (8 or higher on the FTND) dependence on nicotine (Heatherton et al., 1991). Based on self-report, they had not had neurological or psychiatric problems. Informed written consent was obtained from all subjects. This study was approved by the Beijing Normal University Institutional Review Board.

Using polymerase chain reaction (PCR), 569 subjects (310 females, 54.48%) were genotyped (3 subjects failed to be typed because of a technical error). Between 517 and 567 subjects completed and had valid data on tests described below: 549 (304 females) for IGT; 517 (288 females) for LAT; 564 (311 females) for RAPM; 560 (308 females) for WAIS-RC; 567 (311 females) for WMS-Recognition; 558 (307 females) for WMS-Recall; 535 (295 females) for WMT. Three factors contributed to the missing data: first, some subjects did not show up in some testing sessions; second, the program or computer crashed in some testing sessions, causing incomplete data recording; third, some subjects' performance was classified as outliers because their data exceeded ±3 SD of the group means.

2.2. Decision making tasks

2.2.1. The Iowa Gambling Task (IGT)

A computerized version of the IGT (Bechara et al., 2000) was used in the present study (Fig. 1A). It was designed to assess decision making under ambiguity and risk (Bechara et al., 1994, 1997, 2005, 2000). To motivate subjects, they were informed that the amount of their winning would be converted into real money. Subjects were asked to select one card at a time (100 trials in total) from one of the four decks (labeled A, B, C, and D). As described in previous studies and the IGT manual (PAR, Inc.), two of the decks were disadvantageous because they yielded high immediate gain but even a greater loss in the long run (i.e., net loss of 250 *yuan* on average over 10 cards), and two decks were advantageous because they yielded lower immediate gain but even a smaller loss in the long run (i.e., net gain of 250 *yuan* on average over 10 cards).

2.2.2. The Loss Aversion Task (LAT)

In the computerized loss aversion task (Tom et al., 2007), subjects were presented with 256 trials, each of which proposed a gamble of 50/50 chance to win or to lose real money (Fig. 2A). Possible gains ranged from 10 to 40 *yuan* (in increments of 2 *yuan*) and possible losses ranged from 5 to 20 *yuan* (in increments of 1 *yuan*). The 256 trials were the total number of all possible combinations of wins and losses (16×16). Subjects were asked to evaluate whether or not they would like to play each of the gamble by pressing one of the four buttons (strongly accept, weakly accept, weakly reject, and strongly reject). Subjects had 3 s to respond to each trial. They were informed before the game that, in three randomly selected trials, if they had accepted the gamble, the outcome would be decided with a coin toss; if they had rejected, the gamble would not be played. Responses of each subject were re-coded as to gamble or not. The responses were counterbalanced across subjects (i.e., half of the subjects responded to "accept" using their left hand and the other half using their right hand).

2.3. Intelligence and memory tests

Two intelligence tests [Raven's Advanced Progressive Matrices (RAPM) and Wechsler Adult Intelligence Scale-Revised Chinese Version (WAIS-RC)] and three memory tests [Wechsler Memory Scale-Recognition (WMS-Recognition), Wechsler Memory Scale-Recall (WMS-Recall) and Working Memory Test (WMT)] were used to measure subjects' basic cognitive and memory abilities (see Zhu et al., 2010 for detailed description of these tests). Several measures were generated to represent the basic intelligence and memory abilities, including the number of correct response to the test items of RAPM; the three IQ scores (verbal IQ, performance IQ, and total IQ) of WAIS-RC; the total scores of WMS-Recognition and WMS-Recall; and the accuracy of each WMT component (morphology, phonology and semantic). These tests were selected because they are not only among the most widely used intelligence and memory tests in China and elsewhere, but they also have been shown to have good reliability and validity for Chinese subjects.

2.4. Genotype analysis

DNA fragments were amplified by polymerase chain reaction using forward primer 5′-GGC GTT GCC GCT CTG AAT TGC-3′ and reverse primer 5′-GAG GGA CTG AGC TGG ACA ACC AC-3′. The PCR reaction mixture contained a total volume of 25 μl with composition as described in a previous protocol (Collier et al., 1996). After an initial 4 min denaturation step at 95 °C, 35 cycles were performed consisting of 45 s at 96 °C, 90 s at 61 °C, and 90 s at 72 °C. The reaction was ended by a step of elongation at 72 °C for 10 min. PCR products were separated by the long (528 bp) and short (484 bp) variants on 2% agarose gels stained with ethidium bromide for 3 h and then analyzed with a Gel Doc 2000 imaging system (Bio-Rad Laboratories Ltd, UK).

2.5. Procedure

A 4 ml venous blood sample was collected from each subject. Genomic DNA was extracted using the standard method within 2 weeks. 5-HTTLPR polymorphisms were typed using PCR as described above. Subjects were tested over four sessions spread across a period of 11 months. The RAPM test was administered in the first session. The WMS-Recognition and IGT were administered in the second session (5 months after first session). The WAIS-RC and WMS-Recall were administered in the third session (6 months after first session). The WMT and LAT were administered in the last session. Except for the individually administered paper version of the RAPM, WAIS-RC and WMS-Recall, all other tests were administered on computer.

[1] There was no correlation between handedness score and IGT performance (i.e., either IGT score in the first 40 or the last 60 trials, both $rs < .03$, $p > .05$). A small correlation was found between handedness score and loss aversion parameter λ ($r = -.099$, $p = .025$). One-way ANOVA also suggested that handedness score was not biased by 5-HTTLPR genotype ($F(2, 566) = .019$, $p > .05$). Furthermore, there was virtually no change in results after we excluded the left-handed subjects.

[2] There's virtually no change in results after we excluded those subjects with high alcohol problems.

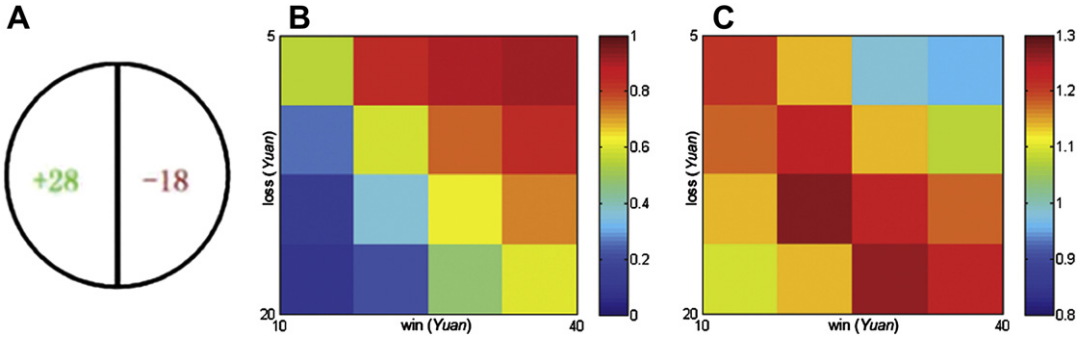

Fig. 2. A) A sample trial of the Loss Aversion Task. On each trial, subjects were presented a display showing the amount of potential gain (in green) and loss (in red). They had to decide to what extent they would like to play this gamble. B) Color-coded heatmap of probability of gamble acceptance at each level of gain/loss. C) Color-coded heatmap of probability of response times (s) at each level of gain/loss.

2.6. Data analysis

For IGT, the 100 trials were divided into 5 blocks of 20 trials. A net score was calculated by subtracting the total number of selections of the disadvantageous decks (A and B) from the total number of selections of the advantageous decks (C and D), separately for each block. In addition, the net score for the first 40 and last 60 trials was also calculated to represent performance in decision under ambiguity and decision under risk, respectively. Higher scores indicated superior performance.

For LAT, following Tom et al. (2007), we collapsed 256 trials into a 4 × 4 win–loss matrix, and calculated the gamble acceptance rate and mean reaction time for each cell. Logistic regression was performed for each subject, using acceptance/rejection as dependent variable (Y), amount of gain (Win) and loss (Loss) as independent variables. The equation was

$$Y = \frac{1}{1 + e^{-\beta_{\mathrm{Win}} \times \mathrm{Win} - \beta_{\mathrm{Loss}} \times \mathrm{Loss}}} + E$$

where β_{Win} and β_{Loss} are the unstandardized regression coefficients for gain and loss, respectively. E represented estimated error. The percent of correct classification was used to represent the goodness of model fit (G^2). Behavioral loss aversion parameter λ was computed as$\lambda = -(\beta_{\mathrm{Loss}}/\beta_{\mathrm{Win}})$. Higher λ value indicates higher loss aversion.

After removing the outliers (exceeded ±3 SD of the mean), the data were inputted into SPSS software (SPSS Inc., Chicago, IL) for statistical analysis, using analysis of variance (ANOVA), analysis of covariance (ANCOVA), t-tests, chi-square tests and correlation analysis. ANOVAs and ANCOVAs were followed by post-hoc comparisons.

3. Results

Out of 569 subjects, 52 were l allele homozygotes (l/l), 219 were heterozygotes (l/s), and 298 were homozygous for the s allele (s/s). The distribution is consistent with Hardy–Weinberg Equilibrium (χ^2 (1) = 1.615, p = .204). There were 24 males with two copies of the l allele, another 99 heterozygotes, and 143 males with two copies of the s allele, consistent with Hardy–Weinberg Equilibrium (χ^2 (1) = 2.563, p = .109). And of all the females, 28 were l homozygotes, 127 were heterozygotes, and 155 were s homozygotes, consistent with Hardy–Weinberg Equilibrium (χ^2 (1) = .074, p = .786). More specifically, the frequency of genotype (9.14% of l/l, 38.49% of l/s and 52.37% of s/s) in the present study was comparable with other studies with Asian subjects (Huang et al., 2004; Joo et al., 2007; Katsuragi et al., 1999; Tsai et al., 2002; Zhong et al., 2009).

3.1. Intelligence and memory tasks

Intelligence and memory test scores for each genetic subgroup are summarized in Table 2. Overall, statistics showed no genotype group difference (all p's > .05), i.e., subjects in different genetic subgroups got comparable scores in all the intelligence and memory tests.

3.2. The Iowa Gambling Task

As can be seen in Fig. 1B, subjects on average chose more advantageous cards as the task went on. One-way repeated-measure ANOVA showed significant trial block effect (F(4, 2192) = 149.567, p < .001). Indeed, multiple comparisons suggested that subjects increasingly chose advantageous decks from block to block (linear: $F(1, 548) = 295.023, p < .001$; quadratic: $F(1, 548) = 48.910, p < .001$). The first 40 trials were grouped together to obtain performance scores in decision under ambiguity and the last 60 trials were also grouped together to obtain performance scores in decision under

Table 2
Intelligence and memory scores for each genotype group.

	l/*l*	*l*/*s*	*s*/*s*	Statistics
RAPM	26.00 (3.73)	25.70 (3.84)	25.46 (4.09)	F (2, 558) = .530, p = .589
WAIS-RC				
Verbal	125.37 (8.83)	123.26 (9.00)	124.24 (8.66)	F (2, 554) = 1.482, p = .228
Performance	123.71 (8.53)	123.53 (9.69)	122.94 (10.23)	F (2, 554) = .287, p = .751
Total	126.82 (7.56)	125.33 (8.16)	125.70 (8.12)	F (2, 554) = .707, p = .494
WMS				
Recognition	14.94 (1.31)	14.60 (1.51)	14.74 (1.34)	F (2, 561) = 1.455, p = .234
Recall	17.47 (1.68)	17.58 (1.91)	17.28 (2.07)	F (2, 552) = 1.471, p = .231
WMT				
Semantic	.856 (.135)	.864 (.108)	.856 (.108)	F (2, 537) = .360, p = .698
Phonology	.830 (.092)	.826 (.098)	.811 (.112)	F (2, 536) = 1.399, p = .248
Morphology	.887 (.104)	.876 (.076)	.881 (.075)	F (2, 537) = .454, p = .626

Numbers represent the mean (SD).
RAPM: Raven's Advanced Progressive Matrices; WAIS-RC: Wechsler Adult Intelligence Scale-Revised Chinese Version; WMS: Wechsler Memory Scale; WMT: Working Memory Test.

risk. Although we did not ask subjects to report what they knew about the task when they were performing it, a previous study that adopted this method had shown that on average, decisions in the first 40 trials were made under ambiguous conditions, but after that, subjects began to develop some subjective sense of the probabilities and thereby began to make decisions under risk (Bechara et al., 1997). This distinction has also been widely adopted by several other studies (e.g., Homberg et al., 2008; van den Bos et al., 2009).

3.3. The Loss Aversion Task

On average, the rate of gamble acceptance for all subjects was 55.06% (SD = 27%), with an average reaction time of 1.16 s (SD = .31). Subjects showed indifference to gambles in which potential gains were twice as likely as losses (Fig. 2B). Also, they needed more time to decide whether or not to accept those gambles (Fig. 2C). The mean λ value was 1.92 (SD = .75), ranging from .34 to 6.65. The average G^2 was 85.34% (SD = 7.4%, ranging from 52% to 100%), suggesting good fit of the model to the data. This result was consistent with Tom et al. (2007).

3.4. Correlations between tasks

Decision under ambiguity (i.e., performance in the first 40 trials) was highly correlated with decision under risk (i.e., performance in the last 60 trials) tested by the IGT ($r = .377$, $p < .01$), but neither of them was correlated with loss aversion λ (decision under ambiguity: $r = .011$; decision under risk: $r = -.011$; both $ps > .05$), suggesting they were testing different decision making processes.

Correlation analysis also showed a few significant correlations between decision making performance and basic intelligence and memory abilities (Table 3). Three correlations were significant: The net score of the first 40 IGT trials and phonological working memory ($r = .096$, $p < .05$), the net score of the last 60 IGT trials and the RAPM score ($r = .089$, $p < .05$), the net score of the last 60 IGT trials and the WAIS-RC performance IQ ($r = .097$, $p < .05$). The loss aversion λ did not correlate with basic intelligence and memory abilities (all p's $> .05$). These intelligence and memory test scores thus were used as covariables in ANCOVAs to determine the unique effect of 5-HTTLPR polymorphism on economic decision making, and also to increase the statistical power.

3.5. Gender, 5-HTTLPR and decision making under ambiguity

For decision making under ambiguity, two-way ANCOVA using 5-HTTLPR polymorphism and gender as independent variables showed that 5-HTTLPR polymorphism (*s*/*s*, *s*/*l* and *l*/*l*) had a significant effect on the IGT score in the first 40 trials ($F(2, 489) = 3.703$, $p < .05$). But there was no effect of gender ($F(1, 489) = .026$, $p > .05$) or gender by 5-HTTLPR interaction ($F(2, 489) = 1.518$, $p > .05$). Further analysis suggested that subjects with the *l*/*s* genotype ($M = -3.85$, SD = 10.569) had significantly higher scores (i.e., choosing more advantageous cards) than *s*/*s* ($M = -6.43$, SD = 10.459) in the first 40 IGT trials ($t(496) = 2.709$, $p < .01$, *Cohen's d* = .25), but there was no difference between the *l*/*l* ($M = -4.58$, SD = 10.363) and *l*/*s* individuals ($t(256) = -.437$, $p > .05$, *Cohen's d* = −.07) or *l*/*l* and *s*/*s* ($t(334) = 1.134$, $p > .05$, *Cohen's d* = .18). We then grouped subjects with the *l*/*l* and *l*/*s* genotypes together (*l carriers*) to attain more statistical power. The pattern of results was similar but stronger: a significant effect of 5-HTTLPR polymorphism ($F(1, 491) = 7.517$, $p < .01$), no effect of gender ($F(1, 491) = 1.129$, $p > .05$), but with a trend of interaction of gender by 5-HTTLPR polymorphism ($F(1, 491) = 2.902$, $p = .089$). Subjects with the *l* allele *(l carriers)* had significantly higher IGT scores than *s* allele homozygotes (Fig. 3A). This effect was significant for male subjects ($F(1, 210) = 6.960$, $p < .01$) but not significant for female subjects ($F(1, 272) = .427$, $p > .05$). To be comparable with Stoltenberg and Vandever (2010), we also examined the gender by genotype interaction using the first 20 trials as decision making under ambiguity. The result was similar to that with the first 40 trials but stronger ($F(1, 491) = 3.909$, $p < .05$). Males with *l* allele performed more advantageously than *s* allele homozygotes.

3.6. Gender, 5-HTTLPR and decision making under risk

For decision making under risk, two-way ANCOVA suggested that gender had a significant effect on the IGT score in the last 60 trials ($F(1, 489) = 4.026$, $p < .05$). But there was no effect of 5-HTTLPR polymorphism ($F(2, 489) = .414$, $p > .05$) or gender by 5-HTTLPR interaction ($F(2, 489) = .313$, $p > .05$). After grouping the *l*/*l* and *l*/*s* genotypes together (*l carriers*), the analysis showed the same pattern but stronger results: a significant effect of gender ($F(1, 491) = 6.516$, $p < .01$), no effect of 5-HTTLPR polymorphism ($F(1, 491) = .817$, $p > .05$) or gender by 5-HTTLPR interaction ($F(1, 491) = .578$, $p > .05$). Male subjects ($M = 12.84$, SD = 27.535) showed a marginally significant higher IGT score than females ($M = 8.55$, SD = 24.456) (Fig. 3A, $t(547) = 1.933$, $p = .054$, *Cohen's d* = *.17*).

3.7. Gender, 5-HTTLPR and loss aversion

For LAT, two-way ANCOVA showed a marginally significant main effect of 5-HTTLPR on λ ($F(2, 483) = 2.876$, $p = .057$), but no effect of gender ($F(1, 483) = .381$, $p > .05$) or gender by 5-HTTLPR interaction ($F(2, 483) = .722$, $p > .05$). Multiple comparisons showed that subjects with the *s*/*s* ($M = 1.99$, SD = .836) genotype showed significantly higher loss aversion (i.e., higher λ value) than those with *l*/*s* ($M = 1.84$, SD = .639) genotype ($t(465) = 2.149$, $p < .05$, *Cohen's d* = 20), and marginally significant higher loss aversion than those with *l*/*l* ($M = 1.81$, *SD = .577*) genotype ($t(321) = 1.922$, $p = .058$, *Cohen's d* = .23), but there was no significant difference between the *l*/*s* and *l*/*l* groups ($t(242) = .312$, $p > .05$, *Cohen's d* = .05). The results were similar but stronger after we grouped subjects with the *l*/*l* and *l*/*s* genotypes together. Two-way ANCOVA results showed a significant 5-HTTLPR polymorphism effect on λ ($F(1, 485) = 5.384$, $p < .05$) with the *s* allele homozygotes showing higher λ value than the *l carriers* (Fig. 3B), but no effect of gender ($F(1, 485) = 1.534$, $p > .05$) or gender by 5-HTTLPR interaction ($F(1, 485) = 1.488$, $p > .05$).

Table 3
Correlations between decision making tasks and basic intelligence and memory tests.

	RAPM	WAIS-RC			WMT			WMS	
		Verbal	Performance	Total	Semantic	Phonology	Morphology	Recognition	Recall
IGT-first 40	−.013	−.034	−.053	−.056	−.003	.096*	−.032	−.074	−.008
IGT-last 60	.089*	.017	.097*	.066	.075	.05	−.004	−.037	.01
LAT λ	.013	−.017	.061	.02	.046	−.059	.038	.000	−.008

*$p < .05$.
IGT: Iowa Gambling Task; LAT: Loss Aversion Task; RAPM: Raven's Advanced Progressive Matrices; WAIS-RC: Wechsler Adult Intelligence Scale-Revised Chinese Version; WMS: Wechsler Memory Scale; WMT: Working Memory Test.

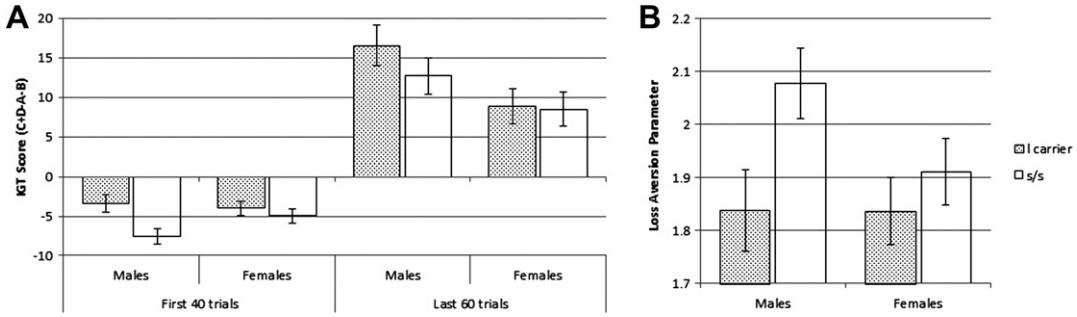

Fig. 3. A) 5-HTTLPR polymorphism had a significant effect on decision under ambiguity (the first 40 trials) but not on decision under risk (the last 60 trials) tested by IGT. Subjects with *l* allele (*l* carriers) had a significantly higher mean IGT score than *s* allele homozygotes on the first 40 trials of IGT. Moreover, this effect was modulated by gender, with only males showing the effect. But for the last 60 trials of IGT, although there was no effect of 5-HTTLPR polymorphism, the IGT score was modulated by gender. Males chose more advantageous cards than females. B) 5-HTTLPR also influenced the loss aversion parameter λ tested by LAT task. Subjects homozygous for *s* allele showed higher λ value than *l* carriers. Error bars indicate standard errors.

4. Discussion

In the present study, two decision making tasks (i.e., the IGT and LAT) were used to test the effect of 5-HTTLPR polymorphism on decision making under ambiguity and risk. Basic intelligence and memory tests were also used to control for potential confounding effects of basic cognitive abilities. The large Han Chinese sample used in this study enabled us to obtain stable and comprehensive results. Results indicated that 5-HTTLPR influences both decision under ambiguity and loss aversion, and this effect is modulated by gender.

Consistent with previous studies (Bechara et al., 1994, 2000), the healthy young college students in our study learned to choose cards from advantageous decks across five blocks of 20 trials. Although the overall performance showed no difference, males performed more advantageously than females in decision under risk but not under ambiguity, consistent with previous studies (Bolla et al., 2004; Overman et al., 2006; Reavis and Overman, 2001). The loss aversion parameter λ (close to 2) in the LAT task was also comparable to previous studies (e.g., Pennings and Smidts, 2003; Schmidt and Traub, 2002; Tom et al., 2007; Tversky and Kahneman, 1992). A few studies showed that women were more risk averse than men (e.g., Bajtelsmit and Bernasek, 1998; Charness and Gneezy, 2007; Schmidt and Traub, 2002), but there was no significant gender difference in the present study. One possible reason for this incongruity might be that we used a task that involved a relatively small amount of money (wins from 10 to 40 *Yuan* and loss from 5 to 20 *Yuan*) rather than large amounts of investment in previous studies.

Results showed no correlation between λ and either of the two IGT scores, suggesting the LAT tested aspects of decision making that are different from those involved in the IGT. Loss aversion is a specific phenomenon that reflects people's tendency of being more sensitive to the possibility of losing objects or money than to the possibility of gaining the same objects or amounts of money (Tom et al., 2007). Indeed, neuroimaging studies have found that these two tasks involve distinct neural substrates, with the amygdala playing an important role in the IGT (Li et al., 2009), but not in the LAT (Tom et al., 2007). Correlations between decision making tasks and general intelligence and memory abilities suggested that the decision making process is partly correlated with general intelligence and memory abilities, which is consistent with previous reports of the importance of basic cognitive functions in decision making (e.g., Gupta et al., 2009; Morsanyi and Handley, 2008; Yechiam and Busemeyer, 2005; Yechiam et al., 2008). This result thus suggests that general intelligence and memory abilities should be controlled in evaluating effects of genetic factors.

Central to the present study, 5-HTTLPR polymorphism was found to significantly influence performance in both the IGT and LAT. Subjects homozygous for the *s* allele had lower IGT score than the *l* carriers in the first 40 trials of the IGT task, and the former also showed higher loss aversion than the latter in the LAT task. These results are consistent with previous studies with healthy European or American subjects (Crisan et al., 2009; Homberg et al., 2008; Kuhnen and Chiao, 2009; Roiser et al., 2009; van den Bos et al., 2009), but not with one recent study with Chinese population which only showed a trend (Zhong et al., 2009). Since this effect was independent of subjects' intellectual or memory abilities, our results add to the literature that emphasizes the important role emotion plays in both decision under ambiguity and loss aversion (one specific form of decision under risk).

Cumulative evidence has suggested that decision making not only involves cognitive processes, but is also modulated by emotional (i.e., homeostatic) signals (e.g., Loewenstein et al., 2001). Decision making tasks usually engender strong subjective excitement or arousal, which is associated with strong physiological changes in heart rate, blood pressure, electromyogram, cortisol level, skin temperature, and skin conductance response (see Goudriaan et al., 2004 for a review). There has been mounting evidence that 5-HTTLPR gene has a significant impact on emotional processing (for reviews, see Canli and Lesch, 2007; Hariri and Holmes, 2006), not only in healthy subjects (e.g., Caspi et al., 2003; Kendler et al., 2005), but also in depression patients (e.g., Smits et al., 2006; Zalsman et al., 2006). Serotonin transporter gene *s* allele carriers are more prone to succumbing to the depression effects of stressful life events than those homozygous for the *l* allele. We found that subjects homozygous for 5-HTTLPR *s* allele chose more disadvantageous cards than those with *l* allele, suggesting that the former subjects tended to be less efficient when performing the Iowa Gambling Task. They also showed an impaired emotional process that disrupted rational choice, which led to a higher level of loss aversion than the *l* carriers. This view is compatible with Sokol-Hessner et al's. (2009) recent report that using effective emotion regulation strategies (i.e., "thinking like a trader", which results in less emotional involvement) significantly reduced both behavioral and physiological loss aversion. Low serotonin transporter activity (*s* allele) might also reflect a functional "hypofrontality" that is reminiscent of that seen in frontal lobe patients, in that they are insensitive to the distant consequences of their decisions. This view is supported by two neuroimaging studies showing that *s* carriers had lower functional coupling between amygdala and rostral anterior cingulate cortex (Pezawas et al., 2005) and amygdala and prefrontal cortex/anterior cingulate cortex (Roiser et al., 2009), although the *s* carriers have an increased functional coupling between the amygdala and ventromedial prefrontal cortex (Heinz et al., 2005). Also, in the study of Bechara et al. (2000), the frontal patients were risk averse (they avoided the

high penalty decks) but also performed disadvantageously in the IGT. More recent versions of the somatic marker model (e.g., Bechara and Damasio, 2005) have speculated that somatic signals manifested in the body and carried through the vagus nerve, or manifested solely within the brain, ultimately reach the neurotransmitter cell bodies within the brainstem, including serotonin, which in turn exert influence on motor and cognitive systems in the brain involved in the implementation of decisions. Thus it has been proposed that one way by which "somatic markers" bias decisions is actually through the release of neurotransmitters (Bechara and Damasio, 2005). The current study provides empirical support for this view.

Several brain regions are important for emotional decision making, including the amygdala, the ventromedial prefrontal cortex and the insula cortex. The amygdala has been emphasized by existing literature, because evidences had shown that 5-HTTLPR genotype influences activation of the amygdala, a vital brain area associated with basic emotional process (see Munafo et al., 2008 for a review and meta-analysis). Lesion studies showed that amygdala (e.g., Bechara et al., 2003, 1999), VMPFC (e.g., Bechara et al., 1994, 1999) and insular cortex (e.g., Bar-On et al., 2003; Clark et al., 2008) are all important in the decision making process, which had also been shown in neuroimaging studies (e.g., De Martino et al., 2006; Li et al., 2009; Tom et al., 2007; Xue et al., 2010, 2009). In addition, there are strong anatomical connections among these areas, which might also be modulated by 5-HTTLPR polymorphism. For example, a recent study showed that 5-HTTLPR modulated the amygdala-frontal coupling (Roiser et al., 2009). Future studies need to combine functional MRI and decision making tasks to examine how the 5-HTTLPR polymorphism can affect decision making under ambiguity and risk through modulating insular activation.

In decision under ambiguity (as measured by the early trials of the IGT), the effect of 5-HTTLPR tended to be modulated by gender: male subjects with the *l* allele had significantly higher IGT scores than males who were *s* allele homozygotes, but only a trend in the same direction was found for females. Gender by 5-HTTLPR interaction was also found in the LAT task, with stronger genetic effect (i.e., higher loss aversion for *s*/*s* than *l* carriers) for males than for females (see Fig. 3B). One study also showed gender by 5-HTTLPR interaction on the performance of the IGT (Stoltenberg and Vandever, 2010), that is, the IGT score in the first 20 trials was lower for *l*/*l* than for *s* carriers in males, but higher for *l*/*l* than for *s* carriers in females. Although the results for the female subjects are generally consistent (Homberg et al., 2008; van den Bos et al., 2009), the lack of significant 5-HTTLPR effect in our female subjects might be due to higher variance in this group. For example, females have higher variance in mood status than males (e.g., Kessler et al., 2007, 2005). In addition, the mRNA and binding site densities for 5-HTT were shown to be regulated by estrogen (e.g., McQueen et al., 1997, 1999), which varies at different stage of menstrual cycle. It should be noted that the menstrual cycle *per se* might not affect the overall IGT performance of females as one group (Reavis and Overman, 2001; Van den Bos et al., 2007), and future studies need to examine the interaction between menstrual cycle and 5-HTTLPR polymorphism in affecting decision making under risk and ambiguity. Our results for the male subjects, however, are in opposite direction to that of Stoltenberg and Vandever (2010). It remains unclear why this difference emerged. Potential reasons include the fact that there is a difference in allele frequency among Eastern and Western populations (e.g., relatively more *l*/*l* in Western population and more *s*/*s* in Eastern population, see Table 1), Furthermore, subjects were grouped in different ways in the two studies (*s* carries vs. *l*/*l* in their study and *s*/*s* vs. *l* carries in the present study). Another potential reason is that the gene–behavior relationship is modulated by ethnicity and/or culture (e.g., Mizuno et al., 2006). Culture differences in decision making remains one of the most understudied topics, and future studies are certainly needed to examine these intriguing differences.

The present study focused on the effect of 5-HTTLPR polymorphism on decision making under ambiguity and risk. Many previous studies have found that decision making is affected by other genes, including COMT (e.g., Boettiger et al., 2007; Camara et al., 2010; Dreher et al., 2009; Kang et al., 2010; Roussos et al., 2008; van den Bos et al., 2009; Yacubian et al., 2007), DRD4 (e.g., Camara et al., 2010; Ha et al., 2009; Kuhnen and Chiao, 2009), DAT (e.g., Dreher et al., 2009; Yacubian et al., 2007; Zhong et al., 2009), MAOA (e.g., Jollant et al., 2007), or BDNF (e.g., Kang et al., 2010), as well as their interactions (e.g., Camara et al., 2010; Dreher et al., 2009; Kang et al., 2010; van den Bos et al., 2009; Yacubian et al., 2007). Future studies should examine the effects of multiple genes and their interactions on decision making to significantly advance our understanding on the neural mechanisms of decision making.

In conclusion, this study found significant effects of 5-HTTLPR polymorphism on both decision making under ambiguity and risk in a large sample. These effects were independent of subjects' intelligence and memory abilities, but tended to be modulated by gender. Our results add to the cumulative evidence emphasizing the important role of emotion in decision making under both ambiguity and risk. Future studies need to combine genetic, behavioral, and functional imaging techniques to examine the neural mechanisms underlying the genetic effects on decision making, which could potentially contribute to the diagnosis and treatment of specific psychiatric disorders associated with decision deficits, such as addiction, schizophrenia, or depression.

Conflict of interests

None.

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