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



**Abstract:** Indi iduals tend to a oid risk in a gain frame, in hich options are presented in a positi e a , but seek risk in a loss frame, in hich the same options are presented negati el . Pre ious studies suggest that emotional responses pla a critical role in this Maraming effect. Gi en that the Met allele of *COMT* Val158Met pol morphism (rs4680) is associated ith the negati it bias during emotional processing, this stud in estigated hether this pol morphism is associated ith indi idual susceptibilit to framing and hich brain areas mediate this gene beha ior association. Participants ere genot ped, scanned in resting state, and completed a monetar gambling task ith options (sure s risk ) presented as potential gains or losses. The Met allele carriers sho ed a greater framing effect

Additional Supporting Information ma be found in the online ersion of this article.	*Correspondence to: Dr Xiaolin Zhou; Department of Ps cholog , Peking Uni ersit , 5 Yihe uan Road, Beijing 100871, China.
Contract grant sponsor: National Basic Research Program of	E-mail: 7104@pku.edu.cn
China; Contract grant number: 973 Program: 2015CB856400; Con- tract grant sponsor: Natural Science Foundation of China; Con-	Recei ed for publication 2 No ember 2015; Re ised 13 Januar 2016; Accepted 8 Februar 2016.
tract grant numbers: 91232708 and 31170972; Contract grant sponsor: China Postdoctoral Science Foundation; Contract grant number: 2015M582399. X. Gao, P. Gong, and J. Liu contributed equall to this stud .	DOI: 10.1002/hbm.23142 Published online 25 Februar 2016 in Wile Online Librar ( ile onlinelibrar .com).

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than the Val/Val homo<sup>\*</sup> gotes as the former gambled more than the latter in the loss frame. Moreo er, the gene beha ior association as mediated b resting-state functional connecti it (RSFC) bet een orbitofrontal corte (OFC) and bilateral am gdala. Met allele carriers sho ed decreased RSFC, thereb

indi idual susceptibilit to framing, ith the Met allele carriers sho ing a stronger framing effect than the Val/Val carriers.

Moreo er, accumulating e idence has implicated the role of COMT Val158Met pol morphism in modulating the resting-state net ork properties of the prefrontal corte, hich ma in turn contribute to indi idual differences in a number of cogniti e and affecti e processes, including orking memor , e ecuti e functions, and emotion regulation (Baeken et al., 2014; Liu et al., 2010; Me er et al., 2016; Tian et al., 2013; Tunbridge et al., 2013). In light of this, treating brain acti it as an intermediate phenot pe (Bigos and Weinberger, 2010), e h pothesi' ed that the potential gene beha ior association ma be mediated b the resting-state net ork properties of the prefrontal regions associated ith the framing effect (e.g., dACC, mPFC, and OFC) (De Martino et al., 2006; Roiser et al., 2009; Xu et al., 2013). Thus, in this stud, e emplo ed resting-state functional connecti it (RSFC) to re eal the neural correlates that pla this mediation role. The RSFC detects the spatial patterns of temporall correlated blood o genation le el-dependent (BOLD) acti it across the brain during resting-state, allo ing one to map out the functional net ork of the brain (Bis al et al., 1995), ith impro ed signal-to-noise ratio and ithout being confounded b a speci c task (Fo and Greicius, 2010; Fo et al., 2012). This task-free measurement is relati el reliable across indi iduals (Damoiseau et al., 2006; Sheh<sup>7</sup> ad et al., 2009), and has been idel used in identif ing the neural correlates underl ing the genetic in uence on beha iors (Gordon et al., 2015; Long et al., 2013; Me er-Lindenberg, 2009).

### MA E IAL AND ME H D

One hundred and ele en unrelated Chinese Han college students (64% males, mean age  $21.78 \pm 1.92$  ears) ere recruited from Shanghai, China. All of them ere righthanded. Fi e of them (see belo , 1 Met/Met carrier, 1 Val/Met carrier and 3 Val/Val carriers) ere e cluded from the beha ioral data anal sis because of their lo accurac in the catch condition, in hich the e pected alues of the sure option and the gamble option ere not equi alent. Eight participants (3 Val/Met carriers and 5 Val/Val carriers) ere further e cluded in the imaging data anal sis because of their e cessi e head mo ement (>2 mm translation or 2° rotation, 4 participants) or equipment malfunction (4 participants). None of the participants reported an histor of ps chiatric, neurological, or cogniti e disorders. Written informed consents ere obtained from each participant. This stud as performed in ith the Declaration of Helsinki and accordance as appro ed b the Ethics Committee of the Department of Ps cholog , Peking Uni ersit .

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We collected 3 5 hairs ith hair follicle cells from each participant. The genomic DNA as e tracted from hair follicle cells b using Chele -100 method (de Lamballerie et al., 1994). The COMT gene as ampli ed and genot ped using pol merase chain reaction (PCR) and restriction digestion techniques. The PCR s stem comprised 2.50  $\mu$ L 2  $\times$  reaction MIX (Golden Eas PCR S stem, TIAN-GEN), 0.50 µL DNA Template, 2.50 µL ddH<sub>2</sub>O, 0.25 µL (25 pmol) upstream primer (5'-CCAGCGGATGGTGG ATTTCGCACGC-3') and 0.25 µL (25 pmol) do nstream primer (5'-TGGGGGGGGTCTTTCCTCAGCC-3'). The AC in upstream primer as a site-directed mutagenesis for introducing a restriction site for MluI. Thermal c cling consisted of 4 min of initial denaturation at 94°C follo ed b 30 c cles of 94°C (30s), 63.5°C (30s), 72°C (30s), and ith a nal e tension step of 72°C (3 min). The PCR products

ere digested using MluI (FERMENTAS, MBI) at 37°C o ernight. According to the pro ided protocols, the 5.0  $\mu$ L incubation s stem contained 1.5  $\mu$ l PCR products, 4.0 U MluI (10 U/ $\mu$ l), 0.4  $\mu$ l R buffer, and 3.1  $\mu$ L ddH<sub>2</sub>O. The digested products ere anal <sup>7</sup>ed using 8% pol acr lamide gel electrophoresis ith 200 V for 1.5 h follo ing sil er staining. Finall , the genot pes ere scanned b using the Bio-imaging S stem.

The distribution of genot pes in the current sample (Met/Met = 7, Val/Met = 49, Val/Val = 55) sho ed no de iation from the Hard Weinberg Equilibrium,  $\chi^2 = 0.82$ , p = 0.37. The allele frequencies ere similar to those of the Chinese in the HapMap dataset (http:// .hapmap.org). Considering the limited number of Met/Met participants, e grouped Met/Met and Val/Met participants into the

Met allele carriers group in the subsequent anal sis.

## В

We used a standard monetar gambling task to assess the framing effect (De Martino et al., 2006) (Fig. 1). At the beginning of each trial, participants ere endo ed ith an initial amount of monetar re ard. The ere asked to perform a gambling task, in hich the made choices bet een recei ing a certain guaranteed amount of monetar remuneration from the initial amount (i.e., the sure option) and taking a risk option that could enable them,

ith a certain probabilit , to recei e all or none of the initial amount (i.e., the risk or gamble option). The sure option as formulated as either mone retained from the initial amount (i.e., the gain frame) (e.g., MKeep 20 out of a total of 50 ) or as mone lost from the initial amount (i.e., the loss frame) (e.g., MLose 30 out of a total of 50 ). The gamble option as identical for both frames and

as represented b a pie chart indicating the certain probabilit to recei e all or none of the initial amount.

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



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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

The gain and loss frames consisted of 4 initial amounts (25, 50, 75, and 100) and 4 le els of probabilit (20%, 40%, 60%, and 80%) of the gamble option. For the gain and loss trials, the e pected alues (utilities) in each trial ere equi alent bet een the t o options. Each Match trial (8 gain trials and 8 loss trails in each session) had t o options in hich the e pected alues of the sure option and the gamble option ere not equi alent (e.g., MKeep 10 out of a total of 50 s. MKeep all of the 50 ith a probabilit of 60% ). Participants ere supposed to choose the option ith the higher utilit (the risk option in this e ample). The inclusion of the catch trials as to ensure that participants ere acti el engaged in the task. Fi e participants ith accurac lo er than 75% in the catch trials ere e cluded from data anal sis.

MR imaging as performed using a 3.0 T MR scanner (GE MR750 scanner). Functional images ere obtained

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.

using an echo planar imaging (EPI) sequence sensiti e to BOLD contrast ith the follo ing parameters: 40 slices, 2000/30 ms (TR/TE), 3 mm slice thickness, 192 × 192 mm (FOV), 64 × 64 (resolution ithin slice), and 90° (ip angle). During the resting-state scanning, participants ere instructed to close their e es, keep still, not sleep, and not think about an thing in particular. A T1- eighted sagittal three-dimensional magneti<sup>7</sup> ation-prepared rapid gradient echo sequence as also acquired for each participant ith the follo ing parameters: 146 slices, 8.188/3.184/450 ms (TR/TE/TI), 1 mm slice thickness, 256 × 256 mm (FOV), 256 × 256 (resolution ithin slice), and 12° (ip angle). For each subject, the resting-state scanning lasted for 400 s and pro ided 200 olumes.

## D –

Preprocessing of the resting-state fMRI data as conducted using Statistical Parametric Mapping soft are (SPM8; http:// . l.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (DPARSF; Yan and Zang, 2010) in the follo ing steps: (1) discarding the rst 5 olumes of the functional images to allo for stabili<sup>7</sup> ation of magneti<sup>7</sup> ation; (2) correcting for ithin-scan acquisition time difference bet een slices; (3) realigning the remaining olumes to the si th olume 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 gra matter (GM), hite matter, and cerebrospinal uid b using a uni ed segmentation algorithm (Ashburner and Friston, 2005); (6) spatiall normali<sup>7</sup>ing the functional images to the Montreal Neurological Institute (MNI) space and resampling to  $3 \times 3 \times 3$  mm<sup>3</sup> isotropic o el; (7) remo ing the linear trend of the time courses; (8) conducting temporal band-pass ltration (0.01 0.1 H<sup>r</sup>); and (9) performing linear regression to remo e the in uence of head motion, the mean global signal, hite matter signals, and cerebrospinal uid signals.

Ninet -eight participants ere included in the nal imaging data anal sis, ith 51 Met allele carriers and 47 Val/Val homo' gotes. To focus on the signals in the gra matter, the follo ing anal sis as conducted ithin a gra matter mask ( $N_{o els} = 67,632$ ), hich as generated b thresholding (cutoff = 0.2) a prior gra -matter probabilit map in SPM8.



Functional connecti it anal sis as conducted follo ing the steps suggested b pre ious studies (Gordon et al., 2015; Long et al., 2013). OFC, dACC, mPFC, and bilateral am gdala ere selected as seed regions based on De Martino et al. (2006). These regions ere con rmed b other studies to pla important roles in the framing effect (Roiser et al., 2009; Xu et al., 2013). Brain regions that displa ed positi e functional connecti it ith each seeds ere e tracted out as masks since pre ious studies ha e demonstrated that the negati e connecti ities arising from the correction for the global signal ma e hibit lo er stabilit and reliabilit than positi e connecti ities (Shehr ad et al., 2009; Tian et al., 2007). We performed t o-sample t tests to identif hich brain regions' ( ithin the masks) connecti ities ith the seed regions differed bet een the t o COMT genot pe groups. Then e tested hether indi idual differences in these connecti ities could predict the susceptibilit to framing in decision-making.

## Functional connectivity map and mask creations

The functional connecti it anal sis as carried out using the Resting-State fMRI Data Anal sis Toolkit (REST; http:// .restfmri.net; Song et al., 2011) and the toolbo for Data Processing & Anal sis of Brain Imaging (DPABI; http://rfmri.org/dpabi). Functional connecti it seeds ere created as spheres of radius 6 mm centered on peak MNI coordinates of the e regions (dACC [2, 24,

44], mPFC [-4, 38, -8], OFC [24, 30, -10], bilateral am gdala [-14, 2, -24], and [12, 2, -20]; see De Martino et al., 2006). The functional connecti it map and mask creations ere conducted in the follo ing steps: (1) computing the a erage time series across all o els in each seed region and performing hole-brain correlation anal sis bet een the time series of each seed and the time series of each o el outside of the seed for each participant to obtain a participant-le el functional connecti it map; (2) con erting these maps to z-functional connecti it (FC)maps b conducting Fisher *z* score transformation; (3) spatiall smoothing the *z*-FC maps using 4 mm FWHM Gaussian kernel; (4) performing one-sample t tests, for the t o COMT genot pes respecti el, on the z-FC maps to map out hich regions' z-FC alues ere signi cantl abo e <sup>*r*</sup> ero (FDR corrected, p < 0.01, t o-tailed); and (5) combining the t tests maps for the t o genot pe groups into a joint net ork mask for further anal sis. We conducted the further anal sis ithin these joint net ork masks.

# The effects of COMT Val158Met polymorphism on connectivity

For each seed, e tested for the difference in functional connecti it bet een the genot pe groups b performing t o-sample *t* tests ithin the joint net ork mask of each seed hile controlling for gender, age, and t o headmotion parameters (the root mean squares of both o erall head motion displacement and rotation for each participant). Results ere corrected for multiple comparisons using the threshold of o el- ise p < 0.05 (uncorrected) ith cluster-le el threshold of p < 0.05 (FWEcombined corrected). This cluster-le el threshold (number of o els in the cluster) as determined using a Monte Carlo simulation (Ledberg et al., 1998) as implemented in the AFNI AlphaSim program (http://afni.nimh.nih.go /pub/dist/ doc/manual/AlphaSim.pdf). The cluster-le el threshold for dACC, mPFC, OFC, left am gdala, and right am gdala ere 34 o els (918 mm<sup>3</sup>), 30 o els (810 mm<sup>3</sup>), 34 o els (918 mm<sup>3</sup>), 22 o els (594 mm<sup>3</sup>), and 23 o els (621 mm<sup>3</sup>), respecti el .

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

To search for the connecti ities in uenced b COMT that can predict indi idual susceptibilit to framing in decision-making, e e amined correlations bet een the connecti ities in uenced b COMT and our beha ioral tests. First, e de ned regions of interest (ROIs) as the clusters of brain regions, in hich connecti it strength ith each seed signi cantl differed bet een COMT genot pe groups (Supporting Information, Table S2). The Fisher *z* score of each o el as e tracted and the scores for each ROI ere a eraged for each participant. Then e conducted linear regression anal sis ith the a erage Fisher *z* score for each ROI as a single predictor and the

susceptibilit to framing (i.e., the rate of taking the risk option or the gamble option in the loss frame minus the rate in the gain frame) as the dependent ariable. Age, gender, and t o head-motion parameters of each participant ere controlled as co ariates.

To guard against spurious associations as a result of multiple statistical testing and to further alidate the abo e ndings, e conducted the Monte Carlo permutation tests for each regression model b using lmPerm package in R .r-project.org). The permutation test is a (http:// idel accepted correction approach in multiple statistical testing (Belmonte and Yurgelun-Todd, 2001; Camargo et al., 2008; Gome<sup>\*</sup>-Villegas et al., 2014; Nakaga a, 2004), hich resamples the total number of obser ations for certain times to estimate the regression coef cient in each shuf ed sample and the probabilit of the estimated regression coef cients being greater than the obser ed regression coef cient (i.e., permutation *p*). This approach estimates statistical signi cance directl from the data being anal "ed and includes irregularities of the data in the estimation of the permutation probabilit (Che erud, 2001).

## Μ 🚬 Α

Treating brain acti it as an intermediate phenot pe (Bigos and Weinberger, 2010), e conducted mediation anal ses to e amine hether the effect of COMT Val158Met pol morphism on indi idual susceptibilit to framing could be mediated b the OFC-left am gdala connecti it and the OFC-right am gdala connecti it . These mediation anal ith age and gender as co ariates, ses, ere conducted ith the SPSS ersion of INDIRECT macro (http:// afha es.com/; Preacher and Ha es, 2008) ith 20000 bootstrap iterations. First, t o separate single mediation models ere tested ith COMT genot pe as the independent ariable, the susceptibilit to framing as the dependent ariable, and the OFC-left am gdala connecti it and the OFC-right am gdala connecti it as mediators, respecti el . Considering the correlation bet een the OFC-left am gdala connecti it and the OFC-right am gdala connecti it (adjusted  $R^2 = 0.357$ , p < 0.001), t o separate simple mediation models ma suffer from an inabilit to tease apart indi idual mediating effects attributable to the t o connecti ities,

hich could lead to biased parameter estimates. Therefore, e tested a multiple mediation model ith these t o connecti ities as mediators simultaneousl to reduce the likelihood of parameter bias and to compare the indi idual mediating effects of the t o mediators, as suggested b Preacher and Ha es (2008).

## **E**'ML

## Β.

Consistent ith pre ious studies (De Martino et al., 2006; Roiser et al., 2009; Xu et al., 2013), a signi cant framing effect



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.

as obser ed for the rate of taking the risk or gamble options: 53.2%  $\pm$  0.2% (SD) in the loss frame s. 38.2  $\pm$  0.2% in gain the frame,  $t_{(105)} = 9.337$ , p < 0.001. Gi en that pre ious studies ha e demonstrated signi cant roles of age (Dumontheil et al., 2011) and gender (Amstadter et al., 2012) for the effect of COMT on brain acti it and decisionmaking, these t o factors ere controlled as co ariates in the follo ing anal sis. A 2 (genot pe: Met allele carrier s. Val/Val homo<sup>\*</sup> gote) × 2 (frame: gain s. loss) mi ed measures anal sis of ariance (ANOVA) on the gambling rate re ealed a signi cant interaction bet een COMT genot pe 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, respectiel. The Met allele carriers more often took the risk option than the Val/Val homo" gotes in the loss frame,  $F_{(1,102)} = 4.450$ , p = 0.037, but the t o groups did not differ in the gain frame,  $F_{(1,102)} = 0.108$ , p = 0.743 (Fig. 2). The interaction bet een *COMT* genot pe and frame remained signi cant if the beha ioral data of the 8 participants ho ere e cluded in the imaging data preprocessing ere e cluded,  $F_{(1,94)} = 4.708$ , p = 0.033. Thus, consistent ith our h pothesis, these results demonstrated that COMT Met allele carriers are more susceptible to framing in decision-making than the Val/Val homo<sup>\*</sup> gotes.

## Ν.

The brain regions that demonstrated signi cantl different connecti it ith each seed region bet een COMT genot pe groups are listed in Supporting Information, Table S2. We conducted linear regression to e amine hether connecti ities in uenced b COMT genot pes ere predicti e of indi idual susceptibilit to framing. With age, gender, and t o head-motion parameters as co ariates, the susceptibilit to framing as predicted b the connecti it bet een the OFC seed and left am gdala (peak o el in MNI space coordinates: -15, 6, -18, cluster si<sup>7</sup> e = 1134 mm<sup>3</sup>;  $\beta = -0.233$ , t = -2.312, p = 0.023, adjusted  $R^2 = 0.062$ ), and the connecti it bet een the OFC seed and right am gdala (peak o el in MNI space coordinates: 18, 0, -12, cluster si<sup>*r*</sup> e = 2403 mm<sup>3</sup>;  $\beta$  = -0.217, t = -2.139, p = 0.035, adjusted  $R^2 = 0.054$ ), respecti el . No functional connecti it of other seeds as found to be predicti e of the susceptibilit to the framing in decision-making.

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We conducted permutation tests for each regression model to guard against spurious associations in multiple statistical testing. After the Monte Carlo permutation test

ith 5000 permutations of the beha ioral data (indi idual susceptibilit to framing), the t o regression models remained signi cant (left am gdala: permutation p = 0.015, adjusted  $R^2 = 0.062$ ; right am gdala: permutation p = 0.010, adjusted  $R^2 = 0.068$ ) (Fig. 3).

The t o separate single mediation models sho ed that the



#### F. 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 headmotion 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 pair ise comparison sho ed that the indirect effect of the t o mediators did not differ signi cantl in magnitude (95% con dence inter al is [-0.0239, 0.0232]) (Fig. 4). After adding the t o head-motion parameters to the mediation model as co ariates, the total indirect effect remained signi cant (indirect effect estimate = -0.0137, SE = 0.0081, 95% bias-corrected con dence inter al is [-0.0344, -0.0013]). Therefore, relati e to the Val/Val homo- $^{7}$  gotes, the Met allele carriers sho ed decreased functional connecti it bet een OFC and both the left and the right am gdala, hich in turn contributed to the larger framing effect.

## Α,

Four supplementar anal ses ere conducted to alidate the robustness and the reproducibilit of our ndings: (1) Because of the small number of the Met/Met homo' gotes, e tested hether the main results sustained after remo ing the data of the Met/Met homo' gotes and found that both the genot pe effect on the framing effect and the mediating effect of OFC bilateral am gdala connecti it remained signi cant (Supporting Information). (2) To alidate the reproducibilit of our

main results, e used the risk preference model in Chung et al. (2015) on our beha ioral data to estimate indi idual risk preference parameters in t o (gain and loss) frames. Model-based results again re ealed a marginall signi cant gene beha ior association and a signi cant mediating role of OFC bilateral am gdala connecti it (Supporting Information). (3) T o further anal ses ere conducted during imaging data preprocessing. First, as head mo ement has a confounding effect on resting-state functional connecti it (Po er et al., 2012; Van Dijk et al., 2012), e conducted the Macrubbing procedure in addition to the realignment procedure. Second, since it is still under debate hether regressing out the global signal is an appropriate procedure (Fo et al., 2009; Murph et al., 2009; Wang et al., 2014), e reanal <sup>7</sup>ed our data ithout regressing out the global signal. The pattern of results is consistent ith our results (Supporting Information). (4) We also used left OFC [-24, 30, -10] (s mmetric to peak MNI coordinates of OFC in De Martino et al., 2006) as the center of the seed region to conduct functional connecti it anal sis, though De Martino et al. (2006) did not nd an association bet een the acti ation of left OFC and the susceptibilit to framing. We used one sample t test to e amine hether the connecti it bet een the left OFC seed and bilateral am gdala as larger than 0 and found that there as no signi cant (FDR corrected, p < 0.01) connecti it bet een left OFC and bilateral am gdala during resting state (e en after e tending the threshold to p < 0.05, uncorrected).

#### DIGMIN

Pre ious research has sho n that the indi idual difference in susceptibilit to framing can be attributable to the differences in gene e pression, ith moderate heritabilit (Simonson and Sela, 2011; Cesarini et al., 2012; Cronq ist and Siegel, 2012). Ho e er, ho genes in uence this indiidual difference is still unkno n. In this stud, b using a monetar gambling task in hich sure and risk options ere presented in terms of either gains or losses, e in estigated the association bet een *COMT* Val158Met pol morphism and indi idual susceptibilit to framing in decision-making. Consistent ith our h potheses, the Met allele carriers sho ed a greater framing effect than

the Val/Val homo<sup>\*</sup> gotes as the former gambled more than the latter in the loss frame. This effect as absent in the gain frame. Pre ious research has sho n a relationship bet een the serotoninergic gene (5-HTTLPR) and indi idual susceptibilit to framing (Roiser et al., 2009). An important ad ance made b this stud is that e identied *COMT* Val158Met pol morphism, a common func-

tional pol morphism that has no direct link to the serotoninergic s stem, as a genetic contributor to indi idual difference in the susceptibilit to framing. Moreo er, b anal 'ing the functional connecti it bet een brain regions in the resting-state, e found that the functional connecti it bet een OFC and bilateral am gdala mediated the gene beha ior association. The Met allele carriers e idenced decreased OFC am gdala functional connecti it, accompan ing their higher susceptibilit to framing.

Neuroimaging studies ha e identi ed brain regions that are essential to the framing effect, such as OFC and am gdala (De Martino et al., 2006; Roiser et al., 2009). In De Martino et al. (2006), the acti ation in OFC as predicti e of participants' susceptibilit to framing and the acti ation in am gdala as associated ith indi iduals' tendenc to be risk-a erse in the gain frame and risk-seeking in the loss frame (De Martino et al., 2006; see also Roiser et al., 2009). Ho e er, it is unkno n hether and ho the functional coupling bet een am gdala and OFC pla s a role in the framing effect. Here, e pro ided e idence that the resting-state functional connecti it bet een OFC and am gdala correlated negati el ith the susceptibilit to framing.

It is ell-established that OFC and am gdala ha e bilateral structural connections ith each other (Ca ada et al., 2000) and that their functional connecti it underlies arious cogniti e and affecti e processes (Dolan, 2007; Murra and Wise, 2010; Schoenbaum et al., 2000; Zald et al., 2014). Patients ith emotional d sregulation (major depressi e disorder and social an iet disorder) ere associated ith decreased resting-state OFC am gdala functional connecti it compared ith health participants (Hahn et al., 2011; Tang et al., 2013). This is further supported b the obser ation that am gdala resting-state metabolic acti it positi el correlated ith OFC resting-state metabolic acti it in health subjects, hich ma re eal an important functional relationship bet een these structures; this effect as absent in borderline personalit disorder patients, kno n for emotional d sregulation (Kat<sup>7</sup> et al., 1996; Ne et al., 2007). In light of these ndings, indi iduals ith higher OFC am gdala functional connecti it ma ha e enhanced emotion regulation during decisionmaking under different frames, hich in turn reduces the in uence of emotional biases on choices and enables resistance to the framing effect (Miu and Crisan, 2011).

Moreo er, our results pro ide e idence that the functional coupling bet een OFC and bilateral am gdala, hich is important for emotion regulation, is a potential neural mediator of this gene beha ior association. Based on these results, e suggest that COMT Val158Met pol morphism in uences the susceptibilit to framing ia its in uence on emotion regulation. We have t o lines of e idence supporting this suggestion. First, COMT Val158Met pol morphism ma in uence emotion regulation ia modulation on prefrontal dopaminergic functions. Speci call, according to the frame ork proposed b Bilder et al. (2004), compared ith the *COMT* Val allele, the Met allele is associated ith reduced phasic and increased tonic dopamine (DA) transmission subcorticall and increased DA concentrations corticall . This tonic-phasic difference of DA results in reduced e ecuti e control (e.g., emotion

regulation, task s itching, and inhibition) in the Met allele carriers, mediated b decreased phasic arousal ithin the entrolateral s stem centering on OFC and am gdala (Bilder, 1997; Christensen and Bilder, 2000). For instance, the Met/Met homo' gotes e hibit a markedl increased emotional reacti it to a ersi e stimuli compared ith the Val allele carriers (Montag et al., 2008). Ps chiatric studies ha e demonstrated that the Met alleles increased the susceptibilit to affecti e disorders related to emotional d sregulation, such as an iet 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 abilit of emotion regulation. For e ample, it has been demonstrated that increased distress leads to an increased framing effect (Druckman and McDermott, 2008) hile successful cogniti e reappraisal of emotions associated ith decision frames reduces the susceptibilit to framing (Miu and Crisan, 2011).

In this stud , our results demonstrated that the right (but not the left) OFC bilateral am gdala connecti it mediated the gene beha ior association, hich as consistent ith pre ious studies sho ing preferential right OFC acti it during decision-making (Elliott et al., 1999; Ernst et al., 2002; De Martino et al., 2006; Tanabe et al., 2007) and a right lateralit effect in lesion studies on decision-making, emotional processing, and other purported OFC functions (for a re ie , see Happane et al., 2004; see also Rolls et al., 1994; Stuss and Ale ander, 1999; Manes et al., 2002; Tranel et al., 2002). Se eral possible reasons might contribute to this lateralit effect (for a re ie, see Happane et al., 2004), such as the differential in ol ement of the right and the left hemispheres in a oidance (negati e affect) and approach (positi e affect), respecti el (Bechara, 2004; see also Da idson and Ir in, 1999; Da idson et al., 2000). Ho e er, since lateralit in alue-based decision-making is an issue of debate and the results ere not consistent (Fello s, 2004; Liu et al., 2011), further studies are needed to in estigate the speci c connecti it netork of bilateral OFC during decision-making.

Finall, our ndings raise a fe important questions for future research. First, although our ndings pro ide preliminar e idence that the resting-state OFC am gdala functional connecti it, hich is important for emotion regulation, is an important neural mediator underl ing the effect of *COMT* gene on indi idual susceptibilit to framing, resting-state data ma not pro ide direct e idence for the role of the emotion regulation process in this gene beha ior association. Further research is needed to test

hether *COMT* Val158Met pol morphism is directl associated ith emotion regulation during decision-making under different frames. Moreo er, although resting-state functional connecti it re ects the statistical histor of regional co-acti ation (Dosenbach et al., 2007; Gordon et al., 2016), it does not permit assignment of connecti it directionalit . Thus, future brain structural anal sis and brain stimulation studies are needed to re eal the directionalit of the connecti it and the speci c mechanism under-1 ing the gene beha ior association. Second, although the mediation effect of the functional connecti it bet een OFC and bilateral am gdala as identi ed using OFC seed, the effect as absent hen using bilateral am gdala identi ed b De Martino et al. (2006) as seeds. One possible e planation is that the bilateral am gdala regions identi ed ith the connecti it anal sis here and those in De Martino et al. (2006) represent the t o different subdi isions of am gdala (left am gdala [-15, 6, -18] and right am gdala [18, 0, -12] here s. left am gdala [-14, 2, -24] and right am gdala [12, 2, -20] in De Martino et al.), the super cial group (the centromedial cortical nuclei) and the deeper group (the basal and lateral nuclei), respecti el (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 anal sis in humans (Bach et al., 2011; Mishra et al., 2014) demonstrated that the super cial group of am gdala connects more strongl to OFC than the deeper group, it is possible that the absence of an effect for am gdala seeds might be due to the eak connecti it bet een the deeper group of am gdala neurons to OFC. Ho e er, the speci c roles of these t o subdi isions of am gdala during decisionmaking remain to be e plored.

In conclusion, this stud pro ides the rst e idence linking *COMT* Val158Met pol morphism and indi idual susceptibilit to framing in decision-making and suggests OFC am gdala functional connecti it as an underling mechanism of this gene beha ior association. These ndings contribute to our understanding of the indi idual differences in irrational decision-making.

### ACKN LEDGMEN

The authors thank Dr Yong He and his team for their ad ice in data anal sis, and Dr Yufeng Zang, Dr Qing Cai, Dr Lusha Zhu, and t o anon mous re ie ers for their ad ice on the rite-up of this article.

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