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Genetic Variations in the Dopamine System and Facial Expression Recognition in Healthy Chinese College Students

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Key Words

Facial expression recognition · Gene · Dopamine

Abstract

Objective: This study investigated the relation between genetic variations in the dopamine system and facial expression recognition. **Methods:** A sample of Chinese college students ($n = 478$) was given a facial expression recognition task. Subjects were genotyped for 98 loci [96 single-nucleotide polymorphisms (SNPs) and 2 variable number tandem repeats] in 16 genes involved in the dopamine neurotransmitter system, including its 4 subsystems: synthesis (*TH*, *DDC*, and *DBH*), degradation/transport (*COMT*, *MAOA*, *MAOB*, and *SLC6A3*), receptors (*DRD1*, *DRD2*, *DRD3*, *DRD4*, and *DRD5*), and modulation (*NTS*, *NTSR1*, *NTSR2*, and *NLN*). To quantify the total contributions of the dopamine system to emotion recognition, we used a series of multiple regression models. Permutation analyses were performed to assess the posterior probabilities of obtaining such results. **Results:** Among the 78 loci that were included in the final analyses (after excluding 12 SNPs that were in high linkage disequilibrium and 8 that were not in Hardy-Weinberg equilibrium), 1 (for fear), 3 (for sadness), 5 (for anger), 13 (for surprise), and 15 (for disgust) loci exhibited main effects on the recognition of facial expressions. Genetic variations in the dopamine system ac-

counted for 3% for fear, 6% for sadness, 7% for anger, 10% for surprise, and 18% for disgust, with the latter surviving a stringent permutation test. **Conclusions:** Genetic variations in the dopamine system (especially the dopamine synthesis and modulation subsystems) made significant contributions to individual differences in the recognition of disgust faces.

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Introduction

Human facial expression recognition is a crucial component of social and emotional communication and is shaped by both environmental and genetic influences [1]. There is some evidence that the primary emotions conveyed by the face are innate and universal. Researchers have found evidence of cross-cultural consistency in the expressions and perceptions of specific types of emotions (i.e. happiness, sadness, anger, fear, surprise, and disgust) [2]. Recently, behavioral geneticists found significant genetic contributions to the individual variations in facial expression recognition [3]. Finally, several studies found single-gene variant (e.g. *COMT* val¹⁵⁸met, *BDNF*, and

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5-HTTLPR) contributions to negative facial expression recognition in healthy subjects [4–6]. All of these studies pointed to the deep biological roots of facial emotion expression and recognition.

Among the various biological factors, the dopaminergic system has garnered special attention in recognition of facial expressions. The dopamine (DA) pathways projecting to the prefrontal cortex and the basal ganglia may play a major role in both emotion and cognition processes [7]. For healthy subjects, the neural response to negative facial expression was influenced by the genetic variation in DA neurotransmission associated with the *COMT* genotype [4, 8]. Moreover, the impaired recognition of disgust among patients with Parkinson's disease (PD) is likely due to a deficit in DA transmission in the ventral putamen [9]. Other studies confirmed that dopaminergic neurons are involved in the recognition of disgust using both medicated and nonmedicated PD patients [10, 11]. Psychopharmacological studies also showed that levodopa administration led to decreased amygdalar activation during the processing of emotional faces in both healthy subjects and PD patients [12]. Most relevantly, researchers found that disgust sensitivity (measured by a questionnaire) was associated with the *DRD4* and *COMT* polymorphisms in healthy subjects [13]. In sum, evidence from clinical reports and experimental studies suggests that DA may play a role in emotion recognition processes [14].

The present study examined the relation between genetic variations in the DA system in healthy subjects and individual differences in human facial expression recognition. Moving beyond the single-gene or a small number of haplotype approaches used in typical behavior genetics research, this study examined contributions of the whole DA system (characterized by the major genes and their associated loci) and its subsystems. Several recent studies [15–17] have used this approach to study genetic system level contributions to human variations. The present study aimed to estimate the overall contributions of the DA genes to emotion recognition (especially for disgust) and to investigate which of the subsystems (synthesis, degradation/transport, receptors, and modulation) would make significant contributions.

Participants and Methods

Participants

Four hundred seventy-eight healthy Han Chinese undergraduates were recruited from Beijing Normal University (BNU) in China [age 20 ± 1 years, females 57%, years of education 14 ± 1 ,

intelligence scores 126 ± 8 (measured by the Wechsler Adult Intelligence Scale-Revised); see online suppl. material, www.karger.com/doi/10.1159/000329555]. This study was approved by the IRB of BNU, China. Blood samples were collected for genotyping.

Emotional Facial Expression Recognition Test

This test assessed the ability of Chinese subjects to judge emotional facial expressions represented on Asian and Caucasian faces. Six basic emotions were included: disgust, anger, fear, surprise, sadness, and happiness. For each emotion, there were 12 pictures; all of them were from two previous studies [18, 19]. Subjects selected from the 6 basic emotions to match each face presented. The numbers of correct responses for each kind of emotion were used as the behavioral indices in this study. Possible scores on this scale ranged from 0 to 12. Table 1 shows the descriptive statistics for the recognition of 6 basic facial expressions. These results are similar to those obtained in previous studies of nonclinical samples [19, 20]. In general, subjects were very good at recognizing emotions, resulting in high scores (in the cases of sad and happy faces, almost ceiling effects). Consequently, the reliability (indexed by an index of internal consistency, i.e. Cronbach's α) of these tests was adequate or satisfactory for disgust and anger, low for fear, surprise, and sadness, and unsatisfactorily low for happiness (table 1). Data on happy faces were excluded from further analysis.

Genetic Analysis

Gene Selection

We selected 96 single-nucleotide polymorphisms (SNPs) and 2 variable number tandem repeats (VNTR) on 16 genes which cover 4 subsystems of the DA system (online suppl. tables). This includes: (a) 25 SNPs for DA synthesis [tyrosine hydroxylase (TH) and decarboxylase (DDC)] and DA β -hydroxylase (DBH)], (b) 23 SNPs and the MAOA_VNTR for DA degradation/transport (*COMT*, *MAOA*, *MAOB*, and *SLC6A3*), (c) 28 SNPs and the *DRD4_VNTR* for the DA receptors (*DRD1*, *DRD2*, *DRD3*, *DRD4*, and *DRD5*), and (d) 20 SNPs for DA modulation [4 neurotensin genes (*NLN*, *NTS*, *NTSR1*, and *NTSR2*)]. These genes represent all major genes involved in these 4 DA subsystems in humans.

In order to sample the genetic diversity of these 16 genes, we selected the tag SNPs (tSNPs) defined by the HapMap project [www.hapmap.org (phase 3)]. Additional SNPs were added for some genes in regions of high linkage disequilibrium (LD; i.e. the nonrandom association of alleles at 2 or more loci) uncovered in genomic searches for recent adaptive selection [21]. These SNPs covered both coding and regulatory regions (for the latter up to 10 kb beyond the coding region). Because of the inclusion of both tSNPs and additional SNPs, there was high LD among a number of SNPs. Twelve SNPs were excluded from multiple regression analysis because of their high LD [$r^2 > 0.8$ (r^2 is the squared correlation coefficient measuring LD)] with the other adjacent 10 SNPs. Hardy-Weinberg (HW) equilibrium (i.e. both allele and genotype frequencies in a population should remain constant from generation to generation unless specific disturbing influences are introduced) was examined using the χ^2 and setting the d.f. to 1. Eight of the SNPs showed significant HW disequilibrium (HW $p < 0.05$) and were thus not included in further analyses. The final analyses included the remaining 78 loci.

Table 1. Descriptive statistics and gender differences in facial expression recognition

	Mean \pm SD	α	Gender difference (females > males)	
			F(1, 476)	p
Disgust	9.19 \pm 2.66	0.78	27.60	0.0000
Anger	9.04 \pm 2.19	0.62	0.25	0.6197
Fear	7.71 \pm 2.24	0.59	0.10	0.7490
Surprise	9.89 \pm 1.86	0.59	4.29	0.0390
Sadness	10.79 \pm 1.35	0.52	6.00	0.0147
Happiness	11.98 \pm 0.14	0.28	0.09	0.7660

α = Cronbach's α (internal consistency).

Genotyping Techniques

The SNPs were genotyped using the standard Illumina GoldenGate Genotyping protocol. In addition, 3 genetic markers (*DRD4_VNTR*, *MAOA_VNTR*, and *COMT* rs4680) were ascertained by the standard PCR procedures [22–24]. The GenCall scores of the loci in the current study ranged from 0.45 to 0.95; this is above the conventional cutoff point of 0.25 for inclusion [25]. The GenCall score (ranging from 0 to 1, the higher the better) is a quality measure for each genotype in the Illumina system that indicates how close a genotype is to the center of the cluster of other samples assigned to the same genotypes [26].

Data Analysis

Four major analyses were conducted in the present study:

(1) We tested the gender differences in facial expressions recognition.

(2) A series of ANOVAs were conducted in order to detect the loci with significant main effects on the recognition of facial expression.

(3) Model 1 (loci's main effects): multiple regression analyses were conducted in order to examine the overall contribution of the main effects for the loci in the DA system. Each SNP was recoded into two dummy variables, i.e. heterozygote and minor allele homozygote, with the major allele homozygote as the reference group. Special treatment was needed for the VNTR and X chromosome genes. In terms of the *DRD4_VNTR*, due to the theoretical importance of 2 repeats among Chinese [27], subjects were grouped as those with 2 repeats, those with two copies of 4 repeats (i.e. the majority or reference group), and those with other numbers of repeats. This variable was recorded into two dummy variables: '2R+ vs. 4R/4R' and 'others vs. 4R/4R'. For *MAOA_VNTR*, there were also 3 groups: (1) 3/3 repeats (or 3 repeats only for males), which was the reference group; (2) 3/4 repeats of females, and (3) 4/4 repeats (or 4 repeats only for males). For the 9 loci on x-chromosome genes (*MAO*), which had 2 genetic groups for males and 3 groups for females, we conducted ANOVA and post hoc tests (when there were at least 5 cases per cell) to determine the best way to condense the females into 2 groups. ANOVA results showed that all of the significant main

effects of genetic polymorphisms ($p < 0.05$) were due to significant differences between major homozygotes and heterozygotes, which allowed us to combine heterozygotes with minor homozygotes for females without missing any significant findings.

Next, to assess the likelihood of false positives with the multiple regression approach, a series of permutation analyses (10,000 permutations per model) were run on randomized data (by randomizing behavioral data across subjects) to yield a distribution of R^2 . If model 1 survived the permutation, then we examined the contribution of the main effects of loci in 4 DA subsystems.

(4) Model 2 (loci's main effects plus gender as a covariate): if there were significant gender differences in specific emotion recognition, we estimated the unique contribution of gender by adding it as a covariate into the loci's main effect models using the forward stepwise procedure. If gender entered the model, it meant that its contribution to the behavioral index was not accounted for by genetic factors. In that case, further permutation was repeated for these models.

Results

Table 1 shows the descriptive statistics for the recognition of 6 basic facial expressions. Significant gender differences (females > males) were found for disgust, surprise, and sadness.

Main Effects of Loci on Emotion Recognition

As table 2 shows, a number of loci had significant main effects on the recognition of emotions, ranging from 1 for fear to 15 for disgust. These loci came from different subsystems. Some loci were significant for the recognition of more than one kind of facial expression [such as *TH* (rs2070762) for disgust, anger, and sadness; *MAOA* (rs909525), (rs5906974), and (*MAOA_VNTR*) for disgust and surprise; *DRD5* (rs12233771) for disgust and surprise; (rs7655090) for disgust and sadness; (rs9884669) for disgust and surprise, and *DDC* (rs10499695) for disgust and surprise]. Such overlaps suggest that certain genetic variations may be involved in the processing of more than one emotion, consistent with cognitive models of the relations among emotions. Before we interpret the results for specific loci, however, it would be informative to see whether some of these loci were tapping into the same genetic contribution (i.e. different loci were picked up because they were near the same 'action point').

Multiple Regression Analysis and Permutation Results for the Loci with Significant Main Effects

Model 1: Loci's Main Effects

For the whole DA system, we entered the dummy variables of all significant loci for each emotion. Depending on the type of emotion, the total R^2 ranged

Table 3. Significant regressors in the main effect regression model for the recognition of disgust faces in the whole DA system

Subsystem	Gene	Locus	Significant regressor	B	t	p
Synthesis	TH	rs2070762	heter-rs2070762	0.92	3.51	0.0005
			minor-rs2070762	1.24	3.57	0.0004
	DDC	rs7808025	heter-rs7808025	-0.75	-2.87	0.0043
	DDC	rs10499695	heter-rs10499695	-0.83	-3.07	0.0023
Receptor	DRD5	rs7655090	minor-rs7655090	0.83	2.39	0.0171
Modulation	NTS	rs1024076	minor-rs1024076	-0.91	-2.20	0.0280
	NLN	rs40107	minor-rs40107	-1.29	-2.56	0.0108

See footnote of table 2 for the complete names of the genes.

from 0.03 to 0.18, $p_{\text{default}} < 0.005$, where p_{default} was the probability that the given R^2 was not different from zero. The permutation results (based on randomized behavioral data) showed that only the model for disgust was significant [$R^2 = 0.18$, d.f. = 23, 442; permutation $p = 0.0002$ (online suppl. fig. S1), where the permutation p is the probability of obtaining the given R^2 in the distribution of permuted R^2 based on randomized data]. Regression models for the other emotions explained a much smaller (although still sizable) portion of variance and did not survive the stringent permutation analysis. The R^2 based on regression analysis and p values based on permutation results were as follows: anger ($R^2 = 0.07$, $p = 0.2230$), fear ($R^2 = 0.03$, $p = 0.8407$), surprise ($R^2 = 0.10$, $p = 0.0660$), and sadness ($R^2 = 0.06$, $p = 0.4426$). Because there is little ambiguity about the results in the recognition of disgust and also the higher reliability index of this measure, we focus on the significant contributions of the DA system to recognition of disgust in the remainder of the paper.

Of the 23 dummy-coded regressors of the 13 loci with significant main effects on disgust, 7 made significant unique contributions. These regressors accounted for 18% of the variance in recognition of disgust faces. The significant regressors in this main effect model are presented in table 3. By examining these results together with those from the ANOVA (table 2), we can begin to interpret genetic contributions of DA genes to the recognition of disgust. Based on the ANOVA results, 2 SNPs of the *TH* gene (rs2070762 and rs4929966) showed significant main effects. However, there was only 1 significant SNP (rs2070762) which survived the false discovery rate correction, and it is also the only one in the regression model, with higher recognition scores for individuals with a minor allele (both the minor homozygotes and

heterozygotes). Such results suggest that there might be only one 'action point' near rs2070762.

In terms of the other two genes involved in the synthesis of DA, 4 SNPs were significant in the ANOVA: *DDC* (rs7808025, rs10499695, and rs7786398) and the *DBH* gene (rs1611123). Two of them (rs7786398 and rs10499695) had a relatively high LD. In the main effects regression model, both remaining SNPs for *DDC* were significant regressors (heter-rs7808025 and heter-rs10499695 of the *DDC* gene). Subjects in the heterozygous group had lower scores than the major homozygotes on the recognition test of disgust faces, whereas the latter did not differ from minor homozygotes. These results suggested a heterozygote advantage of these SNPs. The *DBH* gene was not significant in the regression.

In terms of the degradation/transport subsystem, although 3 loci of *MAOA* (rs909525, rs5906974, and *MAOA_VNTR*) had significant main effects, none were significant in the regression analysis.

In terms of the receptor genes, 3 SNPs of the *DRD5* gene (rs12233771, rs7655090, and rs9884669) showed significant effects in ANOVA. Major homozygotes had significantly lower scores on recognition of disgust faces compared to the other two groups. Given that there was only one significant regressor (minor-rs7655090), there was likely to be only one 'action point' near rs7655090.

In terms of the modulation subsystem, 3 SNPs showed significant effects in the ANOVA: *NTS* (rs1024076) and the *NLN* gene (rs40107, rs463911). There were 2 significant regressors (minor-rs1024076 and minor-rs40107) in the main effects regression model for *NTS* and *NLN* genes. Minor homozygotes had significantly lower scores on the recognition of disgust faces than major homozygotes, who did not differ from heterozygotes. This pattern of results indicates that they were possibly recessive

genes. The other SNP for the *NLN* gene (rs463911) was no longer significant in the regression, likely due to its moderate linkage with rs40107. It appears that there is only one 'action point' and it is closer to rs40107 than rs463911.

To ascertain the relative contributions of the 4 subsystems, we reran the model for disgust separately by the synthesis, degradation/transport, receptor, and modulation subsystems. The DA synthesis subsystem made the largest contribution ($R^2 = 0.08$, $p_{\text{default}} < 0.001$, permutation $p = 0.0010$) and the DA modulation subsystem made a moderate contribution ($R^2 = 0.04$, $p_{\text{default}} = 0.001$, permutation $p = 0.0344$). In contrast, contributions made by the DA receptor and degradation/transport subsystems were not significant based on the permutation tests ($R^2 = 0.04$, $p_{\text{default}} = 0.009$, permutation $p = 0.1236$, for the receptor subsystem; $R^2 = 0.01$, $p_{\text{default}} = 0.070$, permutation $p = 0.4887$, for the degradation/transport subsystem) (online suppl. fig. S1).

Model 2: Loci's Main Effects plus Gender as a Covariate

Due to the significant gender difference in disgust face recognition, we added gender as a covariate into the regression models. Gender accounted for about a 5% additional variance in disgust face recognition. All significant SNPs in model 1 remained significant in the new model. The total R^2 increased to 0.22 (permutation $p = 0.0000$) in model 2. In addition, a third model with both gender and intelligence as covariates was run, yielding a higher total R^2 and resulting in one change in significant SNPs (see online suppl. for details).

Discussion

The current study produced a number of major findings. First, 15 loci in 7 genes in the 4 DA subsystems were found to have main effects on the recognition of disgust faces, consistent with the hypothesized polygenic nature of emotion recognition. Second, multiple regression analysis and associated permutation results suggested that the main effects of genetic variations in the whole DA system significantly predicted the recognition of emotions, especially disgust faces. Specifically, the DA synthesis and modulation subsystems made significant contributions to accounting for the variance in the recognition of disgust faces. These results provided the first evidence of differential importance of different subsystems in emotion recognition. Third, the amount of variance in disgust recognition that was accounted for by genetic variations in DA-

related genes was substantial: 18% of the variance in recognition of disgust faces was explained by 13 loci in the DA system. Such an estimate can potentially bridge the wide gap between high estimates of heritability based on traditional behavioral genetics (i.e. twin studies) and the low estimates based on traditional single-gene molecular behavioral studies. Finally, recognition of different types of emotions was found to have a different extent of reliance on the DA system. For the recognition of angry, fearful, surprised, and sad faces, a smaller number of loci in the DA system had significant main effects on recognition; consequently, they did not survive the permutation test (i.e. randomizing the behavioral data).

In terms of specific genes and emotion recognition, one previous study reported a weak association of *DRD4* polymorphisms with disgust sensitivity [13]. In our examination of relevant *DRD4* polymorphisms, we did not find any main effects of *DRD4* loci on the recognition of disgust faces. This nonreplication could have been due to several factors such as sample differences, chance findings, and different measures (recognition of disgust faces in our study but questionnaire data about disgust sensitivity in the previous study).

In our case, based on the main effects regression model of disgust face recognition, there were 7 significant regressors involving 6 SNPs in the DA system: *TH* (rs2070762), *DDC* (rs7808025 and rs10499695), *DRD5* (rs7655090), *NTS* (rs1024076), and *NLN* (rs40107). Among these SNPs, *TH* (rs2070762) is the only one that has been studied in the previous literature to our knowledge. Studies showed that *TH* (rs2070762) was related to essential hypertension in Chinese subjects [28, 29], and it was also associated with migraine in a Spanish population [30]. Researchers suggested that the C allele (susceptible allele for risk of essential hypertension) in rs2070762 may function as an enhancer in regulating gene expression [29]. It is not clear how these traits (though they also need replications) would be related to disgust emotion recognition. Biochemically, TH, which is encoded by the *TH* gene, is the enzyme responsible for catalyzing the conversion of the amino acid L-tyrosine to dihydroxyphenylalanine (DOPA; a precursor for DA). The inhibition of TH might lead to depletion of DA in the brain, which might be related to disgust emotion recognition.

Our study has some limitations. First, we focused on 98 loci in the DA system because of previous evidence for the influence of DA on facial expression recognition. However, other neurotransmitter systems might also have effects on different kinds of emotional facial expression (given our negative findings for emotions other than

disgust). Second, we used a sample of healthy Chinese college students. The homogeneity of this sample helped to control for potential confounding factors, but it might have limited the external validity. Future studies should include other samples, such as PD patients. Finally, it should be noted that, like whole-genome scans, our approach can only show that a number of loci may play an important role in emotion recognition. Functions of many such loci, however, have not been well understood.

A main role of research like the current study is to identify potential loci for future studies to replicate and to examine their biochemical functions.

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