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Authors
Wang, Y
Li, J
Chen, C
et al.

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COMT rs4680 Met is not always the 'smart allele': Val allele is associated with better working memory and larger hippocampal volume in healthy Chinese

Y. Wang[†], J. Li[†,‡], C. Chen[§], C. Chen[†], B. Zhu[†], R. K. Moysis[¶], X. Lei[†,§], H. Li[**], Q. Liu[†,††]D. Xiu[†], B. Liu[†], W. Chen[†], G. Xue[†] and Q. Dong[†,*]

[†]State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China, [‡]LIAMA Center for Computational Medicine, National Laboratory of Pattern Recognition, Institute of Automation, The Chinese Academy of Sciences, Beijing, China, [§]Department of Psychology and Social Behavior , [¶]Department of Biological Chemistry, University of California Irvine, Irvine, CA, USA, [**]Institute of Basic Research in Clinical Medicine, China Academy of Traditional Chinese Medicine, Beijing, China, and [††]Department of Brain and Cognitive Sciences, McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA, USA
**Corresponding author: Prof. Q. Dong, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China. E-mail: dongqi@bnu.edu.cn*

Catechol-*O*-methyltransferase (COMT) Val158Met (rs4680) polymorphism plays a crucial role in regulating brain dopamine level. Converging evidence from Caucasian samples showed that, compared with rs4680 Val allele, the Met allele was linked to lower COMT activity, which in turn was linked to better cognitive performance such as working memory (WM) and to a larger hippocampus (a brain region important for WM). However, some behavioral studies have shown that the function of rs4680 appears to vary across different ethnic groups, with Chinese subjects showing an opposite pattern as that for Caucasians (i.e. the Val allele is linked to better cognitive functions related to WM in Chinese). Using a sample of healthy Han Chinese college students (ages from 19 to 21 years), this study investigated the association of COMT Val158Met genotype with behavioral data on a two-back WM task ($n = 443$, 189M/254F) and T1 MRI data ($n = 320$, 134M/186F). Results showed that, compared to the Met allele, the Val allele was associated with larger hippocampal volume (the right hippocampus: $\beta = -0.118$, $t = -2.367$, $P = 0.019$, and the left hippocampus: $\beta = -0.099$, $t = -1.949$, $P = 0.052$) and better WM performance ($\beta = -0.110$, $t = -2.315$, $P = 0.021$). These results add to the growing literature on differentiated effects of COMT rs4680 polymorphism on WM across populations and offer a brain structural mechanism for such population-specific genetic effects.

Keywords: Brain anatomy, Chinese, COMT rs4680, FreeSurfer, healthy, hippocampus, population difference, volume, working memory, young adults

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Working memory (WM) refers to the retention of information in conscious awareness (Postle 2006), which is essential for cognitive functions such as reading, learning, decision making and planning (Baddeley *et al*. 1986; Engle *et al*. 1999). In the past decade, many studies have been conducted to examine the genetic and neural bases of WM.

Several molecular studies have identified the catechol-*O*-methyltransferase (COMT) gene as playing an important role in WM. *COMT* is located on Chr. 22q and codes for COMT enzyme that metabolizes catecholamines and catechol-estrogens. A G/A substitution at codon 158 in *COMT*, commonly known as Val158Met or rs4680, causes an alteration from valine (Val) to methionine (Met), consequently modulates the activity of COMT (Chen *et al*. 2004; Lachman *et al*. 1996; Tunbridge *et al*. 2006). Catechol-*O*-methyltransferase acts as a chief modulator of dopamine level in the central nervous system and periphery (Lachman 2008). It has been shown that, compared to the Val allele, *COMT* 158Met allele is related to increased tonic and reduced phasic dopamine release in the subcortical regions but increased dopamine levels in the cortex (Bilder *et al*. 2004). Because dopamine is one of the most pivotal neurotransmitters in the brain and plays an important role in WM processing (Castner *et al*. 2000; Mcnab *et al*. 2009), *COMT* val158met polymorphism is related to brain development and cognitive functions such as executive function and WM (Leh *et al*. 2010; Lindenberger *et al*. 2008).

Interestingly, however, the associations between rs4680 and WM or related cognitive performances have been found to vary by population. Several studies with Caucasian samples (Aguilera *et al*. 2008; Bruder *et al*. 2005) indicated that the Met allele is associated with better cognitive function, especially WM, but in a study of Chinese, Yeh *et al*. (2009) found that Val carriers performed better in all basic competency test subtests than the Met homozygotes. Yeh *et al*.'s finding has been supported by many other studies of Asian samples on the associations between *COMT* and cognitive functions (Cheon *et al*. 2008; Ma *et al*. 2007; Qian *et al*. 2009; Tai & Wu 2002; Wu *et al*. 2001; Zhang *et al*. 2007). For example, a study of attention-deficit hyperactivity disorder children (Qian *et al*. 2009) reported that the patients with high-enzymatic activity (Val/Val) of *COMT* Val158Met performed significantly better on an intelligence quotient

test than did patients with mid- or low-level enzymatic activity (Val/Met and Met/Met). In another study, female Met carriers were found to perform significantly poorer on the Freedom from Distractibility task than the other genotype groups (Zhang *et al*. 2007). Such research evidence has led researchers to speculate on the reasons for ethnic differences in gene–behavior associations (Lee & Ham 2008).

One plausible reason for ethnic differences in genetic effects might be physiological in nature – perhaps *COMT* is linked to brain anatomy subserving cognitive functions differently for different groups. It has been widely agreed that the hippocampus plays an essential role in WM, especially when relational encoding process is involved. Neuroimaging studies (Berent-Spillson *et al*. 2010; Bokde *et al*. 2010; Nakao *et al*. 2002; Stepanichev *et al*. 2004; Zarahn *et al*. 2005) indicated that bilateral hippocampi were specifically activated during WM processing. In addition, brain lesion studies have also reported that patients with hippocampal damage had difficulty retaining information just presented (Ezzyat & Olson 2008; Olson *et al*. 2006). These results suggest that the hippocampus is critical for WM and some researchers have even deemed its structure as an endophenotype for WM performance (Axmacher *et al*. 2010; Ranganath & D'esposito 2005; Wang & Cai 2010). Furthermore, researchers have documented that *COMT* expression is widely distributed in the hippocampus (Aalto *et al*. 2005; Bertolino *et al*. 2008; Gill & Mizumori 2006; Li *et al*. 2010; Seamans *et al*. 1998; Takahashi *et al*. 2008; Wilkerson & Levin 1999). Several studies on Caucasian samples have found that the Met allele is associated with larger hippocampal volumes (Cerasa *et al*. 2008; Dutt *et al*. 2009; Ehrlich *et al*. 2010; Honea *et al*. 2009). However, there have been only two structural imaging genetics studies of rs4680 in Chinese subjects and they focused on the effect of rs4680 on white matter connectivity and integrity (Li *et al*. 2009; Liu *et al*. 2010). Neither examined the association between *COMT* and hippocampal volumes. To fill that void, this study aimed to examine the association between the *COMT* gene, hippocampal volume and WM in a large sample of healthy young Chinese.

Material and methods

Participants

Four hundred and forty-six (191 male and 255 female, ages from 19 to 21 years) healthy Han Chinese college students were recruited from Beijing Normal University for this study. Demographic information including age, gender and handedness was collected (see Table 1). All participants reported having normal or corrected-to-normal vision. Data based on the Beck Depression Inventory showed that none of the participants met the criterion for major depression. Participants also reported having had no history of psychiatric diseases, head injuries or stroke/seizure. This experiment was approved by the Institutional Review Board (IRB) of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University, China. Written consent form was obtained from each participant after a full explanation of the study procedure.

Material and cognitive tasks

A two-back WM paradigm with three subtasks (semantic, phonological and morphological judgment) was used to assess WM performance (for details, see Li *et al*. 2011). Briefly, participants were asked to make continuous judgments between the word currently presented and the word presented two trials earlier in terms of their semantic (whether they belong to the same semantic category), phonological (whether they rhymed with each other) or morphological relations (whether they were the same Tibetan character) (Xue *et al*. 2004). Data from three participants were excluded because they had too many invalid and missing trials, resulting in a final sample of 443 subjects (189 males and 254 females) in the gene–behavior analysis. Factor analysis was conducted for the three WM tasks and the first principal component was extracted to represent WM ability.

Genotyping

Genotyping was performed as described in a previous article (Chen *et al*. 2011). The genomic DNA for each participant was extracted from a 4-ml venous blood sample according to the standard method. The polymerase chain reaction method was used to genotype rs4680. Samples with ambiguous or unidentifiable results were re-amplified and re-scored. A random subset of the samples (10%) were selected and tested twice for confirmation. Among all 443 subjects, 248 were Val/Val, 168 were Val/Met and 27 were Met/Met. The sample was in Hardy–Weinberg Equilibrium ($\chi^2 = 0.024$, $P = 0.877$). The minor allele frequency of this single nucleotide polymorphism in our sample was 0.25, which is comparable to the HapMap data (29% for Han Chinese in Beijing and 26% for Chinese in Metropolitan, Denver, Colorado, according to HapMap Genome Browser release #28).

MRI data collection and analysis

Three hundred and twenty (186 females and 134 males) of the subjects participated in the MRI experiment. Three-dimensional MRI scans were performed with a 3.0T Siemens Magnetom Trio scanner (Tim Trio, Siemens, Erlangen, Germany) equipped with a standard head coil at Beijing Normal University Brain Imaging Center. Structural magnetic resonance imaging (MRI) data were acquired with the T1-weighted MPRAGE pulse sequence (TE = 3.75 milliseconds, TR = 2530 milliseconds, flip angle = 7°; FOV = 256 × 256 mm^2, voxel size = 1 × 1 × 1.33 mm^3, number of partitions = 128).

MRI data were analyzed automatically with atlas-based FreeSurfer segmentation software (http://surfer.nmr.mgh.harvard.edu, version 4.5.0) to extract volumetric measures of regions of interest (Fischl *et al*. 2002). Volumes of bilateral hippocampi were generated according to the standard FreeSurfer segmentation and parcellation procedures, relying upon variations in voxel signal intensities, probabilistic atlas location and local spatial relationships between the structures (Fischl *et al*. 2002). Intracranial volume (ICV), including brain tissues and other biological materials such as meninges and cerebrospinal fluid, was taken from the standard output of FreeSurfer analysis as well. Quality control of scan images and segmentation was assured by visual inspection of the whole cortex of each subject, and any inaccuracies in Talairach transformation, skull stripping and segmentation were manually corrected, and re-inspected. Manual corrections included editing gray matter surface for most subjects to exclude membrane tissues, editing white matter surface to add control points in FreeSurfer and obtaining good segmentation of the hippocampus.

Statistical analysis

Linear regression models were used to detect the associations between rs4680 genotype and WM performance and bilateral hippocampal volumes. The 443 subjects were separated into the Val/Val group ($n = 248$, with135 females, coded as 1), the Val/Met group ($n = 168$, with 102 females, coded as 2) and the Met/Met group ($n = 27$, with 17 females, coded as 3). As head sizes vary significantly between individuals, ICV and gender were included as covariates of no interest as well. In addition, gender-by-genotype interaction was also included to detect gender differences in genetic effects. Because of the small sample size of the Met homozygotes, we also reanalyzed the data by combining the heterozygotes and

Table 1: Demographic statistics for different genotypes

Variables	Val/Val	Val/Met	Met/Met	F or χ^2	P
Subjects with data on the WM task ($N = 443$)					
Group size	248	168	27		
Gender (M/F)	113/135	66/102	10/17	$\chi^2 = 1.99$	0.37
Age (mean ± SD in year)	20.45 ± 0.86	20.32 ± 0.86	20.47 ± 1.00	$F = 1.13$	0.32
Handedness (% of right hand)	93.55	92.86	92.59	$F = 0.03$	0.97
Education (mean in year)	14.5	14.5	14.5	$F = 0.00$	1.00
Subjects with data from MRI 3D T1-image ($N = 320$)					
Group size	173	128	19		
Gender (M/F)	81/92	48/80	5/14	$\chi^2 = 4.64$	0.10
Age (mean ± SD in year)	20.46 ± 0.89	20.34 ± 0.89	20.56 ± 0.92	$F = 0.83$	0.44
Handedness (% of right hand)	97.11	97.65	100	$F = 0.33$	0.72
Education (mean in year)	14.5	14.5	14.5	$F = 0.00$	1.00

M/F, male/female.

Met homozygotes into the Met carriers group. Statistical analysis was carried out in SPSS16.0 for Windows.

Results

Demographic statistics

The three genotype groups did not differ in any of the four demographic variables (age, gender, years of education and handedness, see Table 1).

Working memory performance

Working memory performance was computed through a principle component analysis based on the three WM subtasks (Kaiser-Meyer-Olkin measure of sampling adequacy: 0.627; Bartlett's test of sphericity: χ^2 (df = 3) = 108.24; $P < 0{\cdot}001$). The first factor explained 53.39% of the total variance, and the z-score of each WM subtask accuracy loaded almost equally on the factor: 0.71 for semantic WM, 0.74 for phonological WM and 0.74 for morphological WM. No significant gender difference was found for WM performance: mean and SD were −0.04 ± 0.98 for males and 0.03 ± 1.02 for females, F (*1, 441*) = 0.648, $P = 0.421$.

Working memory and hippocampal volume

The relationships between WM and bilateral hippocampal volumes were examined by partial correlation analysis controlling for the effects of gender and ICV. The partial correlation coefficient was not significant for either the left hemisphere [r (316) = 0.08, $P = 0.153$] or the right hemisphere [r (316) = 0.101, $P = 0.071$].

Gene–behavior association

Regression analysis with rs4680 genotype as the independent variable and gender as the covariate revealed a significant genotype difference in WM performance (Table 2). Gender was not a significant covariate, $\beta = 0.045$, $t = 0.958$, $P = 0.338$. *COMT*'s effect was significant, $\beta = -0.110$, $t = -2.315$, $P = 0.021$, with the number of Met allele negatively associated with WM performance: the Val/Val group showed the best WM performance, the Met/Met group the worst performance and the heterozygotes in-between performance (Fig. 1). To examine whether *COMT* showed a sexual dimorphic effect, gender-by-genotype interaction was also added and it was not significant, $\beta = 0.054$, $t = 0.265$, $P = 0.791$. Because of the small sample size of the Met/Met group, we also reanalyzed the data by combining this group with the heterozygotes to form the Met carriers group. In this way, the genetic effect of *COMT* on WM was also significant, $\beta = -0.095$, $t = -1.990$, $P = 0.047$.

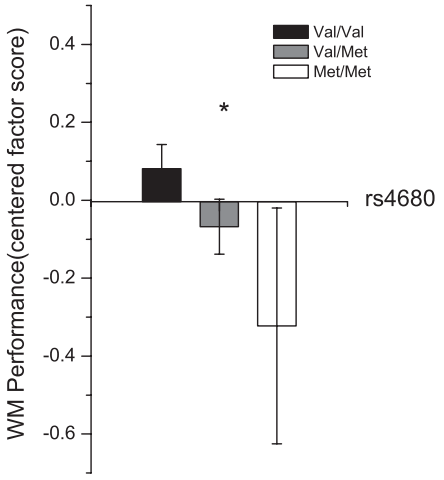

Figure 1: WM factor scores of the three genotypes. The Val/Val individuals ($N = 248$, with 113 males) scored significantly higher than the Met/Val group ($N = 168$, with 66 males) and the Met/Met group ($N = 27$, with 10 males) scored lowest on the WM tasks (factor scores, mean ± SE). Error bar indicates the standard error of the mean. *P value of rs4680 as a regressor less than 0.05.

Table 2: Regression models

Regressor	ICV			Gender			*COMT* rs4680			Model summary			
	β	*T*	*P*	*β*	*T*	*P*	*β*	*T*	*P*	df1	df2	*F*	*P*
WM performance				0.045	0.958	0.338	−0.110	−2.315	0.021*	2	440	3.006	0.050^
Left HPC volume	0.426	6.758	<0.001***	0.001	0.022	0.982	−0.099	−1.949	0.052^	3	316	26.219	<0.001***
Right HPC volume	0.425	6.875	<0.001***	−0.038	−0.611	0.542	−0.118	−2.367	0.019*	3	316	31.018	<0.001***

HPC, hippocampus; WM, working memory; ICV, intracranial volume.
^Marginal significance.
$P < 0.05$, ***$P < 0.001$.

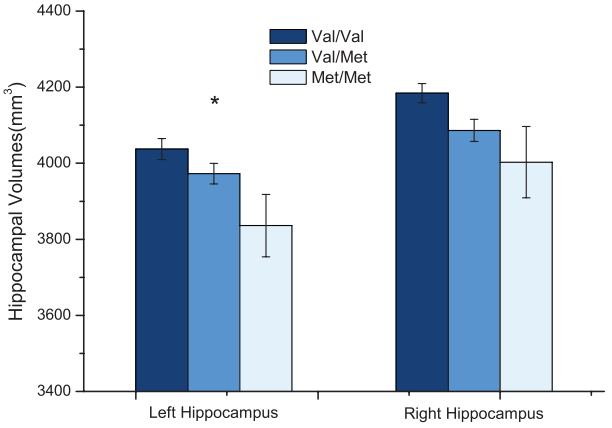

Figure 2: Bilateral hippocampal volumes (mean ± SE) of the Val/Val (*N* = 173, with 81 males), Val/Met (*N* = 128, with 48 males) and Met/Met (*N* = 19, with 5 males) groups. Error bar indicates the standard error of the mean. **P* value of rs4680 as a regressor less than 0.05.

Gene–brain association

Regression analyses showed that, after controlling for gender and ICV, the dose effect of *COMT* rs4680 polymorphism on right hippocampal volume was significant ($\beta = -0.118$, $t = -2.367$, $P = 0.019$, Val/Val > Val/Met > Met/Met), and was marginally significant on left hippocampal volume, $\beta = -0.099$, $t = -1.949$, $P = 0.052$ (see Table 2; Fig. 2). The gender-by-genotype interaction was not significant for either the left ($\beta = -0.135$, $t = -0.582$, $P = 0.561$) or the right hippocampus ($\beta = -0.223$, $t = -0.983$, $P = 0.326$). Again because of the small sample size of the Met/Met group, we also reanalyzed the data by combining this group with the heterozygotes to form the Met carriers group. Results showed that the genetic effect was significant for the right hippocampal volume ($\beta = -0.117$, $t = -2.352$, $P = 0.019$), but not significant for the left hippocampal volume ($\beta = -0.082$, $t = -1.606$, $P = 0.109$). Finally, to examine whether *COMT* might have a more generalized effect on the whole brain, we analyzed its association with ICV. Regression results (with gender included as a control variable) showed that ICV did not differ by *COMT* rs4680 genotype ($\beta = -0.036$, $t = -0.795$, $P = 0.427$).

Discussion

Working memory has been found to show considerable heritability (Ando *et al*. 2001), indicating its substantial genetic basis. Previous studies have reported the contributions of dopamine-related genes to WM (Barnett *et al*. 2008; Bertolino *et al*. 2006; Li *et al*. 2011; Markett *et al*. 2010; Parasuraman *et al*. 2005; Wilkosc *et al*. 2010). The *COMT* val158met polymorphism (i.e. rs4680) regulates the activity of COMT enzyme directly in the form of dose effect of gene expression: the number of Val allele is positively associated with activity of COMT enzyme (Syvanen *et al*. 1997).

This study reported significant associations of rs4680 polymorphism with WM performance and right hippocampal volume (and a marginal association with left hippocampal volume). The number of Val alleles was positively associated with WM, namely, Val homozygotes performed better than heterozygotes, followed by Met homozygotes. Further two-group (Val homozygotes vs. Met carriers) analysis showed that participants with the Val allele (high activity of COMT function) in our Chinese sample performed better on the two-back WM task than the Met allele carriers. These results are in clear contrast with previous reports based on Caucasian samples (Aguilera *et al*. 2008; Bruder *et al*. 2005; Farrell *et al*. 2012; Kennedy *et al*. 2011), but are consistent with previous studies of Asian samples using tasks related to WM (Cheon *et al*. 2008; Ma *et al*. 2007; Qian *et al*. 2009; Tai & Wu 2002; Wu *et al*. 2001; Yeh *et al*. 2009; Zhang *et al*. 2007). Similarly, our finding that the Val allele rather than the Met allele was associated with larger hippocampi also contradicted the finding from studies of Caucasians (Cerasa *et al*. 2008; Honea *et al*. 2009). No such study has been conducted with Asian samples. Taken together, these results suggest the existence of a systematic ethnic difference in the role of *COMT* rs4680 in WM, which may have been due to ethnic differences in *COMT*'s effect on WM-related brain structure. It is worth noting that, the effect size of *COMT* appeared to be larger on brain structure than on WM. This might suggest a closer connection between genes and the brain than between genes and behavior. Alternatively, it may have been due to unsatisfactory measurement of behaviors than that of brain structure. Perhaps hippocampal volume is a reliable endophenotype of WM. Finally, it should be mentioned that *COMT*'s effect on brain structure may be direct or indirect. As mentioned earlier, *COMT* directly modulates

dopamine levels in the hippocampus. Indirectly, dopamine is associated with several neurotrophic factors including BDNF (brain-derived neurotrophic factor) (Kuppers & Beyer 2001), which promotes the development of cerebral cortex (e.g. enlarging the brain area and increasing the cortical thickness) (Ho *et al*. 2007).

Several factors need to be considered when discussing possible explanations of ethnic differences in genetic effects. First, allele frequencies vary greatly across ethnic populations. The frequency of low activity allele (Met) of rs4680 in Caucasians is about 0.5: for example, 0.50 in a study by Kunuqi *et al*. (1997), 0.42 in Cerasa's study (Cerasa *et al*. 2008) and 0.48 in Utah residents with Northern and Western European ancestry from the CEPH (Centre d'Etude du Polymorphisme Humain) collection of the HapMap group. In contrast, the Met allele's frequency is much lower in Asian populations: 0.29 in a Japanese sample (Kunugi *et al*. 1997), 0.25 in our sample and 0.29 for Han Chinese in Beijing and 0.26 for Han Chinese in Denver, Colorado, in the HapMap data.

The most likely explanation of population-specific genetic effects is gene–gene interaction. A number of genes are involved in the dopamine system and they may interact with the *COMT* gene. For example, there is evidence that Monoamine oxidase A (MAOA) pathway might compensate for blockade of COMT pathway of monoamine catabolism (Eisenhofer & Finberg 1994). *MAOA* also varies greatly in allele frequencies across ethnic groups. The same is true for other enzymes such as tyrosine hydroxylase, dopa decarboxylase and dopamine transporter. Future research needs to explore the gene–gene interactions and to see whether they would explain ethnic differences in genetic effects (Munafo *et al*. 2008).

In summary, our results indicate that *COMT* val158met polymorphism was significantly associated with WM performance and hippocampal volume in a Chinese sample. Direction of the genetic effect was opposite of that found in Caucasian samples, suggesting ethnic differences in *COMT*–hippocampus–WM association.

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