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COMT *Val*^{158}*Met* polymorphism interacts with stressful life events and parental warmth to influence decision making

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Both genetic and environmental factors have been shown to influence decision making, but their relative contributions and interactions are not well understood. The present study aimed to reveal possible gene-environment interactions on decision making in a large healthy sample. Specifically, we examined how the frequently studied COMT *Val*^{158}*Met* polymorphism interacted with an environmental risk factor (i.e., stressful life events) and a protective factor (i.e., parental warmth) to influence affective decision making as measured by the Iowa Gambling Task. We found that stressful life events acted as a risk factor for poor IGT performance (i.e., high reward sensitivity) among *Met* carriers, whereas parental warmth acted as a protective factor for good IGT performance (i.e., higher IGT score) among *Val/Val* homozygotes. These results shed some new light on gene-environment interactions in decision making, which could potentially help us understand the underlying etiology of several psychiatric disorders associated with decision making impairment.

Decision making is a complex process that involves weighing alternative outcomes' desirability and their probabilities[1,2]. Affective decision making is associated with differing probabilities of reward and punishment, as well as their induced emotional responses[3]. It is an important type of decision making in our daily life, which has been initially described and studied in patients with frontal lobe damages[4,5]. Some of the original decision-making tasks that have been developed to detect and study decision-making impairments in brain lesion patients, as well as patients with neuropsychiatric disorders, include the Iowa Gambling Task (IGT)[6,7] and the Cambridge Gambling Task[4,8–10].

Affective decision-making is a complex process that depends on an anatomical circuitry that includes several brain regions[11]. It has been hypothesized that this neural circuitry, and consequently decision-making capacities in risky and uncertain situations, is influenced by a variety of neurotransmitter systems, including dopamine (DA)[11]. The influence of processes involving DA-related reward, risk and uncertainty[5,7,12] on individuals' decision-making has become especially significant in light of the impressive advances in research on the role of the mesolimbic DA in mechanisms of reward prediction errors[13–23]. While pathologies in these anatomical and pharmacological systems lead to a wide range of decision-making impairments such as those manifested in clinical populations, including patients with brain damage or some neuropsychiatric disorders, the fact remains that decision-making capacities can vary among normal individuals. Understanding the variations in decision-making capacities among normal individuals is especially important in light of the argument that these differences can serve as underlying biological markers for rendering some individuals more vulnerable than others to certain conditions associated with poor decision-making, such as addiction[24], depression[25,26], and schizophrenia[27]. Indeed, previous studies have shown that individual differences in affective decision making have both genetic[28,29] and environmental sources[30]. However, their interactions are not well understood.

One of the frequently studied genes associated with human decision making process is the Catechol-o-methyl transferase (COMT) gene located on the 22nd chromosome. The COMT gene encodes COMT enzyme, one of the major enzymes to degrade DA in the prefrontal cortical areas[31]. The most common variation of the COMT gene is

the *Val*^{158}*Met* polymorphism (rs4680) in which a single G/A base-pair substitution leads to a valine (*Val*) to methionine (*Met*) substitution at codon 158[32]. This *Met* substitution reduces the activity of COMT enzyme to one-quarter of what is originally encoded by the *Val* allele[32]. Thereby, *Met* carriers have higher extracellular DA level in the prefrontal cortex[33], a region that is vital for affective decision making, as suggested by both lesion[5,7,34,35] and fMRI studies[36–40].

Three studies have examined the influence of COMT polymorphism on affective decision making measured by the IGT[41–43] and a monetary decision making task[44]. The results are mixed. In a pioneering study, Roussos et al.[43] reported that the G allele at COMT rs4818 polymorphism, which is in high linkage disequilibrium with the *Val* allele at rs4680, was associated with better performance of the IGT in healthy males. This result was confirmed by van den Bos et al.[42] who directly examined the COMT *Val*^{158}*Met* polymorphism and found that subjects with the *Val/Val* genotype chose more advantageously than the *Met* allele homozygotes. These results suggested that *Met* allele carriers, who have increased levels of tonic DA and reciprocal reduction of phasic DA in subcortical regions[45], tended to have lower IGT scores. In a placebo-controlled pharmacological study, Farrell et al.[44] found that a COMT inhibitor (Tolcapone) made *Met* subjects more risk seeking but *Val* subjects more risk averse in a monetary decision making task, suggesting decision making can be altered by COMT inhibitors. However, in another study, Kang et al.[41] failed to find a significant correlation between COMT *Val*^{158}*Met* polymorphism and IGT performance. Several factors might have contributed to the discrepancy in the literature. In most of the existing studies, the sample size is relatively small (no more than 200 subjects), and the effect size is usually small. In addition, these studies have not considered the environmental factors and possible gene-environment interactions, which have gained increasing attention in recent literature.

Cumulative evidence has suggested that environmental factors, such as stress and parental warmth, can influence affective decision making. On the one hand, both acute and chronical stress have been widely recognized as risk factors that influence affective decision making[46]. For example, Gray[47] showed that students who reported high stress due to impending exams earned less money in a monetary decision making task compared with students who did not report high stress when faced with impending exams and students without impending exams. On the other hand, family relationship has been shown to be a protective factor against poor affective decision making[30]. Children in better parent-child relationships showed significant improvements on IGT scores in a one-year longitudinal study[30].

Many studies suggest that human behavior is determined by the combination of genes and environments (i.e., gene-environment interaction). For example, Caspi et al.[48] found that COMT *Val*^{158}*Met* polymorphism interacted with cannabis use to influence the development of psychotic symptoms and schizophreniform disorder. However, potential gene-environment interactions on affective decision making are largely unknown. Biologically, COMT *Val*^{158}*Met* polymorphism mainly influences the activity of the COMT enzyme, and leads to different DA levels in the prefrontal cortex[33,49]. Animal studies have suggested that both stress and maternal care could alter brain DA levels. For example, Abercrombie et al.[50] found that intermittent tail-shock stress increased extracellular DA levels relative to the baseline by 25% in the striatum, 39% in the nucleus accumbens, and 95% in the medial frontal cortex. In a later study, Gambarana et al.[51] found that chronic stress decreased DA level in the nucleus accumbens. Hall et al.[52] found that maternal deprivation was associated with increased mesolimbic DA level. The present study analyzed the main effects of COMT *Val*^{158}*Met* polymorphism and two environmental variables (parental warmth and stressful life events) as well as their interactions on affective decision making measured by the IGT.

Results

Out of the 556 subjects, 310 were *Val* allele homozygotes (*Val/Val*), 210 were heterozygotes (*Val/Met*), and 36 were homozygous for the *Met* allele (*Met/Met*). The distribution is consistent with Hardy-Weinberg Equilibrium (χ^2 *(1) = .003, p = .96*). There was no gender difference in the genotype distribution. The allele frequencies in the present study are comparable to other studies with Chinese participants[66–68]. Because of the limited number of subjects in the *Met/Met* group, we grouped the *Val/Met* and *Met/Met* subjects into the *Met*-carrier group in all subsequent analysis.

In our sample, the mean score for the Stressful Life Events Scale (SLES) was 9.84 (SD = 5.42) and the mean score for the Parent Warmth Scale (PWS) was 53.08 (SD = 7.45). Neither SLES (*t(531) = 1.09, p = .28*) nor PWS (*t(531) = 1.49, p = .14*) showed significant gender difference. These two environmental measures were negatively correlated (Spearman *r(533) = −.20, p < .01*). Because neither environmental measures was normally distributed (SLES: K-S test of normality = 0.064, p < .001; PWS: K-S test of normality = 0.105, p < .001), we split the subjects into two groups by group median. After splitting, there were 278 (52.2%) participants in the low stress group (mean SLES score 6.16, SD = 2.14) and 255 (47.8%) in the high stress group (mean SLES score 13.84, SD = 5.05). There were 295 (55.3%) participants in the low parental warmth group (mean PWS score 47.93, SD = 5.64) and 238 (44.7%) in the high parental warmth group (mean PWS score 59.46, SD = 3.34). COMT genotype did not affect either stress grouping (χ^2 *(1) = .33, p = .57*) or parental warmth grouping (χ^2 *(1) = 1.67, p = .20*).

According to traditional IGT analysis[6,34,35], the mean scores (*SD*) for each block was −4.81 (6.58), −.47 (7.53), 2.29 (9.35), 3.52 (10.36) and 4.58 (10.62), suggesting that subjects learned to select more from the advantageous decks as the task progressed. There was no gender difference in IGT score (*t(531) = .99, p = .32*). The revised expectancy valence model[61] worked well in our sample as the mean model fit was adequate (4.71 on average). The mean (SD) for reward sensitivity was .65 (.30). There was no gender effect on W (*t(531) = 1.18, p = .24*). Reward sensitivity (*W*) was negatively correlated with IGT scores (*r (533) = −.43, p < .01*).

The mean scores and *SD* of the dependent variables (IGT scores and reward sensitivity) by genotype and environmental variables are shown in Table 1. Three-way ANCOVA (minimum N = 46 in each cell) was performed on reward sensitivity (*W*) with COMT, stress, and parental warmth as independent variables and three IQ measures as covariates. Results showed that there was a significant interaction between COMT genotype and stress (F(1,522) = 6.57, p = .01). Further analysis on COMT by stress interaction showed that *Met* carriers with higher stress were more sensitive to gains (reward sensitivity, *W*) than those with lower stress (Figure 1A, t(239) = 2.78, p < .01, Cohen's d = .36), but no difference was found for *Val/Val* homozygotes (t(290) = .38, p = .70). There was no main effect of COMT genotype (F(1,522) = .34, p = .56), stress (F(1,522) = 2.28, p = .13), or parental warmth (F(1,522) = 1.42, p = .23). The other two two-way interactions (F(1,522) = 2.51, p = .11 for COMT by parental warmth; and F(1,522) = .60, p = .44 for stress by parental

Table 1 | Means (SD) of the dependent variables by independent variables

		IGT Score	*W*
COMT	*Val/Val*	5.95 (32.07)	.65 (.30)
	Met/-	4.08 (30.66)	.64 (.31)
Stress	Low	7.49 (29.75)	.63 (.30)
	High	2.51 (33.02)	.67 (.30)
PW	Low	3.08 (32.11)	.67 (.30)
	High	7.62 (30.44)	.62 (.31)

Met/-: COMT *Met* carriers; PW: parental warmth; *W*: reward sensitivity.

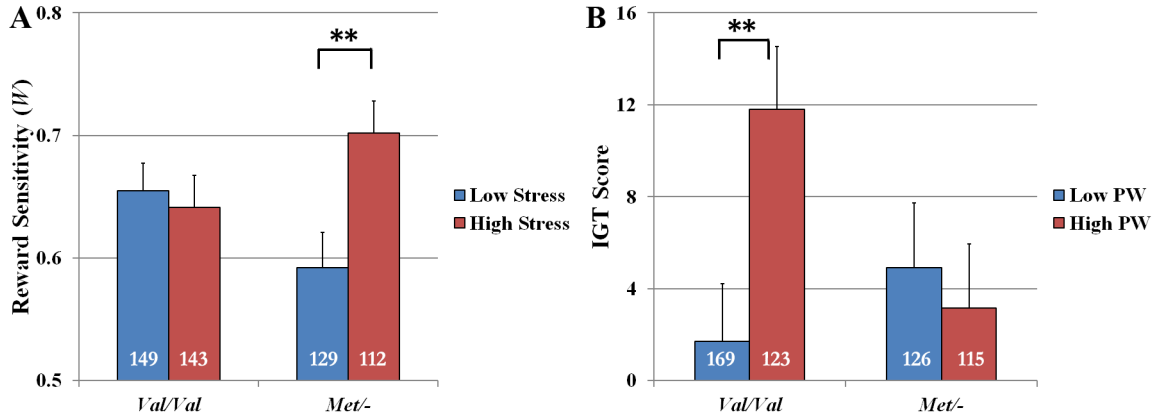

Figure 1 | Results of Gene-Environment interactions. COMT genotype interacted with stress to influence reward sensitivity (A), and interacted with parental warmth to influence the IGT scores (B). The number on each bar denotes the number of subjects in each group. Error bars indicate standard errors. **: $p < .01$.

warmth) and the three-way interaction ($F(1,522) = 2.84$, $p = .09$) were not significant.

To rule out the possibility that parental warmth could mediate the interaction between COMT genotype and stress, a two-way ANCOVA was performed on *W* with COMT genotype and Stress as independent variables and the three IQ measures as well as the standardized parental warmth score as covariates. The interaction of COMT by stress on *W* was still significant ($F(1,525) = 4.97$, $p < .05$), and no significant main effect was found (both $ps > .10$).

Using the IGT scores as the dependent variable, the three-way ANCOVA found a significant COMT by parental warmth interaction ($F(1,522) = 4.77$, $p = .029$). Further analysis showed that *Val/Val* homozygotes with higher parental warmth chose more advantageously than those with lower parental warmth (Figure 1B, $t(290) = 2.68$, $p < .01$, Cohen's $d = .32$), but no difference was found for *Met* carriers ($t(239) = .44$, $p = .66$). There was no significant main effect of COMT genotype ($F(1,522) = 1.22$, $p = .27$), stress ($F(1,522) = 2.86$, $p = .09$), or parental warmth ($F(1,522) = 1.17$, $p = .28$). The other two-way interactions, COMT by stress ($F(1,522) = .02$, $p = .89$) and stress by parental warmth ($F(1,522) = .44$, $p = .51$), and the three-way interaction ($F(1,522) = 1.61$, $p = .21$) were not significant.

Similarly, to rule out the possibility that stress could mediate the interaction between COMT genotype and parental warmth, a two-way ANCOVA was performed on the IGT scores with COMT genotype and parental warmth as independent variables and the three IQ measures as well as the normalized stress scores as covariates. The interaction of COMT by stress on IGT score was still significant ($F(1,525) = 4.39$, $p < .05$), although none of the main effects was significant (both $ps > .10$).

Discussion

The present study showed that COMT polymorphism not only interacted with a protective factor (i.e., parental warmth) but also with a risk factor (i.e., stressful life events) to influence affective decision making. COMT *Met* carriers showed more reward sensitivity (i.e., more sensitive to gains) if they experienced high stress, whereas *Val/Val* homozygotes showed better IGT performance if they experienced high parent warmth. Previous studies reported mixed findings about the association between COMT $Val^{158}Met$ polymorphism and human decision making. Two studies[42,43] showed that the *Val* (or *Val* equivalent G allele at rs4818) allele was associated with higher IGT scores, but another study[41] failed to replicate this result. In addition, van den Bos et al.[42] revealed no effect of COMT $Val^{158}Met$ polymorphism on any components of the Expectancy Valence Model[61]. This discrepancy might have been due to their omission of relevant environmental factors and/or the relatively small sample sizes. Using a large sample, the present study found gene-environment interactions, suggesting that the effect of genotype depends on environmental factors.

Stress is usually considered as a risk factor for many psychiatric disorders[69] as well as unhealthy lifestyle behaviors, such as smoking, drinking or unhealthy diet[46]. Both cross-sectional[70] and longitudinal[71] studies have shown that recent stressful life events are associated with self-reported psychotic experiences. Many studies have also examined the effect of stress on decision making in normal subjects[46] and drug abusers[72–74]. It is suggested that the current stress level is related to heightened reward sensitivity and lowered punishment sensitivity in normal subjects[46], and is related to drug craving and relapse in addicts[72–74]. In the Expectancy Valence Model, reward sensitivity (*W*) is a motivation parameter with small values denoting strong attention to losses, and large values denoting heightened attention to gains. In the IGT, a high *W* thus indicates a preference for the high-gain, disadvantageous decks, and therefore poor affective decisions. For example, Yechiam et al.[75] showed that drug offenders, sex offenders, dangerous drivers, chronic cocaine abusers, and theft criminals were characterized by high reward sensitivity (*W*). In the present study, we found that stressful life events interacted with COMT $Val^{158}Met$ polymorphism to influence decision making: COMT *Met* carriers were more reward sensitive (i.e., more sensitive to gains over losses) if they had experienced more stressful events. Although our study is the first to document a COMT by stress interaction on affective decision making, a number of previous studies have demonstrated a similar interaction between COMT $Val^{158}Met$ polymorphism and stress on other behaviors. For example, several studies showed that COMT *Val* allele was more susceptible to the effect of stress on psychosis or paranoia[76,77]. Other studies suggest that the COMT *Met* allele is more susceptible to the effect of stress on psychosis[78,79]. A recent fMRI study by Ursini et al.[49] suggested that COMT and stress interacted through methylation, and this interaction tended to modulate prefrontal activities in a working memory task. It is not clear, however, why the effect of stress was evident for subjects with one allele in some studies but for subjects with a different allele in other studies. More research is needed to clarify these relations.

Parental warmth is usually considered as a protective/promotional factor for many behaviors. For example, researchers have revealed that parental warmth significantly predicted later social adjustment and school achievement[80], and that it is associated with less adolescent problem behaviors and lower levels of depressed mood[58]. In the area of decision making, Xiao et al.[30] found that children in better parent-child relationship showed significant improvement on the

IGT scores in a one-year longitudinal study. Other studies suggested that parental warmth acted as a protective factor in gene-environment interaction. For example, Propper et al.[81] found that higher parental warmth was associated with decreased externalizing behavior only for African American children possessing the short polymorphism of the DRD4 gene. The present study found that among *Val/Val* homozygotes, higher parental warmth was associated with higher IGT scores. Although previous studies have found that *Val/Val* homozygotes tend to have higher IGT score[42,43], we showed that when paired with higher parental warmth, this effect was larger.

Biologically, compared to the COMT *Met* allele, the COMT *Val* allele is associated with increased phasic and reduced tonic DA transmission subcortically and decreased DA concentrations cortically[45]. This tonic-phasic difference of DA caused by COMT *Val/Met* polymorphism results in better cognitive flexibility for subjects with the *Val* allele and better cognitive stability for those with the *Met* allele. Although more research is needed to reveal the underlying biological process involved in our finding of gene-environment interactions, some existing studies have already pointed to several possibilities. For example, many studies showed that stress was associated with increased DA level in both cortical (e.g., the medial frontal cortex) and subcortical (e.g., the striatum and nucleus accumbens) regions[50,82,83], although the opposite pattern has been reported by one study[51]. Reward sensitivity has been suggested to be triggered by DA signals in the striatum, a subcortical nucleus vital to reward and decision making[17,84]. Because of the positive relationship between DA and reward[63,64], elevated tonic DA in the striatum plus increased DA when under stress will cause COMT *Met* allele carriers to show higher attention to reward/gain[45]. In terms of the interaction between parental warmth and COMT, previous studies have shown that parental warmth is associated with altered DA levels in rats[52] and elevated cognitive flexibility in children[85]. Consistent with these results, we found that when paired with higher parental warmth, COMT *Val/Val* homozygotes showed higher cognitive flexibility and had higher IGT scores.

The exact mechanisms underlying the gene-environment interactions revealed in the present study still remain to be explored. Although the importance of the DA neurotransmitter system is particularly emphasized in the present study, other neurotransmitter systems could also play a role in decision-making[11,86]. For example, many studies have suggested that decision making was also influenced directly by the serotonin system[29,87–91] or its interaction with the DA system[42]. In particular, Rogers[86] summarized evidence from pharmacological experiments in humans, and provided a detailed review on the role of DA and serotonin in decision making. More research is needed to clarify their specific roles.

In conclusion, the present study showed that COMT *Val*^{158}*Met* polymorphism interacted with parental warmth and stressful life events to influence affective decision making. Stressful life events seemed to cause COMT *Met* carriers to pay too much attention to gains (i.e., reward sensitivity), whereas high parent warmth seemed to cause *Val/Val* homozygotes to obtain high IGT scores. These results showed that the of two environmental factors on affective decision making depended on the genotype of the individual. These interaction effects are likely to occur at the level of DA regulation in the brain. A fundamental question in addiction research is always whether cognitive changes that one observes are a consequence, or a precedent to substance abuse. We have argued that poor decision-making linked to sub-clinically hypo-functioning prefrontal cortex may serve as a predisposing factor that heightens the vulnerability of an individual to succumb to drug abuse[12,24,92]. Indeed not every person who visits a casino turns into a pathological gambler, or every person who has a drink turns into an alcoholic, or a person who experiments with drugs turn into an addict. Only a small percentage of the population succumbs to addiction when conditions are met. We have suggested that since the function of the prefrontal cortex is influenced by neurotransmitter systems[11], then genetic factors that impact the level of activity in these systems can in turn serve as a predisposing factor for poor decision-making, and consequently addiction[12,24,92]. We have also suggested that since the maturity of the prefrontal cortex is delayed until early twenties, environmental factors, such as early life stress, could also lead to alterations in the normal development of decision-making capacities[12,24,92]. The current results provide support for these notions. As such, the results help advance our understanding of some of the underlying mechanisms of certain psychiatric disorders involving decision making deficits, such as addiction, schizophrenia, or depression, and perhaps leading to novel ways of looking into the problems and the strategy for their treatment.

Methods

Participants. Participants were a subsample of a large-scale gene-brain-behavior project[29], which recruited 572 (312 females, aged from 17 to 27 years old, with a mean of 20.47 years, SD = 1.01) Han Chinese undergraduate students. They had normal or corrected-to-normal vision, and had no history of neurological or psychiatric problems according to self-report. Only 4 subjects were identified to have high levels of alcohol problems (scored 16 or higher on the Alcohol Use Disorders Identification Test[53]). The results remained virtually the same after excluding these subjects. No subject was found to show high (6–7) or very high (8 and above) dependence on nicotine according to the Fagerström Test for Nicotine Dependence[54]. Informed written consents were obtained from all participants and the study was approved by the Beijing Normal University Institutional Review Board.

Out of the 572 participants, 556 (306 females) were genotyped (16 participants failed to be genotyped due to technical errors) for COMT *Val*^{158}*Met* polymorphism (rs4680). Genotyping was done on a Gel Doc 2000 imaging system (Bio-Rad Laboratories Ltd, UK) following a polymerase chain reaction (PCR) protocol[55]. All 556 participants completed Stressful Life Events Scale (SLES) and Parental Warmth Scale (PWS). However, only 533 (298 females) subjects completed the IGT and IQ tests, so all analysis in the present study were based on those 533 subjects.

IQ tests. Two intelligence tests, namely the Raven's Advanced Progressive Matrices (RAPM) and the Wechsler Adult Intelligence Scale-Revised Chinese Version (WAIS-RC), were used to measure subjects' general cognitive abilities[29,56]. Three measures were generated and used as covariates in analysis of covariance (ANCOVA), including the number of correct responses to the test items of RAPM, and two IQ scores (verbal IQ and performance IQ) of WAIS-RC.

Decision making task. Participants completed the IGT task, a test of decision making under ambiguity and risk. The IGT was originally designed to test decision making deficits frequently seen in patients with ventromedial prefrontal cortex damage[6], and had been used extensively on other populations, including healthy adults[29], adolescents[30] and drug addicts[57]. A detailed description of the IGT appeared in Bechara et al.[7].

Environmental measures. Two environmental measures were used. The Stressful Life Events Scale (SLES) was modified from Beam et al.[58] to measure a major risk factor—chronic stress. Chronic stress was chosen because previous studies have shown that naturally occurring stressors have more severe impacts on decision making than laboratory-induced acute stress[46]. The SLES is a 24-item questionnaire about stressful family and peer events. Example are "the death of a close friend", and "a parent became seriously ill". Subjects were asked to indicate if that problem happened to him/her one or more times in three time periods: elementary school, middle and high school, and college. To assess the protective factor, the Parental Warmth Scale (PWS), modified from Greenberger and Chen[59] and Greenberger et al.[60], was used. The PWS is an 11-item questionnaire regarding subjects' parents, including questions such as "my parents really enjoy spending time with me". Subjects were asked to rate their agreement with those statements from 1 (strongly disagree) to 6 (strongly agree). Total ratings of all 11 items were added together to represent the parental warmth measure. This measure has been linked to adolescent problem behavior and depressed mood[58,59]. The Cronbach α was .83 for our sample, suggesting good internal reliability.

Data analysis. The IGT 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). To decompose the cognitively-complex IGT, we used the revised expectancy valence model[61] to compute the underlying cognitive and emotional processes that contribute to IGT performance. In particular, the model decomposes IGT performance into three parameters (for detail of the model, see[61,62]): 1) *Reward sensitivity (W)*, ranging from 0 to 1, with higher values denoting increased attention to gains over losses; 2) *Recency (Φ)*, ranging from 0 to1, with higher values indicating rapid discount of past outcomes; 3) *Choice consistency (c)*, ranging from −5 to 5, with higher values representing converging choices toward the decks with the maximum reward expectancy. This model provides additional information regarding the mechanisms underlying IGT performance. For example, this model could

characterize the differential deficits in affective decision making among neurological and psychiatric disorders, although their IGT performance was equally impaired[62]. In the present study, we focused on the reward sensitivity (*W*) parameter due to its tight association with DA functions[63–65]. The descriptive statistics on other parameters are available in Supplemental Materials online. Environment measures were split into "high" and "low" groups by group median. For IGT score and reward sensitivity *W*, three-way ANCOVAs were carried out with COMT genotype and both environment variables as factors and three IQ measures as covariates separately. Effect size (*Cohen's d*) was calculated for each direct comparison.

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Author contributions

Conceived and designed the experiments: Chuansheng Chen, ZL, RKM, QD. Performed the experiments: QH, Chunhui Chen, XL, YL, JL, BZ. Analyzed the data: QH, GX, AB. Wrote the paper: QH, GX, Chuansheng Chen, ZL, AB.

Additional information

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