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The *NTSR1* gene modulates the association between hippocampal structure and working memory performance

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ABSTRACT

The genetic and neural basis of working memory (WM) has been extensively studied. Many dopamine (DA) related genes, including the *NTSR1* gene (a DA modulator gene), have been reported to be associated with WM performance. The NTSR1 protein is predominantly expressed in the cerebral cortex and the hippocampus, the latter of which is closely involved in WM processing based on both lesion and fMRI studies. Thus far, however, no study has examined the joint effects of *NTSR1* gene polymorphism and hippocampal morphology on WM performance.

Participants of the current study were 330 healthy Chinese college students. WM performance was measured with a 2-back WM paradigm. Structural MRI data were acquired and then analyzed using an automated procedure with atlas-based FreeSurfer segmentation software (v 4.5.0) package. Linear regression analyses were conducted with a *NTSR1* C/T polymorphism which was previously reported to be associated with WM (rs4334545), hippocampal volume, and their interaction as predictors of WM performance, with gender and intracranial volume (ICV) as covariates. Results showed a significant interaction between *NTSR1* genotype and hippocampal volume ($p<.05$ for both the left and right hippocampi). Further analysis showed that the correlation between hippocampal volume and WM scores was significant for carriers of the *NTSR1* T-allele ($p<.05$ for both hippocampi), but not for CC homozygotes. These results indicate that the association between hippocampal structure and WM performance was modulated by variation in the *NTSR1* gene, and suggest that further studies of brain–behavior associations should take genetic background information into account.

Introduction

Working memory (WM) refers to the brain function of actively holding information in the mind for complex tasks such as reasoning, comprehension and learning (Baddeley, 1992). WM is involved in the integration and manipulation of information. Recently, an increasing number of studies have explored the genetic basis (Ando et al., 2001; Kremen et al., 2007; Wright et al., 2001) and neural basis (Ranganath, 2006; Ranganath and D'Esposito, 2005) of WM.

It is well known that dopamine (DA) neurotransmission plays a pivotal role in WM (Castner et al., 2000; McNab et al., 2009). Pharmacological studies on both animals (Vijayraghavan et al., 2007) and humans (Kimberg and D'Esposito, 2003) have indicated that dopamine (DA) in the brain modulates WM. Molecular genetics studies have widely reported genetic effects of DA-related genes on WM, and neuronal networks subserving WM. Although these studies covered genes for DA receptor (e.g. *DRD4*), DA degradation (e.g. *COMT*), and DA transporter (e.g. *SLC6A3*) (Bertolino et al., 2006; Froehlich et al., 2007), few studies have focused on the genes that modulate DA. Recently, our group found that the neurotensin receptor 1 (*NTSR1*) gene, a gene involved in DA modulation, was associated with WM, although the underlying biochemical and neuronal mechanisms are not clear (Li et al., 2011).

In terms of the neural structure subserving WM, a number of studies have shown the involvement of the hippocampus. For example, electrophysiological studies with rodents have demonstrated that WM performance is correlated with both the magnitude of long-term depression in the hippocampus (Nakao et al., 2002) and the theta rhythm in the hippocampus (Holscher et al., 2005). A rodent pharmacological study showed that WM impairment was accompanied by the deposition of Amyloid beta-peptide (Abeta) in the hippocampus (Leighty et al., 2004). Moreover, WM damage induced by Abeta administration was correlated with neuronal cell loss in the

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hippocampus (Stepanichev et al., 2004). Lesion studies on humans also showed that patients with medial temporal lobe damages had WM impairment (Ezzyat and Olson, 2008; Olson et al., 2006a,b). Functional MRI studies confirmed that the hippocampus was recruited for WM processing (Davachi and Wagner, 2002; Faraco et al., 2010; Karlsgodt et al., 2005; Toepper et al., 2010), and that hippocampal activation was significantly correlated with WM performance (Berent-Spillson et al., 2010; McGettigan et al., 2011) and/or WM response time (Bokde et al., 2010). Finally, a neural network study reported that the hippocampus was included in a network underlying the maintenance of WM (Gazzaley et al., 2004), suggesting a functional contribution of the hippocampus to WM.

Although there is overwhelming evidence for a role of the hippocampus in WM, some studies have reported negative results. For instance, some studies failed to replicate a WM decline after hippocampal lesion (Cowey and Green, 1996; Jeneson et al., 2010) or after pathological changes in the hippocampus (Baddeley et al., 2010). Investigations of the correlations between hippocampal volume and WM have also yielded inconsistent results. One longitudinal study suggested that decreasing hippocampal volume was associated with a decline in WM (Storandt et al., 2009), but another study did not find an association between hippocampal volume and WM (Piras et al., 2010). The cause for such discrepant results has not been resolved. One possibility is that the association between the hippocampus and WM may be modulated by other factors, such as genetic factors.

Thus far, however, almost all studies have examined separately the contributions of the DA-related genetic factors and those of hippocampus-related neural factors to WM. There is some evidence that these factors are inter-connected. Studies with rats showed that an infusion of a DA receptor D2 (DRD2) agonist into the hippocampus led to a significant improvement in WM accuracy, whereas an infusion of a DRD2 antagonist into the hippocampus led to a significant WM deficit (Wilkerson and Levin, 1999). Studies with humans also showed less DRD2 availability in the hippocampus during a working memory task, suggesting that dopamine release therein might play a specific role in WM (Aalto et al., 2005). A recent imaging genetics study found that the catechol-O-methyltransferase (*COMT*) gene, a DA-related gene, was correlated with activations in the hippocampus elicited by a working memory task (Bertolino et al., 2008). In sum, there appears to be a hippocampal dopaminergic network that is functionally involved in WM processing.

No study thus far has examined the joint contributions of DA genes and the structure of the hippocampus to WM. In the current study, we focused on a polymorphism in the *NTSR1* gene which was found to be strongly linked to WM in a recent study (Li et al., 2011). Human neurotensin receptor 1(NTSR1, coded by the human gene *NTSR1*, on chromosome 20q13) is a high affinity neurotensin (NT) receptor with 7 transmembrane spanning regions and high homology to other G-protein-coupled receptors (Laurent et al., 1994; Le et al., 1997). NT is a well-known neuromodulator, particularly of DA transmission in the brain. NT, acting on NTSR1, reduces the physiological function of the DA receptor (Jomphe et al., 2006) and in turn modulates DA-dependent behaviors. In addition to our study (Li et al., 2011) linking the *NTSR1* gene to WM, a prior rodent study also showed that administration of a NTSR1 antagonist impairs WM in a learning task (Tirado-Santiago et al., 2006). A potential link among the hippocampus, the *NTSR1* gene, and WM is further supported by the following evidence: the high distribution of NT and NT receptors in hippocampus regions (Kohler et al., 1987; Quirion et al., 1987; Roberts et al., 1984), the high expression of NTSR1 mRNA (Lepee-Lorgeoux et al., 1999) and protein (Boudin et al., 2000) in the hippocampus, and the effect of NT on the firing of hippocampus CA1 interneurons (Li et al., 2008) and on neurons that project to the hippocampus (Matthews, 1999).

In sum, previous research has linked the *NTSR1* gene and the hippocampus separately to WM performance, and has found a close connection between the *NTSR1* gene and the hippocampus (i.e., the distribution and predominant expression of NTSR1 protein in the hippocampus). However, no study has combined the genetic and neural factors to investigate how they may interact to affect WM. It is plausible that some of the inconsistent findings in the literature could have been due to a lack of attention to such potential interactive effects. The present study was designed to examine the effects of a *NTSR1* gene polymorphism and hippocampal morphology on WM performance in a large sample of 330 Han Chinese adults.

Materials and methods

Participants

As part of a larger study, genetic and behavioral data were available for 460 healthy undergraduate students from Beijing Normal University (Li et al., 2011), but relevant structural imaging data were available for only 330 (190 females) of them. Data from these 330 subjects were used in the current study. Age for the subgroup ranged from 18 to 23 years, with a mean of 20.4 years, SD = 0.89. All participants were Han Chinese with normal or corrected-to-normal vision. This study was approved by the IRB of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University, China. Written informed consent was obtained from each participant.

Working memory tasks

WM was assessed with a 2-back WM paradigm as described previously (Li et al., 2011). Briefly, participants viewed a series of characters that were presented sequentially, and performed three continuous judgment tasks: semantic judgment (whether the Chinese character on the screen was from the same semantic category as the character presented two characters earlier), phonological judgment (whether the current Chinese character rhymed with the one shown two characters earlier), and morphemic judgment (whether the current Tibetan letter was the same as the one presented two letters earlier). Participants did not know Tibetan letters. Each judgment task consisted of four blocks (10 trials each). Before the judgment tasks, participants had a practice block (judging small circles and squares), in which they had to pass 70% of the trials before they could take the formal tests. The average score (accuracy) of the three WM tasks was used as the index of working memory in the current study.

Genotyping

Genotyping was conducted as described previously (Li et al., 2011). Briefly, a 4 ml venous blood sample was collected from each participant. After blood samples were collected, genomic DNA was extracted according to standard methods. All samples were genotyped using the Illumina GoldenGate Genotyping protocol (see www.southgene.com.cn for details). Sixty genes (384 SNPs) involved in neurotransmitter systems were typed in this project. For each gene, to sample the greatest genetic diversity using the minimum set of SNPs through linkage disequilibrium (LD), several tag SNPs were selected based on the HapMap data (www.hapmap.org [phase3]) (Frazer et al., 2007). Tag SNPs were selected based on the Phase 3 criteria of $r^2 > 0.8$ with major haplotype blocks represented by at least one SNP. For this study, five tag SNPs in the *NTSR1* gene were selected: rs2427399, rs6062460, rs4334545, rs6090453 and rs6089784 (Table 1). In the current study, all five *NTSR1* SNPs passed the criteria of a call rate of >90%, Minor Allele Frequency (MAF) of >0.05, and Hardy–Weinberg equilibrium (HWE) of $p > 0.05$. The location of these SNPs in the *NTSR1* gene and LD structure in our Han Chinese sample (based on Haploview [38]) are shown in Fig. 1.

Table 1
Information on five SNPs in the *NTSR1* gene and their associations with WM performance (adapted from Li et al., 2011 to include individuals used in the current study).

SNP	Position on chr 20	Genotype	Counts (330)	Frequency	WM performance	$F(2,324)$	p (uncorrected)
rs2427399	60801890	GG	191	0.579	0.86(0.06)	0.722	0.49
		AG	122	0.370	0.85(0.06)		
		AA	17	0.052	0.85(0.07)		
rs6062460	60820535	CC	294	0.891	0.86(0.07)	0.42	0.66
		CT	35	0.106	0.87(0.04)		
		TT	1	0.003	0.85		
rs4334545	60823622	CC	189	0.573	0.87(0.58)	5.93	2.97×10^{-3}
		CT	118	0.358	0.85(0.67)		
		TT	23	0.070	0.83(0.73)		
rs6090453	60825807	GG	160	0.486	0.87(0.06)	4.55 ($F(2,323)$)	0.01
		CG	140	0.426	0.85(0.06)		
		CC	29	0.088	0.84(0.07)		
rs6089784	60870007	CC	197	0.599	0.86(0.06)	0.15 ($F(2,323)$)	0.86
		CT	114	0.347	0.85(0.06)		
		TT	18	0.055	0.86(0.08)		

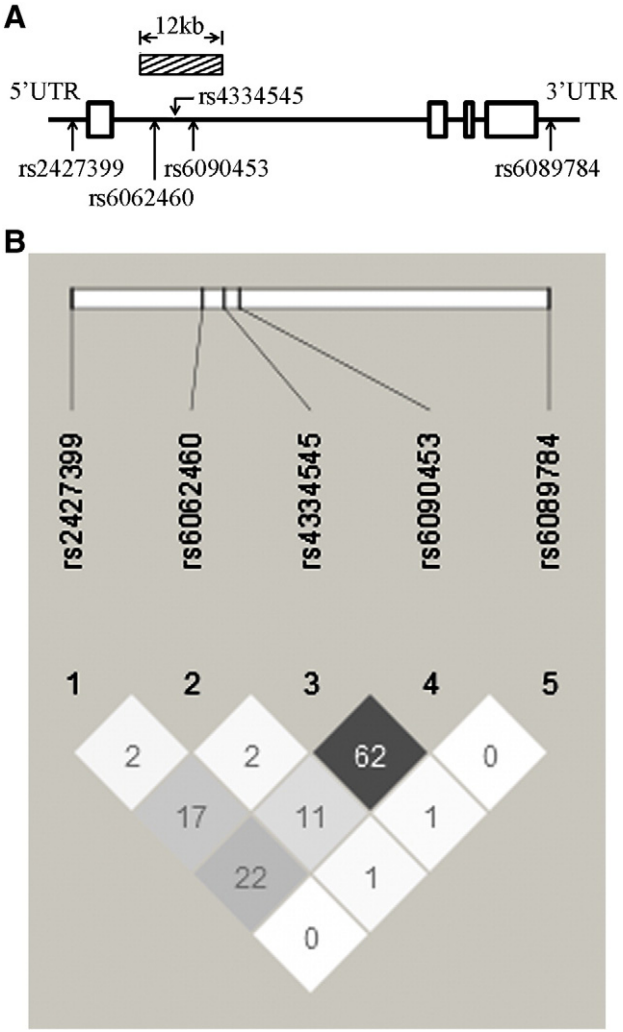

Fig. 1. Schematic representation of the *NTSR1* gene and linkage disequilibrium map of tagSNPs. (A) Schematic representation of the 53,935 bp *NTSR1* gene, and the relative positions of the 5 tagSNPs selected based on HapMap data (Li et al., 2011). The *NTSR1* gene is comprised of 4 exons (represented by boxes) and 3 introns. A 12 kb haplotype tagged by SNPs rs6062460, rs4334545 and rs6090453 is indicated by a bar over the schematic, as determined by imputation analysis (Li et al., 2011). (B) Linkage disequilibrium map based on data from the 330 subjects in the present sample. Pairwise linkage disequilibrium values (r^2 values) are indicated. White, shades of gray, and black squares range from low LD ($r^2=0$), through intermediate LD ($0<r^2<1$), to strong LD ($r^2=1$), respectively.

MRI data acquisition

MRI scans were performed in a 3.0 T Siemens Magnetom Trio scanner equipped with a standard head coil at Beijing Normal University Brain Imaging Center. Structural MRI data were acquired with the T1-weighted MPRAGE pulse sequence (TE = 3.75 ms, TR = 2,530 ms, TI = 1,000 ms, flip angle = 7°; FOV = 256 mm × 256 mm, voxel size = $1\times1\times1.33$ mm^3, number of partitions = 128).

Data analysis

MR image processing

MRI data were analyzed with atlas-based FreeSurfer segmentation software (version. 4.5.0) package (http://surfer.nmr.mgh.harvard.edu/) to extract volumetric measures of regions of interest (Fischl et al., 2002). Volumes of bilateral hippocampi are a standard output of the Freesurfer segmentation procedures (see Fig. 2), based on variations in voxel signal intensities, probabilistic atlas location, and local spatial relationships between the structures (Fischl et al., 2002). Intracranial volume (ICV), including brain tissue and other biological materials such as meninges and cerebrospinal fluid, was taken from the standard output of FreeSurfer analysis.

Quality control of image and segmentation was assured by visual inspection of the whole cortex in each subject. Any inaccuracies in Talairach-transformation, skull stripping, and segmentation were manually corrected, and then re-inspected.

Statistical model

The mean accuracy of all 330 subjects on the WM task was 0.85 (SD = 0.07). Three subjects were deleted because their accuracy rates were more than three standard deviations lower than the mean (i.e., 0.49, 0.50, and 0.63). The final sample included 327 subjects (188 females).

In a preliminary analysis, five ANOVAs were conducted separately for each SNP to test the main effect of each SNP on WM performance. Results showed that two of the five SNPs in the *NTSR1* gene, rs4334545 ($F(2,324)=5.93$, $p=2.97\times10^{-3}$) and rs6090453 ($F(2,323)=4.56$, $p=0.011$)), were significantly associated with working memory performance (see Table 1). Only rs4334545 survived Bonferroni corrections for multiple comparisons (significance level was set as $p<0.01$ (0.05/5[SNP variants]), so this SNP was used for the following statistics.

The aim of the present study was to test the joint effect of the structure of the hippocampus and *NTSR1* genotype on WM performance. Therefore, linear regression models were used, with hippocampal volume (bilateral hippocampi separately), rs4334545 genotype (CC = 1, CT/TT = 0), their interaction (the product of standardized

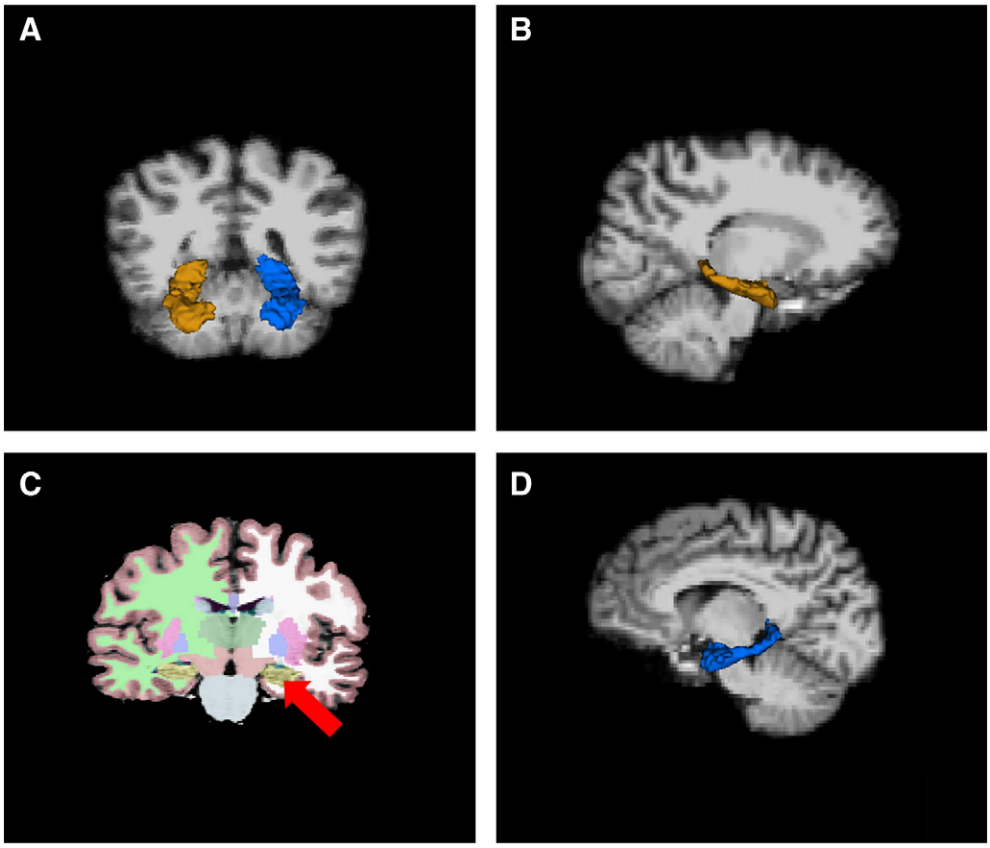

Fig. 2. Freesurfer subcortical segmentation of the hippocampus. Models are displayed on one randomly chosen male subject. Images A, B and D were constructed using Slicer 3.4 (www.slicer.org), and image C was generated using tkmedit (http://surfer.nmr.mgh.harvard.edu/).

(z) scores of hippocampal volume and rs4334545 genotype) as predictors for WM performance. Because head size varies significantly across individuals and between the sexes, the intracranial volume (ICV) and gender were also included as covariates of no-interest.

To further examine the associations between hippocampal volume and WM for subjects with different genotypes, subjects were separated into the CC group ($n = 188$, of whom 112 were females) and the T carrier group ($n = 139$, with 76 females). For each group, WM task scores were correlated with hippocampal morphometrics, again with gender and ICV as covariates. All statistical analyses were carried out in SPSS15.0 for Windows.

Results

Three hundred twenty-seven healthy Chinese college students were genotyped at the *NTSR1* gene and had valid data from the WM tasks and the structural MRI. The mean accuracy of the 327 subjects on the WM task was 0.86(SD = 0.06). Males and females had similar mean accuracy, 0.85(SD = 0.06) and 0.86(SD = 0.07), respectively, $F(1,325) = 1.91$, $p = 0.17$. No significant differences were found among genotypes in age, gender, educational level, handedness, and hippocampal volume (all $p > 0.05$).

The mean measured volume of the left hippocampus was 4138.6 ± 349.0 mm^3 for males, and 3963.6 ± 293.6 mm^3 for females. The mean measured volume for the right hippocampus was 4307.4 ± 346.1 mm^3 for males, and 4078.4 ± 306.5 mm^3 for females. Females had significantly smaller bilateral hippocampal volumes than did males (for the left hemisphere, $F(1,325) = 24.16$, $p = 1.41 \times 10^{-6}$; for the right hemisphere, $F(1,325) = 39.97$, $p = 8.52 \times 10^{-10}$). Therefore, gender was used as a covariate in the subsequent analyses.

Two linear regression analyses (one using the left hippocampal volume and the other using the right hippocampal volume) were conducted for WM performance with the *NTSR1* rs4334545 genotype, lateral hippocampal volume, and their interaction as predictors, with gender and ICV as covariates. Results showed, in both regression analyses, that there were significant main effects for both *NTSR1* genotype and hippocampal volume, and a significant interaction between the two factors (see Table 2).

We further examined the associations between hippocampal volume and WM for two *NTRS1* rs4334545 genotypes separately (189 CC homozygotes and 141 CT/TT individuals). Gender and ICV were again used as covariates. For the CC group, no significant main effects of hippocampal volume were found ($p = 0.56$ and 0.73 for the left and right hippocampus, respectively), but for the CT/TT group, significant positive correlations were found between hippocampal volume and WM performance (for the left hippocampus, $p = 0.020$; for the right hippocampus, $p = 4.11 \times 10^{-3}$) (see Fig. 3).

Table 2
Multiple regression models for left and right hemisphere.

Variables	Left hemisphere			Right hemisphere		
	β	t	p Value	β	t	p Value
rs4334545 genotype	0.16	3.02	2.7×10^{-3}	0.17	3.09	2.2×10^{-3}
Hippocampal volume	0.31	3.22	1.4×10^{-3}	0.34	3.80	1.7×10^{-4}
Interaction	−0.24	−2.60	0.01	−0.26	−3.10	2.1×10^{-3}

The effects of two covariates (gender and ICV) are not shown.

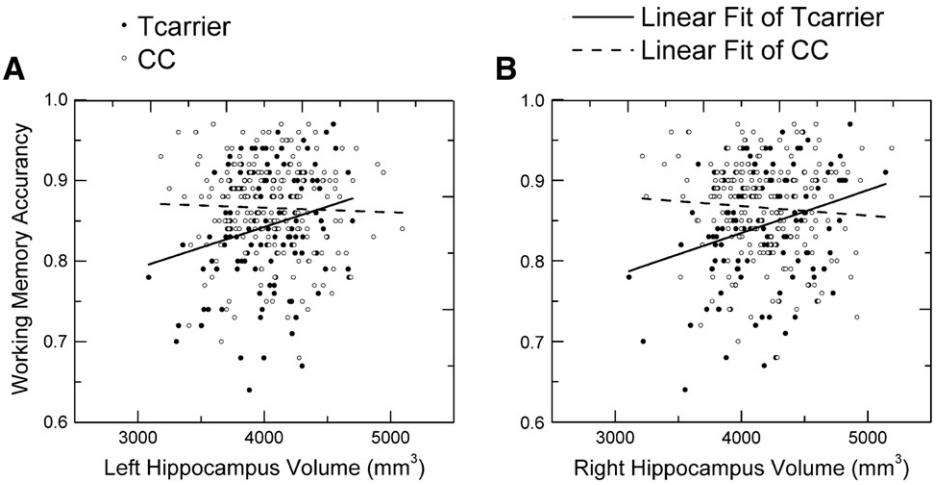

Fig. 3. Scatter plots and regression lines showing the relationship between hippocampal volume and working memory accuracy in rs4334554 T-allele carriers (filled circles, solid regression line) and CC homozygotes (open circles, dashed regression line).

Discussion

This current study was the first to investigate a specific genetic polymorphism that modulated the association between hippocampal structure and working memory. In the large Chinese adult sample, we found significant main effects of both the *NTSR1* gene polymorphism and hippocampal volume and their interaction on WM performance. Further analysis revealed that both left and right hippocampal volumes were positively correlated with WM performance in the CT/TT group, but not the CC group.

The main effects of the *NTSR1* gene and the hippocampus on WM are consistent with reports in the literature. The *NTSR1* gene encodes a high-affinity neurotensin receptor, NTSR1. In the central nervous system, NT and NTSR1 are highly expressed in dopaminergic neurons (Brouard et al., 1992; Studler et al., 1988), which allows functional interactions between the NT and the DA systems at the cellular level (Binder et al., 2001). For example, animal studies suggested that NT enhances DA neuron firing (Jomphe et al., 2006; St-Gelais et al., 2004) and extracellular release of DA (Petkova-Kirova et al., 2008). A recent study also showed reduced DA receptor mRNA expression in NTSR1 null mice (Liang et al., 2010). Rodent studies have further suggested that NT has a positive impact on learning and memory. For example, rats microinjected with NT showed enhanced spatial learning (Laszlo et al., 2010). NT analogs have also been shown to enhance working memory, memory consolidation, and associative learning (Azmi et al., 2006; Grimond-Billa et al., 2008; Ohinata et al., 2007), while infusion of a NTSR1 antagonist impairs working memory (Tirado-Santiago et al., 2006). In humans, a previous study showed an association between *NTSR1* gene polymorphisms and schizophrenia (Lee et al., 1999). This result indirectly supports a connection between the *NTSR1* gene and WM because impaired WM has been found to be an important endophenotype of schizophrenia (Glahn et al., 2003; Saperstein et al., 2006).

Several lines of evidence have shown an important role of the hippocampus in WM. For example, lesion studies showed that rats with complete or dorsal hippocampus lesions had impaired WM (Bannerman et al., 2002). In human patients, medial temporal lobe amnesia was linked to severely impaired WM at 8 s delays, suggesting that the hippocampus per se is critical for accurate conjunction WM (Olson et al., 2006b). Pharmacological studies with rats demonstrated that WM impairment was positively correlated with neuronal cell loss in the hippocampus after the injection of A-beta (Stepanichev et al., 2004). Finally, longitudinal cognitive decline in WM was associated with decreased hippocampus volume in an aging sample of humans (Storandt et al., 2009).

The relation between the hippocampus and WM, however, has not been all consistent. The conflicting results could have been due to differences in the experimental tasks used to measure WM, various components of WM examined, different locations and extent of lesion in the hippocampus, and different gender compositions of the samples (Bannerman et al., 2002; Mendez-Lopez et al., 2009). Our finding of the interaction between *NTSR1* gene variants and hippocampal volumes on WM scores provides a new possible reason for inconsistencies in previous studies, namely, the confounding effect of genetic background, such as *NTSR1* gene variants.

The observed interaction between the *NTSR1* gene and the hippocampus on WM performance can be interpreted in the context of the following evidence. First of all, previous twin studies indicated that the association between general intelligence and brain volume was mediated by genetic factors (Betjemann et al., 2010; Posthuma et al., 2002). Moreover, Li et al. (2009) reported that the association between white matter architecture in the hippocampus formation and intelligence quotient (IQ) was modulated by the *COMT* gene, which codes for a key enzyme responsible for inactivating released DA in the brain. These results are relevant to the current study because WM is considered a major component of general intelligence, and both the *COMT* gene and *NTSR1* gene play an important role in DA transmission. Since genetic factors can mediate the relations between brain volumes and intelligence (Posthuma et al., 2002), it is reasonable to expect that the relation between hippocampal volume and WM is mediated by genes. To our knowledge, the present study is the first to report a specific source of the genetic variation influencing the association between hippocampal volume and WM.

Second, there is anatomical and biochemical evidence for this interaction. Early studies reported moderate to high densities of NT and NT receptors distributed in the hippocampus regions in monkeys and humans (Kohler et al., 1987; Quirion et al., 1987). NT projections acted as a part of the septo-hippocampo-septal loop in regulating hippocampus activity (Morin and Beaudet, 1998). NT may in turn modulate hippocampus-dependent learning and memory processing, such as WM (Matthews, 1999) through the above-mentioned effect.

Finally, the DA–hippocampus–WM relationship has been widely reported in human and animal studies. For example, hippocampal DRD2 activity is positively related to WM performance (Wilkerson and Levin, 1999), whereas WM tasks reduced DRD2 availability in the hippocampus (Aalto et al., 2005). The present result extended such relationship to DA-modulating genes. It is inferred that these

gene variants' differential effects on WM performance may be caused by their differential anatomical expression and biochemical function in the hippocampus.

Why then was the association between hippocampal volume and WM significant in the *NTSR1* CT/TT group, but not the CC group? One explanation is that the CC genotype of rs4334545 in the *NTSR1* gene, in itself, has been shown to be associated with better WM performance than the CT/TT genotype (Li et al., 2011). It is possible, then, that many of the individuals with a CT/TT genotype cannot offset the disadvantageous effect of smaller hippocampal volumes on WM performance (Fig. 3). This, and other possible speculations need to be investigated in future research.

The current study had three main limitations. First, this was an association study. We did not directly investigate the biochemical effects of the rs4334545 (or adjacent) polymorphisms in the *NTSR1* gene. rs4334545 is located in the first intron of the 53,935 bp *NTSR1* gene, part of a 12 kb haplotype block (Fig. 1; Li et al., 2011). As such, it serves as a marker for a number of polymorphisms in the haplotype block. Any of these SNPs may or may not have functional consequences on the amount of NTSR1 protein synthesized. However, it is not uncommon that intron variants can regulate mRNA expression and splicing (Zhang et al., 2007), influence secondary mRNA structure (Nackley et al., 2006) and control transcription (Mizumoto et al., 1997). Therefore, it is possible that the intronic SNP rs4334545 or adjacent SNPs in the haplotype block may affect NTSR1 protein levels and/or function. Further, we do not know if the intronic SNP rs4334545 is the causative site of the association with WM because of LD in this region (Fig. 1). For example, an adjacent *NTSR1* SNP located 2,185 bp from rs4334545 (rs6090453) is in high LD and was also associated with WM in this and a prior study (Li et al., 2011; Fig. 1). Imputation analysis found a number of additional known SNPs in the haplotype block tagged by rs4334545 that are associated with WM (Li et al., 2011). While the initial tag SNPs were chosen from HapMap data to mark haplotypes blocks with the minimum number of SNPs, analysis of LD in our specific sample indicates that large portions of the *NTSR1* gene are likely not adequately "tagged" with these SNPs (Fig. 1). The SNPs used in this study will need further supplementation (Saccone et al., 2009) as additional SNPs are uncovered by DNA resequencing projects (The 1000 Genomes Project, 2010). Future studies need to explore the causative functional variants of the *NTSR1*gene, the physiological mechanisms involved in the *NTSR1* gene variants' impact on NTSR1 protein function, and the biochemical processes involved in these variants' modulation of associations between hippocampal volume and WM.

The second limitation is that only one ethnic group (i.e., Han Chinese college students) was included in the present study. While this homogeneity is usually considered an advantage for genetic studies, avoiding the possible problem of ethnic stratification, it also limits the generalizability of our results to other populations. Previous studies have demonstrated that gene–brain–behavior relationships can be modulated by gender (Nemoto et al., 2006), ethnicity and/or culture (Mizuno et al., 2006; Munafo et al., 2008), and age (Nemoto et al., 2006; Richter-Schmidinger et al., 2010). Further studies are needed to replicate our results in other populations.

Third, because this was a college sample, we used only self-report data to screen for neurological and psychiatric disorders. While this is a reasonable approach, given the stringent requirements of college admission, future research should employ an objective systematic tool to assess such disorders.

In summary, the present study described a significant interactive effect between a *NTSR1* gene polymorphism and hippocampal volume on WM performance. Further analysis showed that both right and left hippocampal volumes were positively correlated with WM performance in individuals with an rs4334545 T-allele (CT/ TT group), but not in the CC homozygote group. These results suggest that the association between hippocampal volume and WM performance is modulated by *NTSR1* gene variants. We suggest that further studies aimed at identifying brain–behavior associations should take genetic background information into account.

Acknowledgments

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