COMT Val<sup>158</sup>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<sup>158</sup>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.
the Val<sup>158</sup>Met polymorphism (rs4680) in which a single G/A base-pair substitution leads to a valine (Val) to methionine (Met) substitution at codon 158<sup>2</sup>. This Met substitution reduces the activity of COMT enzyme to one-quarter of what is originally encoded by the Val allele<sup>2</sup>. Thereby, Met carriers have higher extracellular DA level in the prefrontal cortex<sup>3</sup>, a region that is vital for affective decision making, as suggested by both lesion<sup>27-33</sup> and fMRI studies<sup>34-40</sup>. Three studies have examined the influence of COMT polymorphism on affective decision making measured by the IGT<sup>40-45</sup> and a monetary decision making task<sup>46</sup>. The results are mixed. In a pioneering study, Roussos et al.<sup>47</sup> 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.<sup>48</sup> who directly examined the COMT Val<sup>158</sup>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<sup>49</sup>, tended to have lower IGT scores. In a placebo-controlled pharmacological study, Farrell et al.<sup>44</sup> 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.<sup>41</sup> failed to find a significant correlation between COMT Val<sup>158</sup>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 interaction, 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 chronic stress have been widely recognized as risk factors that influence affective decision making<sup>46</sup>. For example, Gray<sup>49</sup> 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<sup>50</sup>. Children in better parent-child relationships showed significant improvements on IGT scores in a one-year longitudinal study<sup>51</sup>. 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.<sup>52</sup> found that COMT Val<sup>158</sup>Met polymorphism interacted with cannabis use to influence the development of psychotic symptoms and schizophrenia disorder. However, potential gene-environment interactions on affective decision making are largely unknown. Biologically, COMT Val<sup>158</sup>Met polymorphism mainly influences the activity of the COMT enzyme, and leads to different DA levels in the prefrontal cortex<sup>1,3,4</sup>. Animal studies have suggested that both stress and maternal care could alter brain DA levels. For example, Abercrombie et al.<sup>53</sup> 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, Gambara et al.<sup>34</sup> found that chronic stress decreased DA level in the nucleus accumbens. Hall et al.<sup>35</sup> found that maternal deprivation was associated with increased mesolimbic DA level. The present study analyzed the main effects of COMT Val<sup>158</sup>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 ($\chi^2 (1) = .003, p = .96$). There was no gender difference in the genotype distribution. The allele frequencies in the present study are comparable to other studies with Chinese participants<sup>56-58</sup>. 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 ($\chi^2 (1) = .33, p = .57$) or parental warmth grouping ($\chi^2 (1) = 1.67, p = .20$).

According to traditional IGT analysis<sup>52-53,55</sup>, the mean scores (SD) for each block was $-4.81 (6.58), -4.7 (7.53), 2.29 (9.35), 3.52 (10.36)$ 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<sup>54</sup> 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) |
| Low      | 7.49 (29.75) | .63 (.30) |
| High     | 2.51 (33.02) | .67 (.30) |
| **Stress** |          |       |
| Low      | 3.08 (32.11) | .67 (.30) |
| High     | 7.62 (30.44) | .62 (.31) |
| **PW**   |           |       |
| Low      |           |       |
| High     |           |       |

- Met/-: COMT Met carriers; PW: parental warmth; W: reward sensitivity.
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 $p_{s} > .10$).

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 (Figure 1A, $t(239) = .44, p = .66$). 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 $p_{s} > .10$).

**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 parental warmth. Previous studies reported mixed findings about the association between COMT Val$^{158}$Met polymorphism and human decision making. Two studies$^{32,43}$ showed that the $Val$ (or $Val$ equivalent G allele at rs4818) allele was associated with higher IGT scores, but another study$^{42}$ 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$^{32}$. 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$^{49}$ as well as unhealthy lifestyle behaviors, such as smoking, drinking or unhealthy diet$^{50}$. Both cross-sectional$^{50}$ and longitudinal$^{51}$ 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.$^{49}$ 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$^{68,77}$. Other studies suggest that the COMT Met allele is more susceptible to the effect of stress on psychosis$^{68,78}$. 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$^{54}$. In the area of decision making, Xiao et al.$^{30}$ found that children in better parent-child relationship showed significant improvement on the

**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. **: $p < .01$. 

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This image contains a figure with two panels. Panel A shows a bar chart comparing reward sensitivity between different genotypes and stress conditions, while Panel B compares IGT scores under different parental warmth conditions. The charts illustrate how genetic and environmental factors interact to influence decision-making behaviors.
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.47 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 score44–46, 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 cortically36. 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) regions38–40,42, although the opposite pattern has been reported by one study41. Reward sensitivity has been suggested to be triggered by DA signals in the striatum, a subcortical nucleus vital to reward and decision making42. Because of the positive relationship between DA and reward36, elevated tonic DA in the striatum plus increased DA when under stress will cause COMT Met allele carriers to show higher attention to reward/gain36. In terms of the interaction between parental warmth and COMT, previous studies have shown that parental warmth is associated with altered DA levels in rats42 and elevated cognitive flexibility in children36. 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-making43,44. For example, many studies have suggested that decision making was also influenced directly by the serotonin system45–47 or its interaction with the DA system42. In particular, Rogers46 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 Val158Met 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 parental 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 abuse12,46,49. 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 turns 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 systems50, 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 addiction42,44–47. 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 capacities42,44–47. 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 project1, 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 Test43). The results remained virtually the same after excluding these subjects. No subject was found to show high levels of cigarette (defined as a very high 18 or very high 16 or very high 15 and under) or alcohol (defined as a very high 18 or very high 16 or very high 15 and under) smoking according to the Fagerström Test for Nicotine Dependence51. 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 genotyping errors) for COMT Val158Met polymorphism (rs6269). Genotyping was done on a Gen Doc 2000 imaging system (Bio-Rad Laboratories Ltd, UK) following a polymerase chain reaction (PCR) protocol52. 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 abilities44–46. 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 damage53, and had been used extensively on other populations, including healthy adults54, adolescents55 and drug addicts56. A detailed description of the IGT appeared in Bechara et al.

Environmental measures. Two environmental measures were used. The Stressful Life Events Scale (SLES) was modified from Beam et al.57 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 stress58. 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 Chen59 and Greenberger et al., 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 mood57–59. The Cronbach’s 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 cognitive–complex IGT, we used the revised expectancy valuation model21 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, see42–44): 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 to 1, with higher values indicating rapid discount of past outcomes; 3) Choice consistency (c), ranging from 0–5 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. In the present study, we focused on the reward sensitivity (W) parameter due to its tight association with DA functions. 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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**Acknowledgements**

This research was supported by the 111 project (B07008) to Qi Dong, the National Science Foundation of China (31130025) to Gui Xue, and by research grants from NIDA R01DA023051 and NCI R01CA152062 to Antoine Bechara. We would also like to thank all the lab members who helped with the data collection.

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

**Additional information**

Supplementary information accompanies this paper at http://www.nature.com/scientificreports/

**Competing financial interests:** The authors declare no competing financial interests.

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