◆ Human Brain Mapping 37:1880–1892 (2016) ◆

COMT Val158Met Polymorphism Influences the Susceptibility to Framing in Decision-Making: OFC-Amygdala Functional Connectivity as a Mediator

Xiaoxue Gao,[1] Pingyuan Gong,[1,2] Jinting Liu,[1,3,4] Jie Hu,[1] Yue Li,[1] Hongbo Yu,[1] Xiaoliang Gong,[5] Yang Xiang,[5] Changjun Jiang,[5] and Xiaolin Zhou[1,6,7,8]*

[1]*Center for Brain and Cognitive Sciences and Department of Psychology, Peking University, Beijing 100871, China*
[2]*Institute of Population and Health, College of Life Science, Northwest University, Shanxi 710069, China*
[3]*China Center for Special Economic Zone Research, Shenzhen University, Guangdong 518060, China*
[4]*Research Centre for Brain Function and Psychological Science, Shenzhen University, Guangdong 518060, China*
[5]*Key Laboratory of Embedded System and Service Computing (Ministry of Education), Tongji University, Shanghai 201804, China*
[6]*Key Laboratory of Machine Perception (Ministry of Education), Peking University, Beijing 100871, China*
[7]*Beijing Key Laboratory of Behavior and Mental Health, Peking University, Beijing 100871, China*
[8]*PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China*

Abstract: Individuals tend to avoid risk in a gain frame, in which options are presented in a positive way, but seek risk in a loss frame, in which the same options are presented negatively. Previous studies suggest that emotional responses play a critical role in this "framing effect." Given that the Met allele of *COMT* Val158Met polymorphism (rs4680) is associated with the negativity bias during emotional processing, this study investigated whether this polymorphism is associated with individual susceptibility to framing and which brain areas mediate this gene–behavior association. Participants were genotyped, scanned in resting state, and completed a monetary gambling task with options (sure vs risky) presented as potential gains or losses. The Met allele carriers showed a greater framing effect

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: National Basic Research Program of China; Contract grant number: 973 Program: 2015CB856400; Contract grant sponsor: Natural Science Foundation of China; Contract grant numbers: 91232708 and 31170972; Contract grant sponsor: China Postdoctoral Science Foundation; Contract grant number: 2015M582399.

X. Gao, P. Gong, and J. Liu contributed equally to this study.

*Correspondence to: Dr Xiaolin Zhou; Department of Psychology, Peking University, 5 Yiheyuan Road, Beijing 100871, China. E-mail: xz104@pku.edu.cn

Received for publication 2 November 2015; Revised 13 January 2016; Accepted 8 February 2016.

DOI: 10.1002/hbm.23142
Published online 25 February 2016 in Wiley Online Library (wileyonlinelibrary.com).

than the Val/Val homozygotes as the former gambled more than the latter in the loss frame. Moreover, the gene–behavior association was mediated by resting-state functional connectivity (RSFC) between orbitofrontal cortex (OFC) and bilateral amygdala. Met allele carriers showed decreased RSFC, thereby demonstrating higher susceptibility to framing than Val allele carriers. These findings demonstrate the involvement of *COMT* Val158Met polymorphism in the framing effect in decision-making and suggest RSFC between OFC and amygdala as a neural mediator underlying this gene–behavior association. *Hum Brain Mapp 37:1880–1892, 2016.*

Key words: amygdala; *COMT*; framing effect; functional connectivity; orbitofrontal cortex; Val158Met; rs4680

INTRODUCTION

Humans are highly susceptible to the way that options are presented, resulting in a spontaneous decision-making bias known as the "framing effect" (Tversky and Kahneman, 1981). Individuals tend to choose the sure option (i.e., risk-averse) when options are presented in terms of gains but tend to gamble (i.e., risk-seeking) when the same options are presented in terms of losses (Kahneman and Tversky, 1984; Kuhberger et al., 1999). Neuroimaging studies demonstrated that the tendency to be risk-averse in the gain frame and risk-seeking in the loss frame is associated with increased activation in amygdala (and other relevant brain structures including dorsal anterior cingulate cortex, dACC; orbitofrontal cortex, OFC; and ventromedial prefrontal cortex, VMPFC), suggesting that activation of the emotion system plays an important role in this affect heuristic (De Martino et al., 2006; Roiser et al., 2009; Xu et al., 2013). Normal individuals showed stronger skin conductance responses (SCRs), reflecting emotional activity, to options in the loss frame than to the same options in the gain frame; however, this effect was absent for patients with autism, known for their impairment in emotional processing (De Martino et al., 2008; Hill et al., 2004). The involvement of emotion in the framing effect was further supported by behavioral studies demonstrating that increased distress leads to an increased framing effect (Druckman and McDermott, 2008), while cognitive reappraisal reduces the susceptibility to framing by effectively regulating the emotions associated with the decision frames (Miu and Crişan, 2011).

The susceptibility to framing in decision-making varies substantially across individuals (De Martino et al., 2006; Kahneman and Tversky, 1979; Roiser et al., 2009; Sharp and Salter, 1997). Twin studies have established that the susceptibility to framing is moderately heritable (Simonson and Sela, 2011; Cesarini et al., 2012; Cronqvist and Siegel, 2012), suggesting that genetic factors are a strong factor underlying the individual difference in susceptibility to framing. In this study, we aimed to investigate whether a genetic polymorphism, *COMT* Val158Met (rs4680), which is related to negativity bias during emotion processing, was associated with individual susceptibility to framing.

Catechol-o-methyltransferase (*COMT*) gene encodes the COMT enzyme, one of the major enzymes that degrade dopamine (DA) (Gogos et al., 1998; Grossman et al., 1992; Karoum et al., 1994). Within this gene, a transition of guanine (G) to adenine (A) leads to a mutation of valine (Val) to methionine (Met). Relative to the Val/Val genotype, the Met/Met genotype is associated with about 40% decreased enzyme activity, resulting in an increased DA level in the prefrontal cortex (Bilder et al., 2004; Chen et al., 2004; Lachman et al., 1996), a region that is crucial in the affective control of behavior (Roberts and Wallis, 2000). Previous studies have linked the *COMT* Met allele with the negativity bias in emotional processing, such as decreased resilience to negative mood states and increased anxiety levels and limbic reactivity to unpleasant stimuli (for a review, see Heinz and Smolka, 2006). For example, several psychiatric studies showed that the Met alleles increase the susceptibility to affective disorders, such as anxiety disorders (Enoch et al., 2003; McGrath et al., 2014; Olsson et al., 2007), depression (Ohara et al., 1998), and suicidal behavior (Kia-Keating et al., 2007). Moreover, a study using the acoustic affective startle reflex modulation (ASRM) paradigm, a psychophysiological measure of emotional processing, demonstrated that the Met/Met homozygotes exhibit a markedly increased emotional reactivity to aversive stimuli compared with the Val allele carriers (Montag et al., 2008). An event-related potential study (Herrmann et al., 2009) found that the Met/Met genotype manifests enhanced sensory encoding of affective stimuli, which is reflected by increased posterior negativity amplitudes (Schupp et al., 2003), during the processing of unpleasant stimuli. Neuroimaging studies demonstrated that the Met allele carriers have stronger reactivity to negative stimuli (pictures or facial expressions) in the prefrontal cortex and limbic system than the Val allele carriers (Drabant et al., 2006; Smolka et al., 2005; Williams et al., 2010); they also show stronger responses in the ventral striatum to losses, although not to gains, in a monetary incentive delay task (Schmack et al., 2008).

Given the importance of emotion in the framing effect and given the association between the Met allele and the negativity bias in emotional processing, we hypothesized that *COMT* Val158Met polymorphism may influence

individual susceptibility to framing, with the Met allele carriers showing a stronger framing effect than the Val/Val carriers.

Moreover, accumulating evidence has implicated the role of *COMT* Val158Met polymorphism in modulating the resting-state network properties of the prefrontal cortex, which may in turn contribute to individual differences in a number of cognitive and affective processes, including working memory, executive functions, and emotion regulation (Baeken et al., 2014; Liu et al., 2010; Meyer et al., 2016; Tian et al., 2013; Tunbridge et al., 2013). In light of this, treating brain activity as an intermediate phenotype (Bigos and Weinberger, 2010), we hypothesized that the potential gene–behavior association may be mediated by the resting-state network properties of the prefrontal regions associated with the framing effect (e.g., dACC, vmPFC, and OFC) (De Martino et al., 2006; Roiser et al., 2009; Xu et al., 2013). Thus, in this study, we employed resting-state functional connectivity (RSFC) to reveal the neural correlates that play this mediation role. The RSFC detects the spatial patterns of temporally correlated blood oxygenation level-dependent (BOLD) activity across the brain during resting-state, allowing one to map out the functional network of the brain (Biswal et al., 1995), with improved signal-to-noise ratio and without being confounded by a specific task (Fox and Greicius, 2010; Fox et al., 2012). This task-free measurement is relatively reliable across individuals (Damoiseaux et al., 2006; Shehzad et al., 2009), and has been widely used in identifying the neural correlates underlying the genetic influence on behaviors (Gordon et al., 2015; Long et al., 2013; Meyer-Lindenberg, 2009).

MATERIALS AND METHODS

Participants

One hundred and eleven unrelated Chinese Han college students (64% males, mean age 21.78 ± 1.92 years) were recruited from Shanghai, China. All of them were right-handed. Five of them (see below, 1 Met/Met carrier, 1 Val/Met carrier and 3 Val/Val carriers) were excluded from the behavioral data analysis because of their low accuracy in the catch condition, in which the expected values of the sure option and the gamble option were not equivalent. Eight participants (3 Val/Met carriers and 5 Val/Val carriers) were further excluded in the imaging data analysis because of their excessive head movement (>2 mm translation or 2° rotation, 4 participants) or equipment malfunction (4 participants). None of the participants reported any history of psychiatric, neurological, or cognitive disorders. Written informed consents were obtained from each participant. This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Department of Psychology, Peking University.

Genotyping

We collected 3–5 hairs with hair follicle cells from each participant. The genomic DNA was extracted from hair follicle cells by using Chelex-100 method (de Lamballerie et al., 1994). The *COMT* gene was amplified and genotyped using polymerase chain reaction (PCR) and restriction digestion techniques. The PCR system comprised 2.50 μL 2 × reaction MIX (Golden Easy PCR System, TIANGEN), 0.50 μL DNA Template, 2.50 μL ddH_2O, 0.25 μL (25 pmol) upstream primer (5′-CCAGCGGATGGTGG ATTTCGCACGC-3′) and 0.25 μL (25 pmol) downstream primer (5′-TGGGGGGGTCTTTCCTCAGCC-3′). The AC in upstream primer was a site-directed mutagenesis for introducing a restriction site for MluI. Thermal cycling consisted of 4 min of initial denaturation at 94°C followed by 30 cycles of 94°C (30s), 63.5°C (30s), 72°C (30s), and with a final extension step of 72°C (3 min). The PCR products were digested using MluI (FERMENTAS, MBI) at 37°C overnight. According to the provided protocols, the 5.0 μL incubation system contained 1.5 μl PCR products, 4.0 U MluI (10 U/μl), 0.4 μl R buffer, and 3.1 μL ddH_2O. The digested products were analyzed using 8% polyacrylamide gel electrophoresis with 200 V for 1.5 h following silver staining. Finally, the genotypes were scanned by using the Bio-imaging System.

The distribution of genotypes in the current sample (Met/Met = 7, Val/Met = 49, Val/Val = 55) showed no deviation from the Hardy–Weinberg Equilibrium, $\chi^2 = 0.82$, $p = 0.37$. The allele frequencies were similar to those of the Chinese in the HapMap dataset (http://www.hapmap.org). Considering the limited number of Met/Met participants, we grouped Met/Met and Val/Met participants into the Met allele carriers group in the subsequent analysis.

Behavioral Tests

We used a standard monetary gambling task to assess the framing effect (De Martino et al., 2006) (Fig. 1). At the beginning of each trial, participants were endowed with an initial amount of monetary reward. They were asked to perform a gambling task, in which they made choices between receiving a certain guaranteed amount of monetary remuneration from the initial amount (i.e., the sure option) and taking a risky option that could enable them, with a certain probability, to receive all or none of the initial amount (i.e., the risky or gamble option). The sure option was formulated as either money retained from the initial amount (i.e., the gain frame) (e.g., "Keep ¥ 20 out of a total of ¥ 50") or as money lost from the initial amount (i.e., the loss frame) (e.g., "Lose ¥ 30 out of a total of ¥ 50"). The gamble option was identical for both frames and was represented by a pie chart indicating the certain probability to receive all or none of the initial amount.

The behavioral test consisted of three sessions. Each session had 48 trials (16 gain trials, 16 loss trials, and 16 catch trials), ordered randomly (Supporting Information, Table S1).

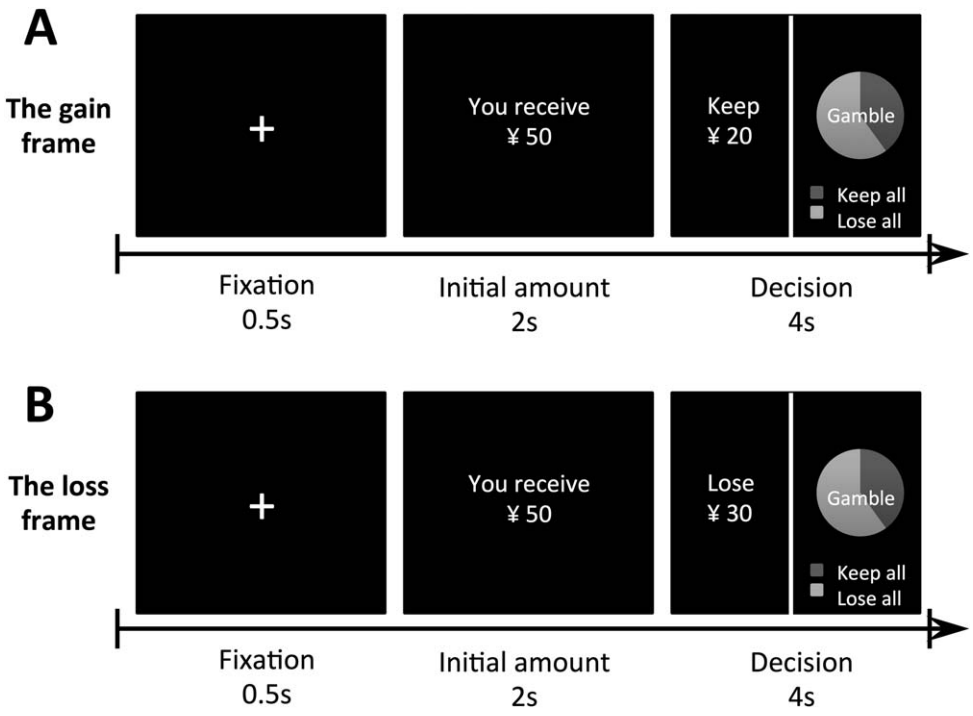

Figure 1.

The monetary gambling task. At the beginning of each trial, participants were faced with a fixation (0.5 s) before being endowed with the initial amount for the current trial (e.g., "You receive 50 ¥") (2 s). Participants then decided between a guaranteed portion of the initial amount of money (i.e., the gain option) or a risky option that could enable them, with a certain probability, to receive all or none of the initial amount (i.e., the gamble option) (4 s). The sure option was formulated as either money retained from the initial amount (e.g., "Keep 20 ¥ of a total of 50 ¥") (i.e., the gain frame, **A**) or as money lost from the initial amount (e.g., "Lose 20 ¥ of a total of 50 ¥") (i.e., the loss frame, **B**). The gamble option was the same for both frames and represented as a pie chart indicating the certain probability to receive all or none amount of the initial amount. The expected outcomes were always equivalent between two options and between two frames. No feedback of the outcomes was given during the task.

The gain and loss frames consisted of 4 initial amounts (¥ 25, ¥ 50, ¥ 75, and ¥ 100) and 4 levels of probability (20%, 40%, 60%, and 80%) of the gamble option. For the gain and loss trials, the expected values (utilities) in each trial were equivalent between the two options. Each "catch" trial (8 gain trials and 8 loss trails in each session) had two options in which the expected values of the sure option and the gamble option were not equivalent (e.g., "Keep ¥ 10 out of a total of ¥ 50" vs. "Keep all of the ¥ 50 with a probability of 60%"). Participants were supposed to choose the option with the higher utility (the risky option in this example). The inclusion of the catch trials was to ensure that participants were actively engaged in the task. Five participants with accuracy lower than 75% in the catch trials were excluded from data analysis.

Image Acquisition

MR imaging was performed using a 3.0 T MR scanner (GE MR750 scanner). Functional images were obtained using an echo planar imaging (EPI) sequence sensitive to BOLD contrast with the following parameters: 40 slices, 2000/30 ms (TR/TE), 3 mm slice thickness, 192 × 192 mm (FOV), 64 × 64 (resolution within slice), and 90° (flip angle). During the resting-state scanning, participants were instructed to close their eyes, keep still, not sleep, and not think about anything in particular. A T1-weighted sagittal three-dimensional magnetization-prepared rapid gradient echo sequence was also acquired for each participant with the following parameters: 146 slices, 8.188/3.184/450 ms (TR/TE/TI), 1 mm slice thickness, 256 × 256 mm (FOV), 256 × 256 (resolution within slice), and 12° (flip angle). For each subject, the resting-state scanning lasted for 400 s and provided 200 volumes.

Imaging Data Preprocessing

Preprocessing of the resting-state fMRI data was conducted using Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm) and Data

Processing Assistant for Resting-State fMRI (DPARSF; Yan and Zang, 2010) in the following steps: (1) discarding the first 5 volumes of the functional images to allow for stabilization of magnetization; (2) correcting for within-scan acquisition time difference between slices; (3) realigning the remaining volumes to the sixth volume to correct for head-motion; (4) coregistering the T1 image to the mean functional image after motion correction using a linear transformation (Collignon et al., 1995); (5) segmenting the T1 image into gray matter (GM), white matter, and cerebrospinal fluid by using a unified segmentation algorithm (Ashburner and Friston, 2005); (6) spatially normalizing the functional images to the Montreal Neurological Institute (MNI) space and resampling to $3 \times 3 \times 3$ mm^3 isotropic voxel; (7) removing the linear trend of the time courses; (8) conducting temporal band-pass filtration (0.01–0.1 Hz); and (9) performing linear regression to remove the influence of head motion, the mean global signal, white matter signals, and cerebrospinal fluid signals.

Ninety-eight participants were included in the final imaging data analysis, with 51 Met allele carriers and 47 Val/Val homozygotes. To focus on the signals in the gray matter, the following analysis was conducted within a gray matter mask ($N_{voxels} = 67{,}632$), which was generated by thresholding (cutoff = 0.2) a prior gray-matter probability map in SPM8.

Functional Connectivity Analysis

Functional connectivity analysis was conducted following the steps suggested by previous studies (Gordon et al., 2015; Long et al., 2013). OFC, dACC, vmPFC, and bilateral amygdala were selected as seed regions based on De Martino et al. (2006). These regions were confirmed by other studies to play important roles in the framing effect (Roiser et al., 2009; Xu et al., 2013). Brain regions that displayed positive functional connectivity with each seeds were extracted out as masks since previous studies have demonstrated that the negative connectivities arising from the correction for the global signal may exhibit lower stability and reliability than positive connectivities (Shehzad et al., 2009; Tian et al., 2007). We performed two-sample t tests to identify which brain regions' (within the masks) connectivities with the seed regions differed between the two *COMT* genotype groups. Then we tested whether individual differences in these connectivities could predict the susceptibility to framing in decision-making.

Functional connectivity map and mask creations

The functional connectivity analysis was carried out using the Resting-State fMRI Data Analysis Toolkit (REST; http://www.restfmri.net; Song et al., 2011) and the toolbox for Data Processing & Analysis of Brain Imaging (DPABI; http://rfmri.org/dpabi). Functional connectivity seeds were created as spheres of radius 6 mm centered on peak MNI coordinates of the five regions (dACC [2, 24, 44], vmPFC [−4, 38, −8], OFC [24, 30, −10], bilateral amygdala [−14, 2, −24], and [12, 2, −20]; see De Martino et al., 2006). The functional connectivity map and mask creations were conducted in the following steps: (1) computing the average time series across all voxels in each seed region and performing whole-brain correlation analysis between the time series of each seed and the time series of each voxel outside of the seed for each participant to obtain a participant-level functional connectivity map; (2) converting these maps to z-functional connectivity (FC) maps by conducting Fisher z score transformation; (3) spatially smoothing the z-FC maps using 4 mm FWHM Gaussian kernel; (4) performing one-sample t tests, for the two *COMT* genotypes respectively, on the z-FC maps to map out which regions' z-FC values were significantly above zero (FDR corrected, $p < 0.01$, two-tailed); and (5) combining the t tests maps for the two genotype groups into a joint network mask for further analysis. We conducted the further analysis within these joint network masks.

The effects of COMT Val158Met polymorphism on connectivity

For each seed, we tested for the difference in functional connectivity between the genotype groups by performing two-sample t tests within the joint network mask of each seed while controlling for gender, age, and two head-motion parameters (the root mean squares of both overall head motion displacement and rotation for each participant). Results were corrected for multiple comparisons using the threshold of voxel-wise $p < 0.05$ (uncorrected) combined with cluster-level threshold of $p < 0.05$ (FWE-corrected). This cluster-level threshold (number of voxels in the cluster) was determined using a Monte Carlo simulation (Ledberg et al., 1998) as implemented in the AFNI AlphaSim program (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). The cluster-level threshold for dACC, vmPFC, OFC, left amygdala, and right amygdala were 34 voxels (918 mm^3), 30 voxels (810 mm^3), 34 voxels (918 mm^3), 22 voxels (594 mm^3), and 23 voxels (621 mm^3), respectively.

Association between the COMT-influenced functional connectivity and the susceptibility to framing

To search for the connectivities influenced by *COMT* that can predict individual susceptibility to framing in decision-making, we examined correlations between the connectivities influenced by *COMT* and our behavioral tests. First, we defined regions of interest (ROIs) as the clusters of brain regions, in which connectivity strength with each seed significantly differed between *COMT* genotype groups (Supporting Information, Table S2). The Fisher z score of each voxel was extracted and the scores for each ROI were averaged for each participant. Then we conducted linear regression analysis with the average Fisher z score for each ROI as a single predictor and the

susceptibility to framing (i.e., the rate of taking the risky option or the gamble option in the loss frame minus the rate in the gain frame) as the dependent variable. Age, gender, and two head-motion parameters of each participant were controlled as covariates.

To guard against spurious associations as a result of multiple statistical testing and to further validate the above findings, we conducted the Monte Carlo permutation tests for each regression model by using lmPerm package in R (http://www.r-project.org). The permutation test is a widely accepted correction approach in multiple statistical testing (Belmonte and Yurgelun-Todd, 2001; Camargo et al., 2008; Gomez-Villegas et al., 2014; Nakagawa, 2004), which resamples the total number of observations for certain times to estimate the regression coefficient in each shuffled sample and the probability of the estimated regression coefficients being greater than the observed regression coefficient (i.e., permutation p). This approach estimates statistical significance directly from the data being analyzed and includes irregularities of the data in the estimation of the permutation probability (Cheverud, 2001).

Mediation Analyses

Treating brain activity as an intermediate phenotype (Bigos and Weinberger, 2010), we conducted mediation analyses to examine whether the effect of *COMT* Val158Met polymorphism on individual susceptibility to framing could be mediated by the OFC-left amygdala connectivity and the OFC-right amygdala connectivity. These mediation analyses, with age and gender as covariates, were conducted with the SPSS version of INDIRECT macro (http://www.afhayes.com/; Preacher and Hayes, 2008) with 20000 bootstrap iterations. First, two separate single mediation models were tested with *COMT* genotype as the independent variable, the susceptibility to framing as the dependent variable, and the OFC-left amygdala connectivity and the OFC-right amygdala connectivity as mediators, respectively. Considering the correlation between the OFC-left amygdala connectivity and the OFC-right amygdala connectivity (adjusted $R^2 = 0.357$, $p < 0.001$), two separate simple mediation models may suffer from an inability to tease apart individual mediating effects attributable to the two connectivities, which could lead to biased parameter estimates. Therefore, we tested a multiple mediation model with these two connectivities as mediators simultaneously to reduce the likelihood of parameter bias and to compare the individual mediating effects of the two mediators, as suggested by Preacher and Hayes (2008).

RESULTS

Behavioral Results

Consistent with previous studies (De Martino et al., 2006; Roiser et al., 2009; Xu et al., 2013), a significant framing effect was observed for the rate of taking the risky or gamble options: 53.2% ± 0.2% (SD) in the loss frame vs. 38.2 ± 0.2% in gain the frame, $t_{(105)} = 9.337$, $p < 0.001$. Given that previous studies have demonstrated significant roles of age (Dumontheil et al., 2011) and gender (Amstadter et al., 2012) for the effect of *COMT* on brain activity and decision-making, these two factors were controlled as covariates in the following analysis. A 2 (genotype: Met allele carrier vs. Val/Val homozygote) × 2 (frame: gain vs. loss) mixed measures analysis of variance (ANOVA) on the gambling rate revealed a significant interaction between *COMT* genotype and frame both before and after controlling for the potential effects of age and gender, $F_{(1,104)} = 5.748$, $p = 0.018$, and $F_{(1,102)} = 5.883$, $p = 0.017$, respectively. The Met allele carriers more often took the risky option than the Val/Val homozygotes in the loss frame, $F_{(1,102)} = 4.450$, $p = 0.037$, but the two groups did not differ in the gain frame, $F_{(1,102)} = 0.108$, $p = 0.743$ (Fig. 2). The interaction between *COMT* genotype and frame remained significant if the behavioral data of the 8 participants who were excluded in the imaging data preprocessing were excluded, $F_{(1,94)} = 4.708$, $p = 0.033$. Thus, consistent with our hypothesis, these results demonstrated that *COMT* Met allele carriers are more susceptible to framing in decision-making than the Val/Val homozygotes.

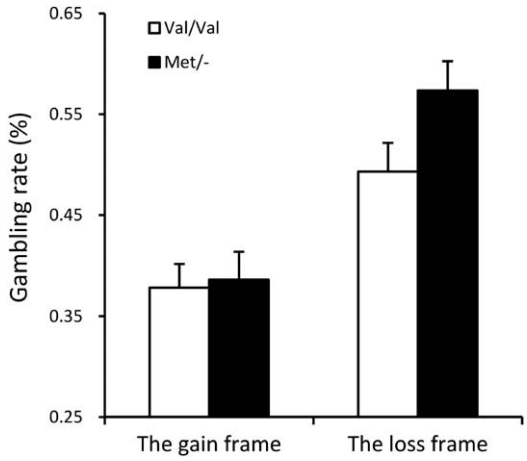

Figure 2.
The association between *COMT* Val158Met polymorphism and the susceptibility to framing in decision-making. Individuals with the Met allele ($N = 56$), which is associated with lower activity of COMT, were more susceptible to framing than the Val/Val homozygotes ($N = 55$) before ($F_{(1, 104)} = 5.748$, $p = 0.018$) and after ($F_{(1, 102)} = 5.883$, $p = 0.017$) controlling for age and gender. Specifically, *COMT* allele carriers showed a higher gambling rate in the loss frame compared with the Val/Val homozygotes ($F_{(1, 102)} = 4.450$, $p = 0.037$), but no difference was found in the gain frame ($F_{(1, 102)} = 0.108$, $p = 0.743$). This pattern of effects remained unchanged if the behavioral data of the 8 participants who were excluded in the imaging data preprocessing or the Met/Met homozygotes were excluded. Error bars represent the standard error of the mean.

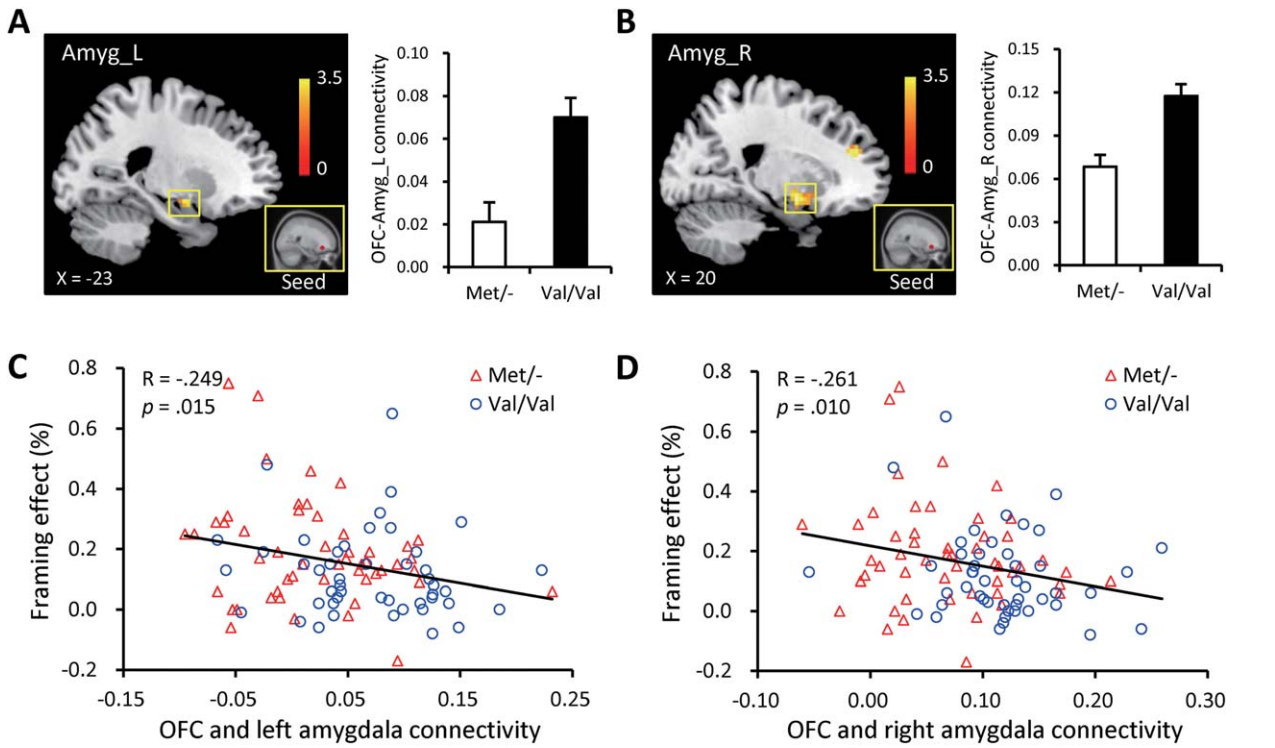

Figure 3.

Neural correlates underlying the gene–behavior association. (A) and (B) The *COMT* Met allele carriers ($N = 51$) were associated with a decreased connectivity between the OFC seed and left amygdala, and a decreased connectivity between the OFC seed and right amygdala compared with the Val/Val carriers ($N = 47$). **(C) and (D)** With age, gender, and two head-motion parameters as covariates, individual susceptibility to the framing effect was predicted by the connectivity between the OFC seed and left amygdala (peak voxel in MNI space coordinates: −15, 6, −18, cluster size = 1134 mm^3; $p = 0.015$, $R^2 = 0.062$, permutation corrected), and the connectivity between the OFC seed and right amygdala (peak voxel in MNI space coordinates: 18, 0, −12, cluster size = 2403 mm^3; $p = 0.010$, $R^2 = 0.068$, permutation corrected), respectively. Error bars represent the standard error of the mean. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Neuroimaging Results

The brain regions that demonstrated significantly different connectivity with each seed region between *COMT* genotype groups are listed in Supporting Information, Table S2. We conducted linear regression to examine whether connectivities influenced by *COMT* genotypes were predictive of individual susceptibility to framing. With age, gender, and two head-motion parameters as covariates, the susceptibility to framing was predicted by the connectivity between the OFC seed and left amygdala (peak voxel in MNI space coordinates: −15, 6, −18, cluster size = 1134 mm^3; $\beta = -0.233$, $t = -2.312$, $p = 0.023$, adjusted $R^2 = 0.062$), and the connectivity between the OFC seed and right amygdala (peak voxel in MNI space coordinates: 18, 0, −12, cluster size = 2403 mm^3; $\beta = -0.217$, $t = -2.139$, $p = 0.035$, adjusted $R^2 = 0.054$), respectively. No functional connectivity of other seeds was found to be predictive of the susceptibility to the framing in decision-making.

We conducted permutation tests for each regression model to guard against spurious associations in multiple statistical testing. After the Monte Carlo permutation test with 5000 permutations of the behavioral data (individual susceptibility to framing), the two regression models remained significant (left amygdala: permutation $p = 0.015$, adjusted $R^2 = 0.062$; right amygdala: permutation $p = 0.010$, adjusted $R^2 = 0.068$) (Fig. 3).

The two separate single mediation models showed that the gene–behavior association could be mediated by OFC-left amygdala connectivity (indirect effect estimate = −0.0125, SE = 0.0068, 95% bias corrected confidence interval is [−0.0313, −0.0029]) and OFC-right amygdala connectivity (indirect effect estimate = −0.0129, SE = 0.0072, 95% bias-corrected confidence interval is [−0.0319, −0.0021]). The multiple mediation model with these two connectivities as mediators simultaneously showed that the total indirect effect of this model was significant (indirect effect estimate = −0.0164, SE = 0.0083, 95% bias-corrected confidence interval is

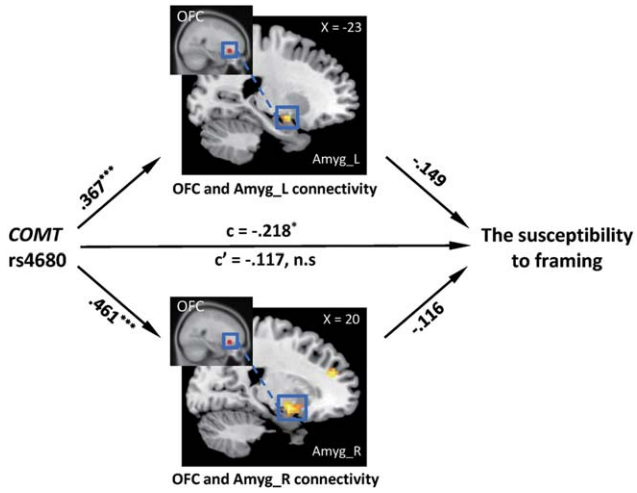

Figure 4.

The mediation analysis. The effect of the *COMT* Val158Met polymorphism on individual susceptibility to framing was mediated by the functional connectivity strength between OFC and left amygdala, and the functional connectivity strength between OFC and right amygdala (indirect effect estimate = −0.0164, SE = 0.0083, 95% confidence interval is [−0.0373, −0.0037]), with age and gender as covariates. After adding the two head-motion parameters to the mediation model as covariates, the total indirect effect remained significant (indirect effect estimate = −0.0137, SE = 0.0081, 95% bias corrected confidence interval is [−0.0344, −0.0013]). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

[−0.0373, −0.0037]). A pairwise comparison showed that the indirect effect of the two mediators did not differ significantly in magnitude (95% confidence interval is [−0.0239, 0.0232]) (Fig. 4). After adding the two head-motion parameters to the mediation model as covariates, the total indirect effect remained significant (indirect effect estimate = −0.0137, SE = 0.0081, 95% bias-corrected confidence interval is [−0.0344, −0.0013]). Therefore, relative to the Val/Val homozygotes, the Met allele carriers showed decreased functional connectivity between OFC and both the left and the right amygdala, which in turn contributed to the larger framing effect.

Supplementary Analyses

Four supplementary analyses were conducted to validate the robustness and the reproducibility of our findings: (1) Because of the small number of the Met/Met homozygotes, we tested whether the main results sustained after removing the data of the Met/Met homozygotes and found that both the genotype effect on the framing effect and the mediating effect of OFC–bilateral amygdala connectivity remained significant (Supporting Information). (2) To validate the reproducibility of our main results, we used the risk preference model in Chung et al. (2015) on our behavioral data to estimate individual risk preference parameters in two (gain and loss) frames. Model-based results again revealed a marginally significant gene–behavior association and a significant mediating role of OFC–bilateral amygdala connectivity (Supporting Information). (3) Two further analyses were conducted during imaging data preprocessing. First, as head movement has a confounding effect on resting-state functional connectivity (Power et al., 2012; Van Dijk et al., 2012), we conducted the "scrubbing" procedure in addition to the realignment procedure. Second, since it is still under debate whether regressing out the global signal is an appropriate procedure (Fox et al., 2009; Murphy et al., 2009; Wang et al., 2014), we reanalyzed our data without regressing out the global signal. The pattern of results is consistent with our results (Supporting Information). (4) We also used left OFC [−24, 30, −10] (symmetric to peak MNI coordinates of OFC in De Martino et al., 2006) as the center of the seed region to conduct functional connectivity analysis, though De Martino et al. (2006) did not find an association between the activation of left OFC and the susceptibility to framing. We used one sample t test to examine whether the connectivity between the left OFC seed and bilateral amygdala was larger than 0 and found that there was no significant (FDR corrected, $p < 0.01$) connectivity between left OFC and bilateral amygdala during resting state (even after extending the threshold to $p < 0.05$, uncorrected).

DISCUSSION

Previous research has shown that the individual difference in susceptibility to framing can be attributable to the differences in gene expression, with moderate heritability (Simonson and Sela, 2011; Cesarini et al., 2012; Cronqvist and Siegel, 2012). However, how genes influence this individual difference is still unknown. In this study, by using a monetary gambling task in which sure and risky options were presented in terms of either gains or losses, we investigated the association between *COMT* Val158Met polymorphism and individual susceptibility to framing in decision-making. Consistent with our hypotheses, the Met allele carriers showed a greater framing effect than the Val/Val homozygotes as the former gambled more than the latter in the loss frame. This effect was absent in the gain frame. Previous research has shown a relationship between the serotoninergic gene (5-HTTLPR) and individual susceptibility to framing (Roiser et al., 2009). An important advance made by this study is that we identified *COMT* Val158Met polymorphism, a common functional polymorphism that has no direct link to the serotoninergic system, as a genetic contributor to individual difference in the susceptibility to framing. Moreover, by analyzing the functional connectivity between brain regions in the resting-state, we found that the functional

connectivity between OFC and bilateral amygdala mediated the gene–behavior association. The Met allele carriers evidenced decreased OFC–amygdala functional connectivity, accompanying their higher susceptibility to framing.

Neuroimaging studies have identified brain regions that are essential to the framing effect, such as OFC and amygdala (De Martino et al., 2006; Roiser et al., 2009). In De Martino et al. (2006), the activation in OFC was predictive of participants' susceptibility to framing and the activation in amygdala was associated with individuals' tendency to be risk-averse in the gain frame and risk-seeking in the loss frame (De Martino et al., 2006; see also Roiser et al., 2009). However, it is unknown whether and how the functional coupling between amygdala and OFC plays a role in the framing effect. Here, we provided evidence that the resting-state functional connectivity between OFC and amygdala correlated negatively with the susceptibility to framing.

It is well-established that OFC and amygdala have bilateral structural connections with each other (Cavada et al., 2000) and that their functional connectivity underlies various cognitive and affective processes (Dolan, 2007; Murray and Wise, 2010; Schoenbaum et al., 2000; Zald et al., 2014). Patients with emotional dysregulation (major depressive disorder and social anxiety disorder) were associated with decreased resting-state OFC–amygdala functional connectivity compared with healthy participants (Hahn et al., 2011; Tang et al., 2013). This is further supported by the observation that amygdala resting-state metabolic activity positively correlated with OFC resting-state metabolic activity in healthy subjects, which may reveal an important functional relationship between these structures; this effect was absent in borderline personality disorder patients, known for emotional dysregulation (Katz et al., 1996; New et al., 2007). In light of these findings, individuals with higher OFC–amygdala functional connectivity may have enhanced emotion regulation during decision-making under different frames, which in turn reduces the influence of emotional biases on choices and enables resistance to the framing effect (Miu and Crişan, 2011).

Moreover, our results provide evidence that the functional coupling between OFC and bilateral amygdala, which is important for emotion regulation, is a potential neural mediator of this gene–behavior association. Based on these results, we suggest that *COMT* Val158Met polymorphism influences the susceptibility to framing via its influence on emotion regulation. We have two lines of evidence supporting this suggestion. First, *COMT* Val158Met polymorphism may influence emotion regulation via modulation on prefrontal dopaminergic functions. Specifically, according to the framework proposed by Bilder et al. (2004), compared with the *COMT* Val allele, the Met allele is associated with reduced phasic and increased tonic dopamine (DA) transmission subcortically and increased DA concentrations cortically. This tonic-phasic difference of DA results in reduced executive control (e.g., emotion regulation, task switching, and inhibition) in the Met allele carriers, mediated by decreased phasic arousal within the ventrolateral system centering on OFC and amygdala (Bilder, 1997; Christensen and Bilder, 2000). For instance, the Met/Met homozygotes exhibit a markedly increased emotional reactivity to aversive stimuli compared with the Val allele carriers (Montag et al., 2008). Psychiatric studies have demonstrated that the Met alleles increased the susceptibility to affective disorders related to emotional dysregulation, such as anxiety and depression (Enoch et al., 2003; Kia-Keating et al., 2007; McGrath et al., 2014; Ohara et al., 1998; Olsson et al., 2007). Second, the magnitude of the framing effect is related to the ability of emotion regulation. For example, it has been demonstrated that increased distress leads to an increased framing effect (Druckman and McDermott, 2008) while successful cognitive reappraisal of emotions associated with decision frames reduces the susceptibility to framing (Miu and Crişan, 2011).

In this study, our results demonstrated that the right (but not the left) OFC–bilateral amygdala connectivity mediated the gene–behavior association, which was consistent with previous studies showing preferential right OFC activity during decision-making (Elliott et al., 1999; Ernst et al., 2002; De Martino et al., 2006; Tanabe et al., 2007) and a right laterality effect in lesion studies on decision-making, emotional processing, and other purported OFC functions (for a review, see Happaney et al., 2004; see also Rolls et al., 1994; Stuss and Alexander, 1999; Manes et al., 2002; Tranel et al., 2002). Several possible reasons might contribute to this laterality effect (for a review, see Happaney et al., 2004), such as the differential involvement of the right and the left hemispheres in avoidance (negative affect) and approach (positive affect), respectively (Bechara, 2004; see also Davidson and Irwin, 1999; Davidson et al., 2000). However, since laterality in value-based decision-making is an issue of debate and the results were not consistent (Fellows, 2004; Liu et al., 2011), further studies are needed to investigate the specific connectivity network of bilateral OFC during decision-making.

Finally, our findings raise a few important questions for future research. First, although our findings provide preliminary evidence that the resting-state OFC–amygdala functional connectivity, which is important for emotion regulation, is an important neural mediator underlying the effect of *COMT* gene on individual susceptibility to framing, resting-state data may not provide direct evidence for the role of the emotion regulation process in this gene–behavior association. Further research is needed to test whether *COMT* Val158Met polymorphism is directly associated with emotion regulation during decision-making under different frames. Moreover, although resting-state functional connectivity reflects the statistical history of regional co-activation (Dosenbach et al., 2007; Gordon et al., 2016), it does not permit assignment of connectivity directionality. Thus, future brain structural analysis and

brain stimulation studies are needed to reveal the directionality of the connectivity and the specific mechanism underlying the gene–behavior association. Second, although the mediation effect of the functional connectivity between OFC and bilateral amygdala was identified using OFC seed, the effect was absent when using bilateral amygdala identified by De Martino et al. (2006) as seeds. One possible explanation is that the bilateral amygdala regions identified with the connectivity analysis here and those in De Martino et al. (2006) represent the two different subdivisions of amygdala (left amygdala [−15, 6, −18] and right amygdala [18, 0, −12] here vs. left amygdala [−14, 2, −24] and right amygdala [12, 2, −20] in De Martino et al.), the superficial group (the centromedial cortical nuclei) and the deeper group (the basal and lateral nuclei), respectively (Pitkanen et al., 2000; Bach et al., 2011; Mishra et al., 2014). Since both the tract-tracing studies in nonhuman primates (McDonald, 1998), and diffusion tensor imaging and RSFC analysis in humans (Bach et al., 2011; Mishra et al., 2014) demonstrated that the superficial group of amygdala connects more strongly to OFC than the deeper group, it is possible that the absence of an effect for amygdala seeds might be due to the weak connectivity between the deeper group of amygdala neurons to OFC. However, the specific roles of these two subdivisions of amygdala during decision-making remain to be explored.

In conclusion, this study provides the first evidence linking *COMT* Val158Met polymorphism and individual susceptibility to framing in decision-making and suggests OFC–amygdala functional connectivity as an underlying mechanism of this gene–behavior association. These findings contribute to our understanding of the individual differences in irrational decision-making.

ACKNOWLEDGMENTS

The authors thank Dr Yong He and his team for their advice in data analysis, and Dr Yufeng Zang, Dr Qing Cai, Dr Lusha Zhu, and two anonymous reviewers for their advice on the write-up of this article.

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