

# Sex Modulates the Associations Between the *COMT* Gene and Personality Traits

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Previous research has shown inconsistent findings regarding the relations between the functional Val158Met polymorphisms of the catechol-O-methyltransferase (*COMT*) gene and individual differences in personality traits. This study attempts to overcome some of the weaknesses of previous research, namely, small sample sizes, clinical samples, ethnic stratification, wide age ranges, neglecting sex differences, and single measures of personality traits. A large sample ( $n = 556$ , 250 male, 306 female) of healthy Chinese college students (mean age =  $20.5 \pm 1$  years) was given a battery of personality scales, including the temperament and character inventory-revised, the behavioral inhibition system and behavioral approach system scale, the Beck depression inventory, and the Beck anxiety inventory. Factor analysis of the affect-related personality traits revealed two factors that corresponded to positive (PEM) and negative emotionality (NEM). We found a consistent *COMT*-by-sex interaction effect on affect-related personality traits. Compared with males with Met/Met alleles, males with Val/Val alleles showed significantly higher scores on NEM, but lower scores on PEM. Females, however, showed an opposite but nonsignificant pattern. Our results supported the role of the *COMT* gene in personality traits for males and contributed to the growing literature on sex differences in gene-behavior connections.

*Neuropsychopharmacology* (2011) **36**, 1593–1598; doi:10.1038/npp.2011.39; published online 6 April 2011

**Keywords:** sex; *COMT*; personality

## INTRODUCTION

Behavioral genetics research has long established that personality traits show a moderate to high level of heritability, suggesting a genetic basis for individual differences in those traits (eg, Bouchard 1994; Bouchard and Loehlin, 2001; Heiman *et al*, 2004; Lin *et al*, 2007). Recent advances in molecular genetics have allowed researchers to begin to investigate specific genes that are relevant to personality traits. The most commonly targeted genes are in the dopaminergic and serotonergic systems, including *SLC6A4* (5HTTLPR), *DRD4* (48-bp VNTR), and *COMT* (Val/Met; Munafo *et al*, 2003).

Catechol-O-methyltransferase (*COMT*) is an S-adenosyl-methionine-dependent methyltransferase enzyme that methylates catechol substrates, notably catecholamines and catechol estrogens. This is a major pathway for

dopamine inactivation. *COMT* has two isoforms: soluble (S-*COMT*) and membrane bound (MB-*COMT*). MB-*COMT* has approximately a 10-fold greater affinity for dopamine than S-*COMT* and predominates in the brain, reflecting its significant role in the prefrontal dopamine system. The *COMT* gene is located on chromosome 22q11, and has a well-known variation, a G→A substitution polymorphism (rs4680) that produces a valine-to-methionine (Val/Met) substitution at codons 108 and 158 of S-*COMT* and MB-*COMT*. This amino acid substitution influences the thermal stability and activity of *COMT*, such that the *COMT* activity in human prefrontal cortex is about 35–50% lower in Met homozygotes than in Val homozygotes (Chen *et al*, 2004). As a result, dopamine signaling is likely to be enhanced in Met carriers as compared with Val carriers, thus resulting in potential differences in prefrontal cognitive function (Savitz *et al*, 2006; Barnett *et al*, 2008; Goldman *et al*, 2009) and personality (Benjamin *et al*, 2000; Eley *et al*, 2003; Enoch *et al*, 2003; Tsai *et al*, 2004; Olsson *et al*, 2005; Reuter and Hennig, 2005; Stein *et al*, 2005; Kim *et al*, 2006; Reuter *et al*, 2006a; Tochigi *et al*, 2006; Golimbet *et al*, 2007; Hashimoto *et al*, 2007; Ishii *et al*, 2007; Lang *et al*, 2007; Light *et al*, 2007).

The *COMT* Val/Met effect on personality has been inconsistent across studies. One reason may be that

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Received 20 September 2010; revised 18 January 2011; accepted 21 February 2011

personality traits have been measured with varying scales. Scales most often used to measure personality include the temperament and character inventory (TCI, or its older version tridimensional personality questionnaire; Cloninger *et al*, 1993), the five factor personality inventory (NEO; Costa and McCrae, 1992), and the behavior inhibition/approach system (BIS/BAS) questionnaire (Carver and White 1994). Recently, researchers have been able to group many affect-related traits into two categories. Traits such as harm avoidance (HA) in TCI, neuroticism in NEO, and BIS all belong to negative emotionality (NEM), whereas novelty seeking (NS) in TCI, extraversion in NEO, and BAS belong to positive emotionality (PEM; Reuter *et al*, 2006b). Associations between COMT Val/Met and PEM/NEM were quite mixed, with nine studies showing no significant associations (Strobel *et al*, 2003; Tochigi *et al*, 2006; Ishii *et al*, 2007; Light *et al*, 2007; Urata *et al*, 2007; Sheldrick *et al*, 2008; Calati *et al*, 2011; Kang *et al*, 2010; Salo *et al*, 2010), seven studies showing the Val allele associated with high PEM or low NEM (Enoch *et al*, 2003; Tsai *et al*, 2004; Reuter and Hennig, 2005; Stein *et al*, 2005; Hoth *et al*, 2006; Hashimoto *et al*, 2007; Wacker and Gatt, 2010), and three studies showing the opposite (Met allele associated with high PEM or low NEM; Kim *et al*, 2006; Golimbet *et al*, 2007; Demetrovics *et al*, 2010), and three studies reported opposite pattern for males and females (Eley *et al*, 2003; Reuter *et al*, 2006b; Lang *et al*, 2007).

Another reason for these inconsistent findings may be that, for association studies such as those mentioned above, statistical power is often an issue. A sample size of fewer than 200 individuals (including all genotypes), which is typical for previous studies, simply does not have sufficient statistical power to detect a true but modest association between a gene and personality (Long and Langley, 1999). Third, most studies have been carried out in countries such as the United States, where ethnic diversity is high, but ethnic stratification problems have often been ignored (Domschke *et al*, 2007). Fourth, health condition and the age of the subjects may have confounded some of the findings. For example, Rujescu *et al* (2003) found that the COMT gene's association with state and trait anger differed for healthy controls than for suicide attempters. Age is another potential confound because it is negatively correlated with traits such as NS (Ishii *et al*, 2007; Light *et al*, 2007) and HA (Hashimoto *et al*, 2007; Light *et al*, 2007). Biochemical studies have also reported that COMT activity level rises considerably in men between the third and fifth decade of life (Tunbridge *et al*, 2007).

Fifth, most studies used single measures of constructs instead of multiple measures that would have yielded more reliable data on personality traits. Although these measures may tap similar aspects of personality they are not exactly the same (Carver and White, 1994). This phenotype difference may have contributed to inconsistencies in results. Finally, and perhaps most importantly, sex may be an important confounding factor (Harrison and Tunbridge, 2008). Sex differences in COMT activity and in personality are well addressed in the literature (Carver and White, 1994; Cloninger *et al*, 2006; Darcan *et al*, 2008; Harrison and Tunbridge, 2008; Schmitt *et al*, 2008). In fact, several studies (Eley *et al*, 2003; Enoch *et al*, 2003; Reuter *et al*, 2006b; Lang *et al*, 2007) have reported sex-dependent COMT effects on

personality, although others (Strobel *et al*, 2003; Reuter and Hennig 2005; Hoth *et al*, 2006; Hashimoto *et al*, 2007; Wacker and Gatt, 2010) reported no interactions between sex and the COMT gene.

To help clarify the role of the COMT gene in personality, studies need to overcome the above weaknesses. In this study, a large, homogeneous (in terms of ethnicity, age, education, and health status) sample was recruited: 556 healthy Chinese college students (250 males and 306 females), with a mean age of 20.5 years ( $SD = 1.0$ ). A wide range of personality traits was measured with multiple measures of related constructs. According to the PEM/NEM hypothesis (Reuter *et al*, 2006b), we selected novelty seeking and HA subscales of the TCI revised (TCI-R; Cloninger *et al*, 1993) and the behavioral inhibition system/behavioral approach system (BIS/BAS) scale (Carver and White, 1994). A warrior/worrier model was proposed regarding the function of the COMT Val/Met polymorphism (Stein *et al*, 2006). This model claims that the Val allele may be associated with advantages in processing aversive stimuli, thus Val carriers tend to exhibit decreased anxiety and better regulatory response to negative stimuli (warrior), whereas the Met allele may be associated with advantages in memory and attention tasks but also increased anxiety (worrier). Given the centrality of anxiety in this model, we also included in the current study the Beck anxiety inventory (Beck and Steer, 1990), and the Beck depression inventory second edition (Beck *et al*, 1996).

## MATERIALS AND METHODS

### Participants

In all, 556 healthy Chinese college students (250 males and 306 females, mean age = 20.5 years,  $SD = 1.0$ ) participated in this study. Written informed consent was obtained from each participant. This experiment was approved by the IRB of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University, China.

### Personality Measures

The following major personality measures were used in this study. The NS subscale of the TCI-R (Cloninger *et al*, 1993) measures individual differences in the extent to which a person is impulsive, quick tempered, and disorderly versus rigid, stoical, and orderly. The HA subscale of the TCI-R measures individual differences in the extent to which a person is anxious, pessimistic, and shy versus risk taking, optimistic, and outgoing. The BIS/BAS scale measures behavioral inhibition and approach systems (Carver and White, 1994). The BIS controls experience of anxiety in response to anxiety-relevant cues and is sensitive to signals of punishment, non-reward, and novelty; and inhibits behavior toward negative or painful outcomes. The BAS controls appetitive motivation and is sensitive to signals of reward and non-punishment. The Beck anxiety inventory and the Beck depression inventory (Beck and Steer, 1990; Beck *et al*, 1996) measure anxiety and depression, respectively.

All scales were translated from English to Chinese and back translated and verified through a bilingual group discussion. They were also pilot tested. The resulting

**Table 1** Personality Measures: Inter-Scale Correlations, Scale Means and Standard Deviations, and Internal Consistency (Cronbach  $\alpha$ )

	Correlation coefficients					Mean	SD	$\alpha$
	BDI	BAI	BIS	BAS	TCL_HA TCL_NS			
BDI						11.02	6.83	0.81
BAI	0.63**					10.79	8.05	0.89
BIS	0.41**	0.34**				20.19	3.58	0.78
BAS	-0.15**	-0.04	0.00			42.28	4.63	0.72
TCL_HA	0.50**	0.40**	0.64**	-0.29**		94.32	16.40	0.91
TCL_NS	-0.03	-0.02	-0.17**	0.25**	-0.32**	101.81	12.47	0.81
NEM	0.84**	0.81**	0.72**	-0.05	0.72**	0	1.00	—
PEM	-0.01	0.13*	-0.19**	0.72**	-0.48**	0.80**	0	1.00

Abbreviations: BAI, Beck anxiety inventory; BAS, behavior approach system; BDI, Beck depression inventory; BIS, behavior inhibition system; NEM, negative emotionality; PEM, positive emotionality; TCL\_NS, novelty seeking in the temperament and character inventory; TCL\_HA, harm avoidance in the temperament and character inventory.

Note: \* $p < 0.01$ , \*\* $p < 0.001$ .

Chinese versions all had high internal consistency. Furthermore, theoretically related constructs were correlated with one another, yielding construct/convergent validity (see Table 1). Specifically, BDI, BAI, HA, and BIS showed high correlations among them, which is consistent with the idea that they all measured NEM; NS and BAS were positively correlated but negatively correlated with the above scales, indicating that they measure PEM (see the Results section for confirming evidence from a factor analysis).

### Genotyping

Subjects donated a blood sample through venipuncture. DNA was extracted and purified following the standard procedure. The genotypes of *COMT* Val158Met were determined in the following manner (see Qian *et al*, 2003). DNA fragments containing the Val158Met polymorphism in the *COMT* gene were amplified using PCR with primers (forward: 5'-TCGTGGACGCCGTGATTCAGG-3' and reverse: 5'-ACAACGGGTCAGGCATGCA-3'). The PCR mixture consisted of 1  $\times$  Taq Buffer (MBI), 0.2 mM dNTP, 0.25 mM primers, 1 mM MgCl<sub>2</sub>, 1 U Taq polymorphism and 100 ng DNA. PCR was initiated at 95°C for 3 min, then at 94°C for 30 s, 68°C for 60 s, 72°C for 90 s for 35 cycles, then extended at 72°C for 7 min. The Val158Met variation was differentiated using NlaIII restriction fragment length polymorphism analysis on 4% agarose gel electrophoresis. Two common fragments (81 and 22 bp) and variable fragments of 114 bp (Val 158/wild type) and 96 + 18 bp (Met 158/mutant) were available. Genotypes were determined from Gel Doc 2000 (Bio-Rad, Hercules, CA). Because the short fragments (22 and 18 bp) diffused in the agarose gel, only three bands (114, 96, and 81 bp) were detectable. Ambiguous or unidentifiable results were reamplified and rescored. A subset of the samples (10%) were randomly selected and tested twice for confirmation.

Among all 556 subjects, 310 were Val/Val, 210 were Val/Met, and 36 were Met/Met. The *COMT* genotype

**Table 2** Number of Subjects by Genotype and Sex

	Val/Val	Val/Met	Met/Met	Total
<i>Our sample</i>				
Male (%)	148 (56.9)	88 (33.8)	14 (5.4)	250 (100)
Female (%)	162 (51.9)	122 (39.1)	22 (7.1)	306 (100)
<i>HapMap sample</i>				
Han Chinese in Beijing (%)	43 (51.2)	32 (38.1)	9 (10.7)	84 (100)
Chinese in Denver (%)	38 (44.7)	43 (50.6)	4 (4.7)	85 (100)

distribution in the overall sample was in the Hardy-Weinberg equilibrium ( $p = 0.975$ ). The frequencies of polymorphism for each sex are presented in Table 2. No distribution differences between males and females were found ( $\chi^2(2) = 2.298$ ,  $p = 0.317$ ). Minor allele (A, code for met) frequency is 25%, which is comparable with the HapMap data (30% for Han Chinese in Beijing, China, and 30% for Chinese in Denver, CO).

### Data Analysis

All data were analyzed using SPSS 15.0 for Windows. To alleviate the multiple comparisons problem and to combine diverse measurements to get a more reliable phenotype, exploratory factor analysis using the principal component extraction method followed by varimax rotation was carried out. Analysis of variance (ANOVA) was used to test the main effects and interaction effects of sex and the *COMT* Met/Val polymorphism on the latent phenotypes. Additional supplementary ANOVAs were conducted to explore which measures of the phenotypes made contributions to our results. When interaction effects were significant, simple effects tests and *post hoc* comparisons were conducted.

### RESULTS

Exploratory factor analysis resulted in a two-factor solution, with Kaiser-Meyer-Olkin index = 0.66, Bartlett's test  $\chi^2(15) = 961.132$ ,  $p < 0.001$ , together indicating that the solution is good. BDI, BAI, HA, and BIS had significant loadings on factor 1, which appeared to be consistent with the construct of NEM, accounting for 43% of the variance; and NS and BAS loaded on factor 2, which we labeled as PEM accounts for another 21% of the variance.

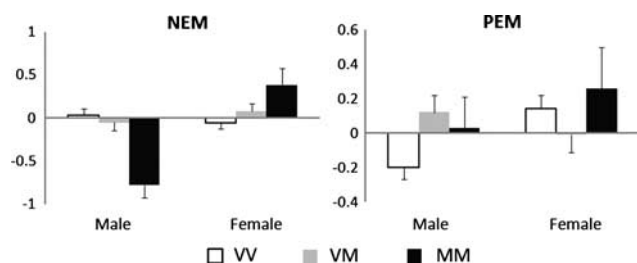
Table 3 shows the results of two-way ANOVA examining the effects of sex and the *COMT* gene Val/Met polymorphism on NEM and PEM. There were significant sex-by-gene interactions for both variables (see also Figure 1). Further one-way ANOVA revealed that these significant interactions mostly resulted from significant effects of the *COMT* gene on males' traits, with an opposite but non-significant pattern for females. Compared with males with Val/Val alleles, males with Met/Met alleles showed significantly lower NEM and higher PEM. Females, in contrast, showed an opposite pattern for NEM (ie, Met/Met individuals had higher scores on NEM than Val/Val individuals), although it did not reach statistical significant in simple effects tests. To

**Table 3** Means (SD) of Two Factors by Sex and Genotype and Associated ANOVA Results

Personality traits	Sex	Val/Val	Val/Met	Met/Met	Post hoc <sup>a</sup>	Simple sex effect	Gene effect F(p)	Gender effect F(p)	Interaction F(p)
NEM	Male	0.03 (1.01)	-0.05 (0.93)	-0.78 (0.55)	vv, vm > mm	f > m for mm	0.66 (0.52)	10.11 (0.00)	6.25 (0.00)
	Female	-0.05 (1.01)	0.08 (1.04)	0.39 (0.89)					
PEM	Male	-0.20 (0.85)	0.12 (0.95)	0.03 (0.66)	vv < vm	f > m for vv	0.82 (0.44)	1.42 (0.23)	3.54 (0.03)
	Female	0.14 (0.98)	-0.01 (1.11)	0.26 (1.11)					

Abbreviations: f, female; m, male; mm, Met/Met; NEM, negative emotionality; PEM, positive emotionality; vm, Val/Met; vv, Val/Val.

<sup>a</sup>Post hoc comparison between three genotype groups (vv, vm, mm) within each sex.

**Figure 1** Means of personality factors by genotype and sex.

ascertain whether these sex-by-gene interactions were because of one or few specific measures or rather the general constructs, we conducted supplementary ANOVA for the six original measures. Results are shown in online Supplementary Table S1 and Figure S1. Briefly, five of the six measures showed significant interactions, indicating that the sex-by-gene interactions were not because of one or few specific measures, but rather the more general constructs we used. Specifically, further one-way ANOVA revealed that, compared with Met/Met males, Val/Val males showed significantly higher scores in anxiety, depression, behavioral inhibition, and HA, but lower scores in NS. Females showed a mostly opposite, but statistically nonsignificant, pattern (see Supplementary Table S1 and Figure S1).

Another way to appreciate the sex-COMT interactions is to examine sex differences for each genotype. Results showed that, for the Val/Val genotype, females consistently showed higher PEM than males,  $F(1,308) = 10.48$ ,  $p = 0.001$ . For Val/Met and Met/Met (ie, Met present) genotypes, females showed higher NEM than males,  $F(1,255) = 4.86$ ,  $p = 0.028$ .

## DISCUSSION

Our main finding is that sex modulates the associations between the COMT gene's Val/Met polymorphism and personality traits. This finding adds to the growing literature on sex-COMT interaction effects on phenotypes ranging from psychiatric disorders (Harrison and Tunbridge, 2008) to personality traits such as sensation seeking (Lang *et al*, 2007) and behavioral inhibition system (Reuter *et al*, 2006b). Beyond the COMT gene and personality, of course, there is a growing literature of sex-dependent genetic effects on behavior, including performance on cognitive tests (O'Hara *et al*, 2006), nicotine dependence (Beuten *et al*,

2006), adolescent delinquency and thrill seeking (Dmitrieva *et al*, 2011), and ADHD (Qian *et al*, 2003).

The main division in personality traits included in our study is between traits representing NEM such as HA, BIS, BDI and BAI, and those (NS, BAS) representing PEM (Reuter *et al*, 2006b). We found that males and females generally had opposite patterns of association between the COMT gene and personality, resulting in significant sex differences among genotypes. For Val/Val carriers, sex differences occurred for PEM, and for Met carriers (both Val/Met and Met/Met), sex differences were evident for NEM.

According to the warrior/worrier model, Met carriers would have higher anxiety (or high NEM in the current study) than would Val/Val individuals. However, our data did not support this general prediction. Instead we found that the effect of the COMT gene differed by gender, which is consistent with Reuter *et al* (2006b) and Lang *et al* (2007). Specifically, for females, COMT's main effect on personality showed the predicted but nonsignificant trend, but for males, the effect of COMT was opposite of the prediction of the warrior/worrier model. Despite the findings of clear sex-COMT interactions across a number of studies, however, the patterns of specific interactions were not always consistent. Our results on the behavioral inhibition system were consistent with those by Reuter *et al* (2006b): Male Met carriers scored lower on BIS than male Val homozygotes. Our results further showed that this pattern was consistent across measures related to NEM such as BDI, BAI, BIS, and HA. Our results on sensation seeking, however, were inconsistent with the pattern found by Lang *et al* (2007) and Tsai *et al* (2004). Their studies found that female Val/Val carriers scored higher in sensation seeking than female Met/Met carriers, whereas we found no significant effect of the COMT gene for females (although the direction of differences were the same as the other two studies). Instead, we found that male Val/Met carriers were higher in sensation seeking than male Val/Val carriers. Lang *et al* (2007) did not find a significant COMT effect for males, and Tsai *et al* (2004) did not include males in their study.

These results have two significant implications. First, they point to the importance of including sex in analyses of gene-personality (perhaps broadly gene-behavior) associations. The role of sex in the relation between the COMT gene and personality has been discussed by Harrison and Tunbridge (2008). They suggested that estrogen may interact with COMT activity. It has been reported that estrogen inhibits COMT mRNA expression and reduces its activity (Xie *et al*, 1999; Jiang *et al*, 2003), consistent with an



earlier study showing that women with high estrogen levels had lower COMT activity than other women (Briggs and Briggs, 1973). Moreover, there is evidence that COMT has an important role in metabolizing catechol estrogens and thereby lowering its levels (Creveling, 2003). Besides, Harrison and Tunbridge (2008) concluded that women appear to have elevated basal striatal dopamine levels, because, compared with men, women have greater pre-synaptic dopamine synthesis, greater dopamine transporter uptake, lower D2 receptor affinity, and lower amphetamine-stimulated dopamine release. These sex differences may interact with the *COMT* gene in their effects on personality.

Second, even when sex is considered in the analyses of gene–behavior associations, there are still inconsistencies in the findings across studies. One reason is that a single gene such as the *COMT* gene is only a part of the complex neural system (eg, the dopamine system). In the case of the dopamine system, other dopamine genes such as receptor genes (*DRD1*, *DRD2*, *DRD3*, *DRD4*, *DRD5*) and transporter genes (*SLC6A3*) and possibly other systems such as the serotonin system may all interact with the effects of the *COMT* gene. A comprehensive understanding of the genetic bases of personality needs to consider the contributions of multiple genes.

A few limitations of the current study should be noted. First, although our results add to the accumulating yet complicated picture of the effect of the *COMT* gene on personality, more replications with different study designs and populations are needed. Second, although we had a decent sample size, the genotype frequency yielded a small Met/Met group. Third, although we used multiple measures and showed consistent results both at the measure and factor levels, it remains to be seen whether there are other measures and factors that should be included as *COMT*-related personality traits.

In summary, our study overcame some of the weaknesses of the previous research (small samples, ethnic stratification, single measures, lacking of attention to sex differences) and reported significant sex–*COMT* interaction effects on personality. Taken together our results and those of previous studies, it is imperative to include sex in future research on gene–behavior relations and to model gene–gene and gene–environment interactions.

## ACKNOWLEDGEMENTS

This study was supported by the 111 Project of the Ministry of Education of China (B07008). We thank all graduate research assistants who helped us with data collection.

## DISCLOSURE

The authors declare no conflict of interest.

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