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

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[2]I H , C L , , x
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[3]C C E m Z , , G 518060,
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[4] C B F , ,
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[5]K L E m m C m (M E),
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[7]B K L B M H , , B 100871,
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Abstract: Individuals tend to avoid risk in a gain frame, in which options are presented in a positive

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.* © Wiley Periodicals, Inc.

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

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

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

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). 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 *CKM* Val158Met polymorphism on individual susceptibility to framing could be mediated by the OFC-left amygdala connectivity and the OFC-right amygdala connectivity. These mediation analy-

Neuroimaging Results

The brain regions that demonstrated significantly different connectivity with each seed region between $^{\prime}CKM$ genotype groups are listed in Supporting Information, Table S2. We conducted linear regression to examine whether connectivities influenced by $^{\prime}CKM$ 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

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connectivity between OFC and bilateral amygdala medi-

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