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Original article

Identifying new susceptibility genes on dopaminergic and serotonergic pathways for the framing effect in decision-making

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Abstract

The framing effect refers the tendency to be risk-averse when options are presented positively but be risk-seeking when the same options are presented negatively during decision-making. This effect has been found to be modulated by the serotonin transporter gene (*SLC6A4*) and the catechol-o-methyltransferase gene (*COMT*) polymorphisms, which are on the dopaminergic and serotonergic pathways and which are associated with affective processing. The current study aimed to identify new genetic variations of genes on dopaminergic and serotonergic pathways that may contribute to individual differences in the susceptibility to framing. Using genome-wide association data and the gene-based principal components regression method, we examined genetic variations of 26 genes on the pathways in 1317 Chinese Han participants. Consistent with previous studies, we found that the genetic variations of the *SLC6A4* gene and the *COMT* gene were associated with the framing effect. More importantly, we demonstrated that the genetic variations of the aromatic-L-amino-acid decarboxylase (*DDC*) gene, which is involved in the synthesis of both dopamine and serotonin, contributed to individual differences in the susceptibility to framing. Our findings shed light on the understanding of the genetic basis of affective decision-making.

Key words: framing effect; decision-making; *DDC*; *COMT*; *SLC6A4*; GWAS

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Introduction

During decision-making, individuals tend to be risk-averse when options are presented in a positive way (i.e. the gain frame) but be risk-seeking when the same options are presented negatively (i.e. the loss frame), a phenomenon known as the 'framing effect' (Tversky and Kahneman, 1981; Kahneman and Tversky, 1984; Kuhberger *et al.*, 1999). This spontaneous bias is observed across different cultures (Kahneman and Tversky, 1979; Sharp and Salter, 1997), and has profound influences on important daily decisions, such as those related to finance, voting, and whether or not to undergo a certain surgery (McNeil *et al.*, 1982; Druckman, 2004).

Previous studies suggested that emotional arousal towards the potential of loss plays an important role in the framing effect. Specifically, psychophysiological evidence demonstrated that choices in the loss frame are associated with more elevated skin conductance responses than choices in the gain frame in normal participants; this effect was absent for autistic participants with emotional impairment (Hill *et al.*, 2004; De Martino *et al.*, 2008). Neuroimaging studies revealed an increased activation of the emotion system (e.g. the amygdala) when participants chose risky options in the loss frame and safe options in the gain frame (De Martino *et al.*, 2006; Roiser *et al.*, 2009; Xu *et al.*, 2013; Gao *et al.*, 2016). Moreover, increased distress results in an increased framing effect (Druckman and McDermott, 2008), while reduced emotional response via cognitive reappraisal decreases individuals' susceptibility to framing (Miu and Crişan, 2011).

The susceptibility to framing in decision-making, which varies substantially across individuals (Kahneman and Tversky, 1979; Sharp and Salter, 1997; De Martino *et al.*, 2006; Roiser *et al.*, 2009; Gao *et al.*, 2016), has moderate heritability (Simonson and Sela, 2011; Cesarini *et al.*, 2012; Cronqvist and Siegel, 2012), suggesting that genetic variations contribute to the individual differences. Although genetic studies on risk-taking have demonstrated the important role of genetic variations on dopaminergic and serotonergic pathways in decision-making under risks (Crişan *et al.*, 2009; Dreber *et al.*, 2009; Kuhnen and Chiao, 2009; He *et al.*, 2010; Frydman *et al.*, 2011; Heitland *et al.*, 2012; Reuter *et al.*, 2013; Set *et al.*, 2014), only a few studies investigated directly the genetic basis of the susceptibility to framing in decision-making. Two studies (Crişan *et al.*, 2009, N = 36; Roiser *et al.*, 2009, N = 30) showed the association between 5-HTTLPR variable number of tandem repeats variation, the genetic variation in the promoter region of the serotonin transporter gene (*SLC6A4*), and individuals' susceptibility to framing. Individuals who are homozygous for the short (s) allele at the 5-HTTLPR are more susceptible to framing than individuals who are homozygous for the long (l) allele. Our recent work (N = 98) on dopamine degradation gene *COMT* indicated that *COMT* Val158Met polymorphism is also associated with the individual differences in susceptibility to framing. Compared with the Val/Val homozygotes, the framing effect is more profound in the Met allele carriers, who have increased prefrontal dopamine concentrations (Gao *et al.*, 2016). However, given that complex molecular networks and cellular pathways contribute to individual differences in complex behaviors (Schadt, 2009; Wang *et al.*, 2010), variations in a few polymorphisms are unlikely to be the whole story behind the genetic basis of susceptibility to framing. Here we sought to further shed light on this genetic basis by investigating variations in a set of genes on the dopaminergic and serotonergic pathways.

Genetic variations related to dopamine metabolism and signaling have been shown to be involved in emotional processing and dysregulation (Meyer-Lindenberg, 2010; Opmeer *et al.*, 2010; Scharinger *et al.*, 2010; Gadow *et al.*, 2014). For example, the Met allele of the *COMT* gene is associated with the negative bias in affective processing, including decreased resilience in response to negative mood states and increased anxiety levels and limbic reactivity (e.g. amygdala) in response to unpleasant stimuli (Ohara *et al.*, 1998; Enoch *et al.*, 2003; Schupp *et al.*, 2003; McGrath *et al.*, 2004; Smolka *et al.*, 2005; Drabant *et al.*, 2006; Kia-Keating *et al.*, 2007; Olsson *et al.*, 2007; Montag *et al.*, 2008; Williams *et al.*, 2010; for a review, see Heinz and Smolka, 2006). Similarly, genetic variations of the monoamine oxidase gene (*MAOA* and *MAOB*) are key candidates in studies concerning the mechanisms of negative emotionality (Dlugos *et al.*, 2009) and psychiatric disorders [e.g. major depression (Kersting *et al.*, 2007; Roohi *et al.*, 2009)].

Genetic association studies also suggest the contribution of gene variations in the serotonin system to affective processing and psychiatric disorders (Meyer-Lindenberg, 2010; Scharinger *et al.*, 2010; Bevilacqua and Goldman, 2011; Fabbri *et al.*, 2013; Jonassen and Landrø, 2014). Specifically, relative to the homozygous long variation (l/l), the short (s) allele of 5-HTTLPR exhibits increased amygdala reactivity to negative environmental stimuli (Hariri *et al.*, 2002; Canli *et al.*, 2005; Heinz *et al.*, 2005) and to negative self-reflection (Ma *et al.*, 2014); it is thus recognized as a risk allele for affective disorders (Bellivier *et al.*, 1998; Lotrich and Pollock, 2004; Lasky-Su *et al.*, 2005; Uher and McGuffin, 2010), although a meta-analysis suggested that the main effect of 5-HTTLPR genotype and the interaction between 5-HTTLPR and SLE on risk of depression are negligible (Munafò *et al.*, 2009). Moreover, a gene involved in the synthesis of both dopamine and serotonin, the aromatic-L-amino-acid decarboxylase gene (*DDC*), is associated with affective disorders, including anxiety state (Costas *et al.*, 2010) and bipolar disorder (Børglum *et al.*, 2003).

Considering both the key role of affective processing in the framing effect and the association between emotional processing and genetic variations on dopaminergic and serotonergic pathways, genes on these two pathways are possible contributors to the individual differences in susceptibility to framing. In the current study, by applying the gene-based principal components regression (PCReg) approach (Wang and Abbott, 2008; Hibar *et al.*, 2011a, b) and pathway-based approach (Wang *et al.*, 2007; Wang *et al.*, 2010) to genome-wide association (GWA) data, we sought to find new genes that contribute to the susceptibility to framing in decision-making. To this end, 26 genes were selected from dopaminergic and serotonergic pathways and subjected to analysis. All genes were selected according to dopaminergic pathway and serotonergic pathway maps in KEGG database (http://www.genome.jp/kegg/), a manually curated collection of pathway maps widely used in gene-set analysis (e.g. Nemoda *et al.*, 2011; Set *et al.*, 2014; Baou *et al.*, 2016). Genes that are lack of expression in the brain were excluded in the current study.

Given the availability of densely spaced single nucleotide polymorphisms (SNPs) within a gene in GWA data, the traditional SNP-based approach suffers from the collinearity arisen from linkage disequilibrium (LD) among SNPs (Wang and Abbott, 2008) and lacks the power to uncover the relatively small effect sizes conferred by most genetic variations (Wang *et al.*, 2010). To address these issues, the gene-based PCReg method takes into account the common variation within a candidate gene jointly by using a few uncorrelated principal components (PCs) computed from the sample covariance matrix of all SNPs (Neale and Sham, 2004; Wang and Abbott, 2008). This

approach reduces dimensionality of the genetic information and the number of tests, which in turn helps to reduce the problem of chance findings (i.e. false positives) due to multiple testing (Neale and Sham, 2004; Klei *et al.*, 2008; Wang and Abbott, 2008). Compared with the SNP-based approach, the gene-based approach is more efficient when there is weak but coordinated effects arising from multiple SNP markers (Wang *et al.*, 2010; Set *et al.*, 2014) and has been widely used in behavioral genetic and neuroimaging studies (Wang and Abbott, 2008; Hibar *et al.*, 2011a,b).

Materials and methods

Participants

Participants were all incoming freshman (Grade 2013) at Chongqing University of Medical Sciences, China, and were recruited from the freshman seminar as they arrived at university. One thousand five hundred and eighty-two unrelated Chinese Han students (80.1% females, mean age 18.66 ± 0.90 years) were recruited. Participants were divided into 15 cohorts. About 100 participants in the same cohort came to a testing room at the same time, completed the behavioral task on computers and submitted their data to the server. Two hundred and sixty-five of them were excluded from data analysis because of their low accuracy in the catch condition in which they were expected to choose the option with an expected value much higher than the other option, indicating a high probability that they did not actively engage in the task (see the later *behavioral test*; De Martino *et al.*, 2006; Gao *et al.*, 2016). In all the 1582 participants, 5 participants reported a history of psychiatric, neurological or cognitive disorders in the self-reported questionnaire. These five persons also performed badly in the catch condition and were hence excluded.

A final sample of 1317 participants was included in the following analysis. None of the participants reported any history of psychiatric, neurological or cognitive disorders in the self-reported questionnaire (see Supplementary data for more details about the self-reported questionnaire). All of them were in the normal range of anxiety symptoms (i.e. scores <50, mean $= 30.58$, SD $= 5.35$) as assessed by the Zung Self-Rating Anxiety Scale (Zung, 1971; Wang *et al.*, 1999) and in the normal range of depressive symptoms (i.e. scores <50, mean $= 33.3$, SD $= 6.31$) as assessed by the Zung Self-Rating Depression Scale (Zung, 1965; Wang *et al.*, 1999), except for nine participants who had higher scores (51, 51, 53, 53, 53, 54, 54, 55 and 59, respectively) beyond the normal range of depressive symptoms and three participants who had higher scores (51, 51 and 56, respectively) beyond the normal range of anxiety symptoms. Given that excluding these 12 participants did not change the pattern of results, we included them in the following reported data analysis. 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 School of Psychological and Cognitive Sciences, Peking University.

The behavioral test

We used the same behavioral task in Gao *et al.* (2016), which is developed by De Martino *et al* (2006) and has been used to assess the framing effect (Roiser *et al.*, 2009; Xu *et al.*, 2013). At the beginning of each trial, participants were endowed with an initial amount of monetary reward. Then they chose between receiving a certain guaranteed amount of money 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'), presented in words. The gamble option was identical for both frames and was represented by a pie chart indicating the probability to receive all or none of the initial amount in the current trial. For both the gain frame and loss frame trials, the expected values of the two options in each trial were equivalent. For catch trials, the expected values of the sure option and the gamble option were extremely unbalanced (e.g. 'Keep ¥80 out of a total of ¥100' *vs* 'Keep all of the ¥100 with a probability of 40%'). These trials were introduced to allow us to examine whether a particular participant was actively engaged in the task. The behavioral test consisted of three sessions. Trial settings were the same for three sessions. Each session had 48 trials (16 different gain trials, 16 different loss trials and 16 different catch trials), ordered randomly. The payment procedure was conducted according to De Martino *et al.* (2006). The participants were informed that they were playing for real money at all times so their task was to be attending through the entire experiment which would allow them to maximize their final scores. At the end of the experiment they would receive a sum proportional (500:1) to what they earned during the experiment. See Gao *et al.* (2016) for more details about the behavioral test.

Two hundred and sixty-five participants were excluded from data analysis because of their low accuracy ($<75\%$, mean accuracy$=57.9\% \pm 17.6\%$; other 1317 participants' accuracy $= 90.5\% \pm 6.5\%$) in the catch condition. The excluded participants also showed much smaller framing effect ($4.44\% \pm 1.75\%$) compared with the remaining 1317 participants ($14.51\% \pm 0.34\%$), $t_{(1580)} = 9.16$, $P < 0.001$. Furthermore, we examined their response times when making choices (using a computer mouse to click on one of the two options presented on the screen). These participants responded faster when making decisions in both catch trials (mean $= 1591$ ms, SD $= 551$ ms) and experimental trials (mean $= 1601$ ms, SD $= 544$ ms) compared with the other participants (mean $= 1776$ ms, SD $= 353$ ms; mean$= 1872$ ms, SD $= 376$ ms), $t_{(1580)} = 6.639$, $P < 0.001$ for catch trials and $t_{(1580)} = 9.375$, $P < 0.001$ for experimental trials, indicating that these participants were careless when facing choices.

Genotyping

We collected ethylenediaminetetraacetic acid anti-coagulated venous blood samples from all the participants and then extracted genomic DNA from their whole blood using the QuickGene-610L Nucleic Acid Isolation System. The whole-genome genotyping was performed on Illumina Human OmniZhongHua-8 version 1 Chips using the standard Illumina genotyping protocol.

Gene selection and preprocessing

Twenty-six genes were selected based on the Kyoto Encyclopedia of Genes and Genomes database (KEGG; http://www.genome.jp/kegg/). We included dopamine genes involved in (i) dopamine synthesis [tyrosine hydroxylase (*TH*), aromatic-L-amino-acid decarboxylase gene (*DDC*), and vesicular monoamine transporter (*VMAT2*)], (ii) coding of dopamine receptors (*DRD1*–5), and (iii) dopamine transport and clearance [sodium-dependent dopamine transporter (*DAT1*, also named

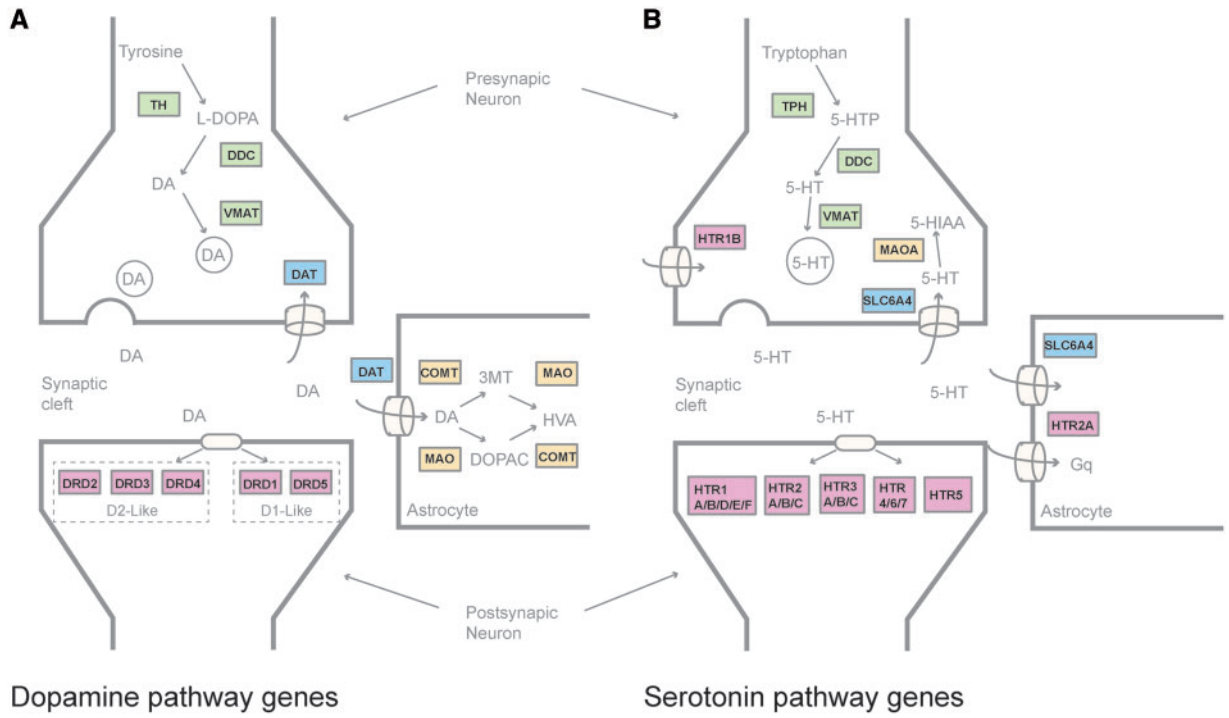

Fig. 1. Dopaminergic pathway genes and serotonergic pathway genes. Dopaminergic pathway genes (A) and serotonergic pathway genes (B) are represented in a stylized version of the synapse and include dopamine genes directly involved in synthesis (green), uptake (blue), and metabolism (yellow) and receptors (pink). Certain details, such as presynaptic auto-receptors, have been omitted for clarity. Adapted from the maps of dopaminergic synapse and serotonergic synapse in the Kyoto Encyclopedia of Genes and Genomes database (KEGG; http://www.genome.jp/kegg/); see also, Set *et al.*, 2014.

SLC6A3), catechol-*O*-methyl transferase (*COMT*), amine oxidase A (*MAOA*) and amine oxidase B (*MAOB*)] (see also, Nemoda *et al.*, 2011; Set *et al.*, 2014) and serotonin genes involved in (i) serotonin biosynthesis [tryptophan 5-hydroxylase (*TPH 1* and *TPH2*)], (ii) coding of serotonin receptors [5-hydroxytryptamine receptor (*HTR1A/B/D/E/F*, *HTR2A/B/C*, *HTR3A/B/C/D/E*, *HTR4*, *HTR5A/B*, *HTR6-7*, *HTRA1-4*)], (iii) serotonin transport [sodium-dependent serotonin transporter (*SLC6A4*)] (see also Baou *et al.*, 2016) (Figure 1). *HTR3D* and *HTR3E* genes were excluded from data analysis due to their lack of expression in the brain (Niesler *et al.*, 2003; see also Bgee: Gene Expression Evolution, http://bgee.unil.ch/). *DRD4*, *DRD5*, *HTR1A/B/D/F*, *HTR5B*, *HTRA2* and *HTRA4* were also excluded from the final analysis due to the failure of extracting SNPs in the sample.

Preprocessing of GWA data was conducted in the following standard steps using PLINK (Purcell *et al.*, 2007; Set *et al.*, 2014): (i) we removed poorly genotyped SNPs, which were significantly depart from the HWE at a threshold of 10^{-4} or with minor allele frequency (MAF) below 0.1 or with genotyping rate below 0.05; (ii) we filtered out poor genotyped individuals with genotyping rate below 0.05 and (iii) we estimated population stratification and generated components of population stratification. To adjust for population stratification, two components indicating population stratification generated from the whole GWA data using the classical multidimensional scaling (MDS) method implemented in PLINK (Price *et al.*, 2006; Purcell *et al.*, 2007) were controlled in the following analysis. SNP extraction and filtering were conducted using PLINK (Purcell *et al.*, 2007) and snpStats (Solé *et al.*, 2006). For each gene, common SNPs were extracted according to hg19 coordinates.

Principle component analysis

All the following data analyses were conducted using R (The R Project for Statistical Computing, http://www.r-project.org). To avoid the collinearity arising from LD among SNPs of the same gene in the statistical model and reduce dimensionality of the genetic information, for each gene, we took all available SNPs in the GWA dataset and performed principal component analysis (PCA) on the SNPs within this gene to account for correlations due to LD (Wang and Abbott, 2008). Specifically, in the current study, each analyzed gene was represented by a set of eigenSNPs (PCs) accounting for at least 90% of the total variation of SNPs in this gene (Wang and Abbott, 2008; Set *et al.*, 2014). The stronger the correlations between the SNP genotype scores (indicating the stronger the extent of LD among the SNPs), the fewer PCs are needed to capture the major variance in the original genotype scores. Consistent with densely spaced SNPs being in LD (Daly *et al.*, 2001; Reich *et al.*, 2001; Gabriel *et al.*, 2002), SNPs within a gene were highly correlated (Table 1). For example, 6 eigenSNPs explained 90.2% of the variation of the *DDC* gene that contained 47 SNPs in our GWA dataset.

Gene-behavior association analysis

To test the joint effect of all variations in one gene on the susceptibility to framing, we employed a series of multiple partial-*F* tests with the susceptibility to framing (i.e. the rate of taking the gamble option in the loss frame minus this rate in the gain frame) as the dependent variable following the steps illustrated by previous studies (Wang and Abbott, 2008; Hibar *et al.*, 2011a,b). Multiple partial-*F* tests are well suited for testing the effects of multiple predictors on a dependent variable. For each

Table 1. Summary of dopamine and serotonin genes and regression analysis

Pathway	Function	Gene	SNPs	PCs	%Var	R^2 change	Adjusted R^2 change	*Partial-F*	p_{unc}	p_{perm}	p_{emp}
Dopamine	Synthesis	*TH*	2	2	100	0.001	<0.001	0.712	0.491	0.484	0.485
		DDC	47	6	90	0.010	0.006	2.329	0.031*	0.031*	0.038*
		VMAT2	17	9	90	0.003	<0.001	0.501	0.875	0.878	0.862
	Transport/	*DAT1*	16	6	91	0.005	<0.001	1.027	0.406	0.408	0.466
	Clearance	*COMT*	18	6	91	0.012	0.009	2.648	0.015*	0.014*	0.027*
		MAOA	6	3	90	0.003	<0.001	1.143	0.331	0.325	0.346
		MAOB	37	5	92	0.005	0.002	1.367	0.234	0.232	0.293
	Receptor	*DRD1*	1	1	100	0.000	<0.001	0.097	0.756	0.756	0.780
		DRD2	16	8	90	0.004	<0.001	0.721	0.673	0.680	0.770
		DRD3	41	12	92	0.014	0.006	1.617	0.081	0.081	0.099
Serotonin	Synthesis	*TPH1*	2	2	100	0.001	<0.001	0.719	0.487	0.476	0.477
		TPH2	6	4	93	0.002	<0.001	0.519	0.721	0.718	0.753
	Transporter	*SLC6A4*	8	3	90	0.006	0.004	2.795	0.039*	0.038*	0.037*
	Receptor	*HTR1E*	16	6	91	0.007	0.003	1.545	0.160	0.158	0.199
		HTR2A	44	12	90	0.013	0.005	1.492	0.120	0.121	0.123
		HTR2B	3	2	100	0.001	<0.001	0.596	0.551	0.551	0.519
		HTR2C	22	8	90	0.006	<0.001	0.920	0.499	0.499	0.517
		HTR3A	4	4	100	0.001	<0.001	0.364	0.834	0.831	0.833
		HTR3B	22	6	90	0.001	<0.001	0.228	0.968	0.967	0.970
		HTR3C	2	1	99	0.000	<0.001	0.124	0.725	0.724	0.677
		HTR4	46	14	91	0.015	0.005	1.422	0.135	0.136	0.075
		HTR5A	7	4	92	0.006	0.003	1.866	0.114	0.114	0.118
		HTR6	2	1	100	0.000	<0.001	0.000	0.990	0.992	0.982
		HTR7	22	6	93	0.006	0.002	1.316	0.247	0.242	0.301
		HTRA1	34	9	91	0.007	<0.001	0.974	0.460	0.456	0.441
		HTRA3	19	5	92	0.004	0.001	1.133	0.341	0.356	0.370

PCs, the number of principal components; % Var, percentage of total variance captured by included PCs; p_{unc}, *P* value using multiple *F*-test; p_{perm}, permutation *P* value; p_{emp}, empirical *P* value.
*Means $P < 0.05$.

gene, the multiple partial-*F* test was conducted by firstly estimating the fit of a 'reduced model' of age, gender, and two components of population stratification (nuisance variables) on individuals' susceptibility to framing. Secondly, we estimated the fit of a second 'full model' with the nuisance variables and eigenSNPs of this gene (see the section *Principle component analysis*) on the same dependent variable. Each association test results in an *F* statistic, which indicates the joint effect of eigenSNPs of this gene on the behavior after controlling for the effects of age, gender and two components of population stratification. The multiple partial-*F* statistic was calculated for each gene using equation (1) (Hibar *et al.*, 2011b). *k* is df(full)− df(reduced) and RSS is the residual sum of squares:

$$Fk, df(full) = \frac{RSS(reduced) - RSS(full)}{df(reduced) - df(full)} / \frac{RSS(full)}{df(full)} \quad (1)$$

Of note, because the MAOA/B genes reside on the X-chromosome, females and males were analyzed separately to investigate the gene-behavior associations for these two genes.

Critically for our goal of identifying dopaminergic and serotonergic genes that are associated with the susceptibility to framing, variations across genes were essentially uncorrelated as shown by the very small proportion of variance explained by the other gene in the canonical correlation analysis (Weenink, 2003), mean variance explained by other gene = 0.62% ± 0.08% (SE) (see Table S1). Additionally, to examine the unique contribution of each gene to behavior while controlling for the contributions of other significant genes, we built a new regression model for each of the four genes that were identified to be associated with framing effect (*COMT*, *SLC6A*, *DDC* and *MAOB*; see *Gene-behavior association results* for details). The new regression model included age, gender, two components of population stratification, as well as the eigenSNPs of the other three identified genes as nuisance variables. Controlling for the contributions of the other genes associated with the framing effect did not change the pattern of results (*COMT*: $P = 0.028$, *SLC6A4*: $P = 0.038$, *DDC*: $P = 0.070$ for all the participants, and *MAOB*: $P = 0.029$ for male participants), demonstrating the unique contribution of each gene to behavior.

Permutation tests

To guard against spurious associations and to further validate the above findings, we conducted the Monte Carlo permutation tests for each regression model (Hibar *et al.*, 2011b; Set *et al.*, 2014). This method is a widely accepted correction approach in statistical testing (Belmonte and Yurgelun-Todd, 2001; Nakagawa, 2004; Camargo *et al.*, 2008; Gomez-Villegas *et al.*, 2014), which resamples the total number of observations for certain times in order 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 includes irregularities of the data in the estimation of the permutation probability (Cheverud, 2001).

Empirical tests

To guard against the possibility that the associations do not rise above the background association compared with the genome

at large, we compared P values in multiple partial-F tests of the genes on the dopaminergic and serotonergic pathways to comparable genes in the GWA dataset to generate an 'empirical' null distribution (Set *et al.*, 2014). Empirical *p* values were determined by comparing across the entire genome. A gene was considered comparable if (i) its SNPs generated the same number of principal components according to the procedure outlined above and (ii) it was represented by the same or similar number of SNPs. A range of SNPs was allowed to generate at least one hundred comparable genes, since an exact match produced too few comparable genes (see Supplementary Table S2). This typically occurred when there were a large number of SNPs within the gene.

Protein–protein interactions

Knowledge about a protein's specific interaction map is an important prerequisite for a full understanding of its function. Here we used the STRING 10 (Search Tool for the Retrieval of Interacting Genes/Proteins) database (http://string-db.org, Szklarczyk *et al.*, 2015) to test the interactions between the proteins encoded by all the dopaminergic genes and serotonergic genes included in the current study. This database aims to provide a critical assessment and integration of protein–protein interactions, including direct (physical) as well as indirect (functional) associations, and generates an interaction confidence score for each interaction using four resources, including genomic context, high-throughput experiments, co-expression data, and previous studies.

Note, cellular functions are carried out by 'modules' made up of many species of interacting molecules (Hartwell *et al.*, 1999; Rives and Galitski, 2003). It is known that proteins of similar cellular functions tend to lie within a short distance in the interaction graph (Brun *et al.*, 2004). Thus, searching for interaction-modules may help us understand the relationship between the organization of a protein network and its function and thus provide independent evidence for the joint contribution of genes to a certain behavior. Using the 'Clustering' function implemented in STRING 10, we performed the MCL algorithm (inflation = 4), which is a widely used algorithm in clustering analysis (http://www.micans.org/mcl/, Brohee and Van Helden, 2006), to extract functional modules in our interaction graph (see Supplementary Figure S1).

SNP–SNP interactions

To estimate SNP–SNP interactions, we extended the eigenSNP approach by performing PCA on the set of regressors produced from a third-order interaction of the underlying SNP data. For example, if a gene contained three SNPs, we performed PCA on the set of seven regressors, resulting from three original SNPs, an additional three second-order interaction terms, and a further additional one third-order interaction term. Using the same procedure as outlined above, we took the set of eigenSNPs that explained at least 90% of the variance and included the concerning interaction terms in our computational model (see Supplementary Table S3).

Results

Behavioral results

Consistent with previous studies (De Martino *et al.*, 2006; Roiser *et al.*, 2009; Xu *et al.*, 2013; Gao *et al.*, 2016), a significant framing effect was observed for the rate of taking the risky or gamble options: 59.75%±0.47% (SE) in the loss frame *vs* 45.23% ± 0.46% in gain the frame, $t_{(1316)} = 42.08$, $P < 0.0001$. The risk attitude change (i.e. the rate of taking the gamble option in the loss frame minus this rate in the gain frame) was defined as an individual's susceptibility to framing in the following analysis. In line with previous studies (Fagley and Miller, 1990; Huang and Wang, 2010), a 2 (gender: Female *vs* Male) × 2 (frame: gain *vs* loss) mixed measures analysis of variance (ANOVA) on the gambling rate revealed a significant interaction between gender and frame both before and after controlling for the potential effects of age, $F_{(1,\ 1315)} = 15.587$, $P < 0.001$, and $F_{(1,\ 1314)} = 14.701$, $P < 0.001$, with female participants evidencing a greater framing effect than male participants. In addition, when controlling for gender, linear regression analysis showed a marginally negative correlation between age and individuals' susceptibility to framing, $\beta = -0.052$, $t = -1.903$, $P = 0.057$. This pattern was consistent with previous developmental studies (Mikels and Reed, 2009; Strough *et al.*, 2011). To exclude the effects of gender and age, these two factors were controlled as covariates in the analysis of gene-behavior association.

Gene-behavior association results

Consistent with our recent study showing the association between the *COMT* gene and the susceptibility to framing (Gao *et al.*, 2016), the regression analysis controlling for age, gender, and two principle components of population stratification indicated that eigenSNPs of the *COMT* gene explained 0.9% of the variance in individuals' susceptibility to framing, adjusted R^2 change = 0.009, partial-$F = 2.648$, $P = 0.015$. Moreover, in line with Roiser *et al.* (2009) which demonstrated that 5-HTTLPR contributes to the individual differences, the entry of the eigenSNPs of the *SLC6A4* gene accounted for 0.4% of the variance, adjusted R^2 change = 0.004, partial-$F = 2.795$, $P = 0.039$. Importantly, our results provide new evidence indicating that the *DDC* gene, which is involved in the synthesis of both serotonin and dopamine, was associated with individuals' susceptibility to framing, adjusted R^2 change = 0.006, partial-$F = 2.329$, $P = 0.031$, accounting for 0.6% of the variance. None of the other genes were found to be predictive of the susceptibility to framing in decision-making in our sample (Table 1).

To guard against spurious associations, we conducted permutation tests for each regression model. After the Monte Carlo permutation test with 10 000 permutations of the behavioral data (individuals' susceptibility to framing), the above results remained significant (Table 1), *COMT*: permutation $P = 0.014$, *SLC6A4*: permutation $P = 0.038$, *DDC*: permutation $P = 0.031$. Given that permutation test was conducted independently for each gene, it did not correct for multiple testing directly. Of note, the results obtained from the regression analyses did not survive the Bonferroni or false discovery rate (FDR) corrections for multiple testing (but see Discussion).

To test for the possibility that our evidence of association did not rise above the background association compared with the genome at large, we compared the fit of models between genes in the dopaminergic pathway and serotonergic pathway and other genes in the GWA dataset to generate an 'empirical' null distribution. Despite varying sizes of the comparison gene sets (see Supplementary Table S1), we found that, against the empirical null distributions, all the three genes showed significant differences (Table 1), *COMT*: empirical $P = 0.027$, *SLC6A4*: empirical $P = 0.037$, *DDC*: empirical $P = 0.038$.

Because the *MAOA/B* genes reside on the X-chromosome, there is substantial uncertainty regarding the interpretation of

allele scores across sex. Thus we estimated the model for these two genes in male and female participants separately. Results showed that the *MAOB* gene was associated with the susceptibility to framing in male participants, which accounted for 2.8% of the variation in male participants, adjusted R^2 change = 0.028, partial-$F = 2.499$, $P = 0.031$. The pattern remained the same in permutation test ($P = 0.038$) and empirical test ($P = 0.043$). This effect was absent in female participants. No effect was observed for the *MAOA* gene.

To address the question of whether there existed variations that could be explained by SNP–SNP interactions, we conducted PCA on regressors generated from first-order, second-order, and third-order interactions of SNPs within a gene. However, we found that incorporating SNP–SNP interactions did not improve model fittings of genes. The effects of the *DDC* gene and the *SLC6A4* gene were similar to the results in single SNP analysis, while the effects of the *COMT* gene and the *MAOB* gene in single SNP analysis were now abolished. We did not find that the previously insignificant genes became significant after accounting for SNP–SNP interactions either (see Supplementary Table S3).

Using the STRING database to test the interactions between the proteins encoded by all genes included in our data analysis and extract functional modules in our interaction graph, we found that the four genes (*COMT*, *SLC6A4*, *DDC* and *MAOB*) associated with the susceptibility to framing in the current study were shown to interact with each other and were clustered into the same module (see Supplementary Figure S1).

Given the PCA analysis here did not allow us to identify which SNPs constituted the principal components that contributed to the framing effect (Harris, 1975), we examined directly how identified gene-behavior associations were distributed across SNPs in the identified genes. SNPs associated with individual susceptibility to framing are shown in Figure S2 (Supplementary data). For the *COMT* gene, although rs4680 did not significantly contribute to the framing effect, a SNP in LD with rs4680, rs165656 (1000Genomes, phase_3, Han Chinese in Beijing, China (CHB): $r^2 = 0.934$, $D' = 1.000$; 1000Genomes, phase_3, Southern Han Chinese, China (CHS): $r^2 = 0.816$, $D' = 0.948$; see also Zhang *et al.*, 2007), *was* significantly associated with the susceptibility to framing (adjusted R^2 change-$= 0.004$, partial-$F = 5.842$, $P = 0.016$). See Supplementary data for more details about individual SNP associations.

Discussion

Twin studies yield a moderate heritability of the susceptibility to framing in decision-making (Simonson and Sela, 2011; Cesarini *et al.*, 2012; Cronqvist and Siegel, 2012). Other studies also demonstrated important roles of genetic variations on dopaminergic and serotonergic pathways in decision-making under risks (Crişan *et al.*, 2009; Dreber *et al.*, 2009; Kuhnen and Chiao, 2009; He *et al.*, 2010; Frydman *et al.*, 2011; Heitland *et al.*, 2012; Reuter *et al.*, 2013; Set *et al.*, 2014). By extending the few studies on the genetic basis of the framing effect (Crişan *et al.*, 2009; Roiser *et al.*, 2009; Gao *et al.*, 2016) and by using a gene-based PCReg approach, we investigated directly the relationship between 26 genes within the dopaminergic and the serotonergic pathways and individuals' susceptibility to framing in decision-making.

Replicating the previous SNP-based studies, which had relatively small sample size, our results confirmed that genetic variations in the *COMT* gene (Gao *et al.*, 2016) and the *SLC6A4* gene (Crişan *et al.*, 2009; Roiser *et al.*, 2009) contribute to the individual differences in susceptibility to framing. Although *COMT* rs4680 did not significantly contribute to the framing effect in the current sample, a SNP in LD with rs4680, rs165656, was significantly associated with the susceptibility to framing. This result raised the possibility that the previously identified effect of rs4680 (Gao *et al.*, 2016) might be due to its LD with rs165656. Moreover, the three previous studies merely investigated a single polymorphism in the candidate gene; an important advance the current study made was that we used the gene-based PCReg approach to search for genes associated with susceptibility to framing in a larger sample. This approach takes into account common variations within a candidate gene to avoid the influence of the LD among SNPs and is more efficient than the SNP-based association method (Wang and Abbott, 2008; Wang *et al.*, 2010; Set *et al.*, 2014). Compared with methods that rely on data from SNPs independently, the gene-based approach is less susceptible to erroneous findings due to genetic differences between populations (Neale and Sham, 2004; Schaid, 2004). Based on this gene-based approach, our results identified a new gene, *DDC*, for the individual differences in susceptibility to framing.

In humans, the *DDC* gene encodes DDC, an enzyme that catalyzes the decarboxylation of 5-hydroxytryptophan to serotonin and L-DOPA to dopamine (Sumi-Ichinose *et al.*, 1992). Given that this gene is involved in both the dopaminergic pathway and the serotonergic pathway, two pathways that play critical roles in emotional processing (Salgado-Pineda *et al.*, 2005; Alcaro *et al.*, 2007; Merens *et al.*, 2007; Cools *et al.*, 2008; Harmer, 2008; Badgaiyan *et al.*, 2009), this gene may contribute to a series of processes involved in affective processing. For example, SNP-based association studies demonstrated that the *DDC* gene is associated with emotional dysregulation such as anxiety (Costas *et al.*, 2010) and bipolar disorder (Børglum *et al.*, 2003). In line with this suggestion, our results provide new evidence that the genetic variations of the *DDC* gene contribute to individual differences in susceptibility to framing, which is related to negative emotional processing in decision-making (De Martino *et al.*, 2006, 2008; Druckman and McDermott, 2008; Roiser *et al.*, 2009; Miu and Crişan, 2011; Xu *et al.*, 2013; Gao *et al.*, 2016). These findings indicate that genetic variations in the *DDC* gene may be a candidate gene for genetic studies on other affective decision-making (e.g. Iowa gambling task).

The effects of genes are not expressed directly at the level of behavior, but are mediated by their effects on brain regions responsible for specific cognitive and emotional processes (Bigos and Weinberger, 2010). A pathway-based approach allows us to utilize prior knowledge regarding relationships between genes and the brain and to shed light on the neural mechanisms underlying the gene-behavior association. Neuroimaging and lesion studies have shown that the prefrontal (PFC)-amygdala circuitry plays important role in the framing effect (De Martino *et al.*, 2006, 2010; Roiser *et al.*, 2009; Gao *et al.*, 2016). In line with this evidence, all the genes associated with the susceptibility to framing in the current study showed high expression in these circuits. Specifically, while the *COMT* gene and the *MAOB* gene are important determinants of dopamine flux in the PFC (Nemoda *et al.*, 2011), the *SLC6A4* expression modulates amygdala activation (Munafò *et al.*, 2008; Kobiella *et al.*, 2011). Moreover, the expression of the *DDC* gene has been observed in the PFC and limbic areas in humans (Gjedde *et al.*, 1991; Sumi-Ichinose *et al.*, 1995; Ikemoto *et al.*, 1999) and other primates (Kitahama *et al.*, 1988). Given the genetic imaging studies demonstrating that both the *SLC6A4* gene 5-HTTLPR variation (Roiser *et al.*, 2009) and the *COMT* Val158Met polymorphism (Gao *et al.*, 2016) influence the susceptibility to framing via the PFC-

amygdala coupling, it is conceivable that genetic variations in the *DDC* gene and the *MAOB* gene may modulate the individual differences in susceptibility to framing via their impacts on the PFC-amygdala circuitry. This hypothesis needs to be tested by further genetic imaging studies.

The current study raises a few more implications for future research. First, in line with a previous study suggesting that the *MAOB* polymorphisms are related to negative emotionality personality (Dlugos *et al*., 2009), our results provide new evidence linking genetic variations of *MAOB* to the susceptibility to framing, which is associated with negative emotional processing. However, this effect exists in male participants, but not in female participants. This sex difference is consistent with previous neuropsychological studies demonstrating that the platelet MAO activity is associated with sex-differentiated features in cognitive processing (Klinteberg *et al*., 1987; Tadić *et al*., 2007) and SNP-based association studies reporting sex-specific effects of the *MAOB* gene variations on different phenotypes [e.g. Parkinson's disease (Kelada *et al*., 2002; Kang *et al*., 2006)]. However, given that the number of male participants was relatively small in the current study, future studies are needed to examine the relationship between the *MAOB* gene and the framing effect. Second, using the protein–protein interaction information and clustering analysis in STRING database, we found that proteins encoded by the four genes associated with the framing effect in the current study are also clustered into the same functional module, demonstrating their strong interactions with each other (Szklarczyk *et al*., 2015). Thus, whether and how the interactions between these four genes influence the individual differences in susceptibility to framing is an important question that remains to be investigated. Third, consistent with the notion that most common genetic variants individually or in combination explain only a small proportion of heritability using GWA method (Manolio *et al*., 2009; Zuk *et al*., 2014), each of the three genes identified here contributed to about 0.5%–1.0% variance of individuals' susceptibility to framing, which was only a small proportion of the heritability estimated in twin studies (Simonson and Sela, 2011; Cesarini *et al*., 2012; Cronqvist and Siegel, 2012). This implies that genetic variations of other underestimated pathways, especially pathways related to affective processing (e.g. the oxytocin pathway and the vasopressin pathway, cf. Ebstein *et al*., 2012; Neumann and Landgraf, 2012), might further explain the remaining variance of individuals' susceptibility to framing. Under-reported genetic variants of smaller effect, rare variants that are poorly detected by available genotyping arrays, and low power to detect gene–gene interactions, may also contribute to this missing heritability (Manolio *et al*., 2009).

Although the current study adds to the limited information on the genetic basis of individual differences in susceptibility to framing, it should be noticed that for the exploratory aim of the study, we examined 26 genes, which may create inflation of type I error rate. Moreover, the fact that none of the identified associations survived Bonferroni or FDR corrections for multiple testing may raise the concern that the significant associations observed could emerge simply by chance. However, several factors mitigate this concern. First, replicating the results of previous SNP-based studies (Roiser *et al*., 2009; Gao *et al*., 2016), the *COMT* gene and the *SLC6A4* gene were associated with the framing effect in the current study. This replication may demonstrate the validity of the current study. Second, in support of our conclusions, proteins encoded by the four genes identified here are clustered into the same functional module in the independent protein–protein interaction analysis, suggesting that these four proteins are crucial components of similar cellular processes (Hartwell *et al*., 1999; Rives and Galitski, 2003; Brun *et al*., 2004), which might in turn influence the same or similar behaviors (i.e. the framing effect). Third, all our results passed the empirical tests that aimed to guard against the possibility that the observed associations do not rise above the background association compared with the genome at large (Set *et al*., 2014). Finally, although multiple corrections such as Bonferroni or FDR correction reduce type I errors, stringent corrections may lead to enlarged type II errors (Nakagawa, 2004). One of the better ways to control for type I errors is to examine these results in another larger sample. Future study investigating the association between *DDC* gene and the susceptibility to framing will be essential.

In conclusion, the current study replicated previous SNP-based association studies by demonstrating that genetic variations of the *SLC6A4* gene and the *COMT* gene contribute to the susceptibility to framing during decision-making. More importantly, the current study provides the first evidence for the role of the *DDC* gene (and, to a less extent, the *MAOB* gene) in individual susceptibility to framing. These findings shed light on our understanding of the genetic basis underlying individual differences in decision-making.

Supplementary data

Supplementary data are available at *SCAN* online.

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