Dopamine beta-hydroxylase gene modulates individuals empathic ability

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Dopamine beta-hydroxylase (DBH), an enzyme that converts dopamine to norepinephrine, has broad influences on social functions. In this study, we examined to what extent two polymorphisms (−1021C/T and a 19 bp insertion/deletion) in DBH gene modulate individuals' empathic perception and response, which were measured, respectively, by reading the mind in the eyes test and the empathic concern subscale of interpersonal reactivity index. Results showed that polymorphism at −1021C/T, but not the 19 bp insertion/deletion, accounts for 2.3% variance of empathic perception and 1.4% variance of empathic response. Individuals with the CC genotype, which is associated with higher DBH activity, manifested greater empathic ability than those with CT/TT genotypes. These findings demonstrate the importance of *DBH* −1021C/T as a genetic basis of empathy and in predicting individual differences in social and affective processing.

Keywords: dopamine beta-hydroxylase; DBH; −1021C/T; polymorphism; empathy

INTRODUCTION

Empathy, the ability to understand and experience the mental state of another person, is fundamental for living in social groups and caring for others. It is composed of two major components, cognitive empathy and affective empathy, both of which can be further divided into a variety of subskills and systems, such as empathic perception (the ability to perceive and identify another person's internal state) and empathic response (the ability to share other persons' feelings) (Baron-Cohen and Wheelwright, 2004; Batson, 2008; Shamay-Tsoory, 2008). These abilities allow us to predict and understand others' motives, intentions, thoughts and emotions, so as to promote altruistic behavior and inhibit aggressive behavior (Mehrabian *et al*, 1988). Impaired empathic ability is a central characteristic of social behavioral abnormalities such as autism spectrum disorders (Dziobek *et al*, 2008) and schizophrenia (Shamay-Tsoory *et al*, 2007).

Empathic abilities vary widely between individuals. A twin study suggested that the heritability of empathy is 0.34–0.47 (Knafo *et al*, 2008). However, the existing evidence is insufficient for us to clearly understand the molecular basis of empathy. The main purpose of this study was to investigate to what extent dopamine beta-hydroxylase (DBH) gene modulates empathic perception and response.

Animal and human studies concerning the biochemical foundation of empathy suggest that the dopaminergic system and noradrenergic system are crucial for empathy-related behaviors. Human studies demonstrated that lower dopamine levels are associated with higher donation of money to a poor child in a developing country (Reuter *et al*, 2011) and with better performance in a theory of mind task measuring the ability to predict the behavior or thoughts of others in a simple social context (Bassett *et al*, 2007). Human studies also showed that higher norepinephrine levels are associated with better recognition and recall of positive emotional stimuli (Harmer *et al*, 2009) and with increased interpersonal cooperation in daily interaction (Tse and Bond, 2003). Given the positive relationship between norepinephrine levels and empathy-related behaviors and the negative relationship between dopamine levels and social behaviors, it is plausible that an enzyme with the ability to modulate the dopamine and norepinephrine levels, would in turn modulate individuals' empathic ability and empathy-related behaviors.

DBH is an enzyme that converts dopamine to norepinephrine. Inhibiting DBH activity increases dopamine levels and decreases norepinephrine levels (Robertson *et al*, 1986). Previous studies confirmed the important role of DBH in social functions. *Dbh* knockout mice exhibit deficits in discriminating familiar and unfamiliar mice (Marino *et al*, 2005) and in retrieving neonates scattered in the home cage (Thomas and Palmiter, 1997). Humans evidencing social dysfunctions such as autistic patients (and their mothers) have lower plasma DBH activity than controls (Lake *et al*, 1977; Robinson *et al*, 2001).

DBH is coded by a single gene *DBH* which is located on chromosome 9q34 (Craig *et al*, 1988; Kobayashi *et al*, 1989). In humans, the genetic variations of *DBH* account for 98% of variance in plasma DBH activity (Oxenstierna *et al*, 1986). Two polymorphisms (−1021C/T, a 19 bp insertion/deletion) are tightly linked to the plasma DBH activity. −1021C/T (also labeled as rs1611115), a genetic variant located in the 5′ upstream region of *DBH*, accounts for 35.52% of variance in plasma DBH activity (Zabetian *et al*, 2001). Homozygosity for the T allele of −1021C/T is associated with lower plasma DBH activity. The 19 bp insertion/deletion (GeneBank: X63418), a polymorphism located in the 4.5 kb upstream of the transcriptional start site, also plays a role

activity (CC of 1021C/T, II of the 19 bp insertion/deletion), would have higher empathic abilities or tendency than individuals with the genotypes leading to lower DBH activity (CT or TT of 1021C/T, ID or DD of the 19 bp insertion/deletion). Moreover, as 1021C/T accounts for a majority of variation in DBH activity (Zabetian *et al*, 2001), it is possible that the genetic variations in 1021C/T could account for more individual differences in empathic perception and response than the variations in the 19 bp insertion/deletion. To measure participants' empathic perception, we used the reading the mind in the eyes test (RMET; Baron-Cohen *et al*, 2001) in which participants recognized or inferred others' emotional states by using visual cues from eye regions. This task has been shown to have high validity in measuring the individual's ability of inferring others' internal emotional state (Baron-Cohen *et al*, 2001; Vellante *et al*, 2012) and it has been widely used in previous studies to link empathic perception with individuals' genetic polymorphisms or hormone levels (Domes *et al*, 2007; Rodrigues *et al*, 2009; van Honk *et al*, 2011). To measure participants' empathic response, we used the empathic concern subscale in interpersonal reactivity index (IRI; Davis, 1983). This subscale has been shown to be sensitive to individuals' empathic response to others' misfortune (Davis, 1983; Rankin *et al*, 2006; Rodrigues *et al*, 2009). Previous studies showed that patients with abnormality in the dopaminergic system, including patients with Parkinson's disease or schizophrenia, have deficits both in tasks measuring empathic perception (Tsuruya *et al*, 2011; Kucharska-Pietura *et al*, 2012) and in tasks measuring empathic response (Smith *et al*, 2012; Narme *et al*, 2013). The DBH polymorphisms, thus, might modulate individuals' empathic perception and response in similar manners. On the other hand, previous neuroimaging studies also showed that empathic perception and response have both the same (e.g. inferior frontal gyrus) and differential neural substrates (e.g. posterior superior temporal sulcus for empathic perception, anterior insular for empathic response) (for reviews, see Adams *et al*, 2010; Bernhardt and Singer, 2012). It is thus also plausible that the DBH polymorphisms modulate individuals' empathic perception and response in different ways.

METHODS

Participants

Three hundred and twenty-nine unrelated, unselected Chinese Han senior students (202 female, mean age ± SD = 22.3 ± 1.0 years) were recruited from Henan University of Science and Technology, China. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Department of Psychology, Peking University. Informed written consents were obtained from each participant.

Genotyping

Genomic DNA was extracted from hair follicle cells using Chelex-100 method (de Lamballerie *et al*, 1994). 1021C/T (rs1611115) in DBH gene was amplified by polymerase chain reaction (PCR). The upstream primer, 5′-GGAGGGACAGCTTCTAGTCC-3′ and the downstream primer, 5′-TCAGTCTCACCACGGCAC-3′ were recruited. A 149 bp product was amplified with an initial 3 min denaturation at 94°C, followed by 35 cycles of 94°C for 30 s, 63°C for 45 s, 72°C for 1 min and a final extension period at 72°C for 10 min. Genotyping was performed by single strand conformation polymorphism method. On genotyping, six samples selected randomly were sequenced for determinate the alleles of genotyping results. The distribution of genotypes (CC = 225, CT = 96, TT = 8) showed no deviation from Hardy–Weinberg equilibrium ($\chi^2 = 0.36$, $P = 0.55$).

The 19 bp insertion/deletion polymorphism (GeneBank: X63418) in DBH gene was amplified using the upstream primer, 5′-GCA AAAGTCAGGCACATGCACC-3′ and the downstream primer, 5′-GTCAGCGAGATGGGGAGGTGGA-3′. Cycling conditions consisted of an initial denaturation at 94°C lasting for 5 min, followed by 35 cycles with denaturation at 92°C for 30 s, an annealing at 60°C for 30 s and an extension at 72°C for 1 min. Finally, an extension period at 72°C was conducted for 5 min, and then the PCR products were genotyped by 8% polyacrylamide gel electrophoresis for 3 h. On genotyping, six of the samples randomly selected from each of genotype groups were sequenced to further determinate the allele of the genotyping results. The distribution of genotypes (II = 109, ID = 148, DD = 59) also showed no deviation from Hardy–Weinberg equilibrium ($\chi^2 = 0.49$, $P = 0.49$).

Reading the mind in the eyes test

RMET is a paper-and-pencil test that consists of 36 items; each item consists of a photograph displaying eye regions of a Caucasian individual and four possible adjectives describing the current emotional or mental state of the pictured individual. These adjectives were presented in both the original English and in Chinese to keep it as close as possible to the original RMET. Participants made a forced choice from the four alternatives without time constraints. The internal consistency (Cronbach's α) in this study was 0.670, which is comparable to what was reported in the previous study (Vellante *et al*, 2012; $\alpha = 0.605$).

Empathic concern

The participants completed the 28-item IRI (Davis, 1983). It consists of four 7-item subscales, two affective subscales (empathic concern, personal distress) and two cognitive subscales (perspective taking, fantasy). Empathic concern measures the feeling of affection and concern in response to the misfortune of others (e.g. 'I often have tender, concerned feelings for people less fortunate than me'). Personal distress taps into 'self-oriented' feelings of personal anxiety and unease when observing the anguish and pain endured by others. Perspective taking evaluates the individuals' cognitive propensity to spontaneously adopt the psychological point of view of others. Fantasy assesses the extent to which people immerse themselves into the feelings and actions of fictitious characters. For each item, the participant judged on a five-point Likert scale to what extent the description applied to himself/herself, with 0 indicating 'does not describe me well' and 4 indicating 'describes me very well'. The internal consistencies for empathic concern, personal distress, perspective taking and fantasy, as measured with Cronbach's α, were 0.630, 0.728, 0.614 and 0.507, respectively. They were slightly lower than the scores reported in the original work (Davis, 1980; $0.68 < \alpha < 0.79$).

RESULTS

Empathic perception

To assess the individuals' ability in emotion recognition and empathic perception, we analyzed the percentage of correct responses on RMET. Seven participants (2.1%, five females) were excluded from analysis because their scores were at chance level (25%). The mean response accuracy for the remaining 322 participants was 59% (s.d. = 11%), which was lower than the 78% (s.d. = 10%) accuracy originally reported in Baron-Cohen *et al*. (2001). However, this difference was consistent with Adams *et al*. (2010) who demonstrated a cultural difference in RMET. Given that there is gender difference in empathic perception (Baron-Cohen *et al*, 2001) and empathic response (O'Brien *et al*, 2013), we include gender as a between-participant factor in the following analyses (Figure 1).

For 1021C/T, a 2 (gender: male vs female) × 2 (genotype: CC vs CT/TT) ANOVA revealed a main effect of gender, $F(1, 318) = 5.242$,

P¼0.023, partial η^2¼0.016, with females performed better than males (60% 11% vs 57% 12%). Importantly, the main effect of genotype was also significant, $F(1, 318)$¼8.975, P¼0.003 and partial η^2¼0.027. This effect of genotype remained to be significant when the seven excluded participants were included, $F(1, 325)$¼5.824, P¼0.016 and partial η^2¼0.018. Individuals with CC genotype (60% 11%) performed significantly better than individuals with CT/TT genotypes (56% 12%). The interaction between gender and genotype was not significant, $F(1, 318)$¼1.445, P¼0.230 and partial η^2¼0.005. Regression analysis with 1021C/T polymorphism (0¼CT/TT, 1¼CC) as a single predictor of RMET indicated that this polymorphism accounted for a significant proportion of the variance in RMET, $F(1, 320)$¼7.460, P¼0.007, β¼0.151, R^2¼0.023 and adjusted R^2¼0.020. This result continues to hold after controlling for gender (step 1, entering gender with 0¼male and 1¼female; step 2, entering both gender and 1021C/T polymorphism) $F(1, 319)$ change¼7.765, P¼0.006, β¼0.153 and R^2 change¼0.023. For the 19 bp insertion/deletion, however, a 2 (gender: male vs female) 3 (genotype: II vs ID vs DD) ANOVA found no significant RMET score difference between individuals with II (58% 12%), ID (59% 11%) and DD (59% 10%) genotypes, $F(2, 303)$¼0.078, P¼0.925, partial η^2¼0.001, nor the interaction between gender and genotype, $F(2, 303)$¼0.752, P¼0.472 and partial η^2¼0.005.

Empathic response

We used the total score on the IRI empathic concern subscale to measure participants' empathic responses. For 1021C/T, a 2 (gender: male vs female) 2 (genotype: CC vs CT/TT) ANOVA showed no main effect of gender, $F(1, 325)$¼2.275, P¼0.132, partial η^2¼0.007, but a main effect of genotype, $F(1, 325)$¼4.895, P¼0.028 and partial η^2¼0.015. Individuals with CC genotype (21.1 3.5) showed greater empathic response to others' misfortune than those with CT/TT genotypes (20.1 3.9). The interaction between gender and genotype was not significant, $F(1, 325)$¼0.098, P¼0.754 and partial $\eta^2 < 0.001$. Regression analysis with 1021C/T polymorphism as the only predictor indicated that this polymorphism accounted for a significant proportion of the variance in empathic concern, $F(1, 327)$¼4.669, P¼0.031, β¼0.119, R^2¼0.014 and adjusted R^2¼0.011. This finding continues to hold after controlling for gender (step 1, entering gender; step 2, entering both gender and 1021C/T polymorphism) $F(1, 326)$ change¼4.872, P¼0.028, β¼0.121 and R^2 change¼0.015. For the 19 bp insertion/deletion, a 2 (gender: male vs female) 3 (genotype: II vs ID vs DD) ANOVA found no significant difference in empathic concern between individuals with II (20.9 3.7), ID (20.5 3.6) and DD (21.3 3.9) genotypes, $F(2, 310)$¼0.672, P¼0.512, partial η^2¼0.004, nor interaction between gender and genotype, $F(2, 310)$¼0.017, P¼0.983 and partial $\eta^2 < 0.001$.

When testing participants, we also included the other three subscales of IRI (fantasy, perspective taking, personal distress). For 1021C/T, when we submitted the scores in these subscales to 2 (gender: male vs female) 2 (genotype: CC vs CT/TT) ANOVAs respectively, we observed neither a main effect of genotype nor an interaction between genotype and gender, all $Ps > 0.10$. For the 19 bp insertion/deletion,

emergency situations, I feel apprehensive and ill at ease') assess emotional self-control rather than the tendency to share others' feelings (Baron-Cohen and Wheelwright, 2004). The null effect on perspective taking and fantasy was inconsistent with the significant effect on RMET, possibly because these tasks measure different aspects of cognitive empathy, as outlined previously. For the 19 bp insertion/deletion, no effect of genotype was found on the combined affective or cognitive subscales.

DISCUSSION

In this population-based study, we found that 1021C/T, but not the 19 bp insertion/deletion, of *DBH* gene modulates individuals' empathic perception and response. As we predicted, individuals with the CC genotype of 1021C/T manifested greater empathic ability than those with one or two copies of the T allele.

The functional dissociations between 1021C/T and the 19 bp insertion/deletion are not entirely surprising given that variations in DBH activity are mainly accounted for by 1021C/T polymorphism (Zabetian *et al*, 2001). Importantly, the present findings concerning 1021C/T polymorphism are consistent with previous observations regarding the positive association between DBH activity and affiliative behavior and social memory (Thomas and Palmiter, 1997; Marino *et al*, 2005). Given that DBH is the unique synthetic enzyme that converts dopamine to norepinephrine (Thoma *et al*, 1998), our findings are also consistent with studies that demonstrated the roles of dopaminergic and noradrenergic systems in empathic abilities and empathy-related behaviors (Tse and Bond, 2003; Bassett *et al*, 2007; Harmer *et al*, 2009; Reuter *et al*, 2011). The important advance made by this study is that we directly demonstrated the link between 1021C/T polymorphism and individuals' empathic abilities.

Our demonstration concerning the importance of *DBH* gene in empathic perception and response may have clinical implications for individuals with severe impairment in empathy-related behaviors. Clinical studies have found that individuals with autism spectrum disorders have lower DBH activity (Lake *et al*, 1977) and perform worse in empathy-related tasks (Baron-Cohen *et al*, 2001; Dapretto *et al*, 2006; Dziobek *et al*, 2008) than controls. Although these studies as a whole evidenced the impaired empathic abilities and lower DBH activity in autistic patients, they failed to directly test the link between DBH activity and autistic symptoms. This study went further by demonstrating that the *DBH* gene, the main determiner of DBH activity, is associated with empathic abilities in healthy population. It would be a fruitful endeavor for further studies to investigate in detail the genotyping of *DBH* 1021C/T and the diagnosis, treatment and prognosis of autism spectrum disorders (and other psychiatric disorders).

Several limitations of this study should be noted. First, the tasks we used to measure participants' empathic abilities may not be optimal in revealing the underlying constructs of empathy. Here, Chinese participants were tested with a Caucasian version of RMET and the cultural differences in expressing emotional cues around the eye regions or in perceiving these cues could have added noises to our measurement (Duchenne and Cuthbertson, 1990; Jack *et al*, 2012). These noises could lead to either false positive in statistical analysis or underestimation of the contribution of *DBH* gene polymorphism to individuals' empathic abilities. Second, we focused on the modulatory role of a single gene in empathic abilities while these abilities are likely to be influenced by multiple genes and by the interaction between genetic variations and environment. More systematic studies are needed to take into consideration a variety of genetic, neurophysiological and social factors in revealing the underlying mechanisms for individual differences in empathic and affective processing. Finally, all the participants in this study were Chinese. As some studies showed that the relations between genes and social behaviors can be modulated by culture (Kim *et al*, 2010, 2011), it would be interesting to investigate the potential cultural differences in the association between *DBH* polymorphisms and empathic abilities.

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