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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

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%±17.6%; other 1317 participants' accuracy = 90.5%±6.5%) in the catch condition. The excluded participantsition.rti21(d2576)0(u).4(a)-4606hov

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*, *HTR*4, *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

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

amygdala coupling; it is conceivable that genetic variation in the PDC ... (overprinted text)
ale 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. arkinson's disease (Kelada et al. 2002; Kang et al. 2006)]. ven that the number of male participants was rela in the current study, future studies are needed to e relationship between the *MAOB* gene and the ct. Second, using the protein–protein interaction in nd clustering analysis in STRING database, we proteins encoded by the four genes associated with effect in the current study are also clustered into nctional module, demonstrating their strong inter each other (Szklarczyk et al. 2015). Thus, whether eractions between these four genes influence fferences in susceptibility to framing is an im that remains to be investigated. Third, consist otion that most common genetic variants n combination explain only a small proportion ng GWA method (Manolio et al. 2009; Zuk et al. genes identified here contributed to of individuals' susceptibility to fram all proportion of the heritability esti monson and Sela, 2011; Cesarini et al. 2). This implies that genetic vari d pathways, especially pathways g (e.g. the oxytocin pathway and Ebstein et al. 2012; Neumann and ain the remaining variance of ing. Under-reported genetic ants that are poorly detected d low power to detect gene– bute to this missing heritabil

the limited information ences in susceptibility to e exploratory aim of the may create inflation of at none of the identified corrections for multiple significant associations ce. However, several fac ting the results of previ Gao et al. 2016), the with the fram n may demon , in support of enes identified ule in the inde uggesting that

PDC 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 *PDC* 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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Conflict of interest. None declared.

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