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Authors
Zhu, Bi
Chen, Chuansheng
Loftus, Elizabeth F
et al.

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True but not false memories are associated with the *HTR2A* gene

Bi Zhu [a], Chuansheng Chen [b], Elizabeth F. Loftus [b,*], Robert K. Moyzis [c], Qi Dong [a,*], Chongde Lin [a]

[a] State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China
[b] Department of Psychology and Social Behavior, University of California, Irvine, USA
[c] Department of Biological Chemistry and Institute of Genomics and Bioinformatics, University of California, Irvine, USA

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ABSTRACT

Previous research reported that serotonin receptor 2A gene (*HTR2A*) polymorphisms were associated with memory. However, it is unknown whether these genetic variants were associated with both true and false memories. The current study of 336 Han Chinese subjects tested 30 single nucleotide polymorphisms (SNPs) within the *HTR2A* gene for potential associations with true and false memories. False memories were assessed using the Deese–Roediger–McDermott (DRM) paradigm, in which people falsely remember semantically related (but unpresented) words. We found that 11 SNPs within the *HTR2A* gene were associated with true memory ($p = 0.000076$–0.043). The associations between true memory and seven adjacent SNPs (i.e., rs1923888, rs1745837, rs9567739, rs3742279, rs655888, rs655854, and rs2296972) were still significant after multiple testing corrections. Haplotype-based association analysis revealed that, true memory was positively associated with haplotype A-C-C-G-C-T-A for these seven adjacent SNPs ($p = 0.000075$), which was still significant after multiple testing correction. Only one SNP rs655854 was associated with false memory ($p = 0.023$), and it was not significant after multiple testing correction. This study replicates, in an Asian population, that genetic variation in *HTR2A* is associated with episodic memory, and also suggests that this association is restricted to true memory.

1. Introduction

Researchers who study human memory often distinguish memories of different types, such as semantic memory versus episodic memory, or short-term memory versus long-term memory. Within each type, there also are systematic individual differences in memory performance, some of which might be due to genetic factors. Previous twin and family studies have found the heritability of different forms of memory to be between 0.22 and 0.72 (Plomin, Owen, & McGuffin, 1994; Wilson et al., 2011). Several previous studies detected associations between memory and genetic variants using candidate-gene and genome-wide association approaches. These studies suggested that memory was associated with many genetic variants, such as *APOE*, *BDNF*, *SCN1A*, and *CTNNBL1* (Bondi et al., 1995; Egan et al., 2003; Papassotiropoulos et al., 2011, 2013).

Several studies have shown that variations in the serotonin receptor 2A (*HTR2A*) gene are associated with human memory performance (mainly measured by the verbal delayed episode memory task using semantically unrelated words as stimuli). Researchers reported that a single nucleotide polymorphism (SNP), rs6314 located in exon 3 of the *HTR2A* gene and associated with the intracellular signaling cascade of the receptor, was related to verbal memory performance in 349 healthy young Swedish adults (de Quervain et al., 2003). In a later study, researchers from the same lab expanded the subjects to 622 healthy Swedish subjects aged from 18 to 90 years and found that this SNP was related to memory only in young adults (Papassotiropoulos et al., 2005). In addition, another group of researchers replicated the association between this SNP and verbal delayed recall and recognition in 133 healthy German adults (Wagner, Schuhmacher, Schwab, Zobel, & Maier, 2008). The SNP rs6314 has also be referred to as H452Y. Based on this SNP, subjects could be divided into three categories, including His/His homozygotes, His/Tyr heterozygotes, and Tyr/Tyr homozygotes. All three studies mentioned above suggested that His/His homozygotes performed better than His/Tyr heterozygotes in a delayed verbal memory test (equal to or longer than 5 min after word presentation). A neuroimaging study also suggested

Abbreviations: SNP, single nucleotide polymorphism; DRM, Deese–Roediger–McDermott, HTR2A, serotonin receptor 2A; ApoE, apolipoprotein E; BDNF, brain-derived neurotrophic factor; SCN1A, sodium channel, voltage-gated, type I, alpha subunit; CTNNBL1, catenin, beta like 1; MAF, minor allele frequencies; LD, linkage disequilibrium; HWE, Hardy–Weinberg equilibrium; PET, positron emission tomography.

* Corresponding authors. Address: State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, 100875, China (Q. Dong), Department of Psychology and Social Behavior, University of California, Irvine, 2393 Social Ecology II, Irvine, CA 92697, USA (E.F. Loftus).

E-mail addresses: eloftus@uci.edu (E.F. Loftus), psydongqi@126.com (Q. Dong).

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that *HTR2A* Tyr carriers had reduced brain volume in the temporal lobes and hippocampus (Filippini et al., 2006). But this genotype did not affect performance on an immediate memory test, nor on measures of attention and executive function (Wagner et al., 2008).

Recently, studies also reported that several other SNPs within the *HTR2A* gene were also related to memory. Using the same group of subjects from the study of de Quervain et al. (2003), a fine-mapping at the *HTR2A* locus revealed the existence of two other SNPs (rs9526240 and rs9534496) located within intron 2 that were associated with memory performance independently of rs6314 (Sigmund, Vogler, Huynh, de Quervain, & Papassotiropoulos, 2008). Taken together, the above studies suggest that *HTR2A* plays an important role in memory.

However, all these previous studies used European samples, and the identified SNPs have different minor allele frequencies (MAF) in different ethnic populations based on the HapMap Data (www.hapmap.org [phase 3]). For example, MAF for SNPs rs6314, rs9526240, and rs9534496 were respectively 6%, 21%, and 22% in Europeans, but only 0.6%, 3%, and 2% in Chinese. It is unclear whether these SNPs would show the same associations with memory performance in Chinese and whether other SNPs within *HTR2A* would play a role in memory in Chinese subjects. Moreover, no previous study has examined the potential association of *HTR2A* and false memory.

Compared with the memory tests used in the previous association studies with the *HTR2A* gene, the Deese–Roediger–McDermott (DRM) test is also a delayed verbal memory test, but it measures both true and false memories using semantically related words as stimuli. True memory (or veridical memory) involves the accurate encoding, storage, and retrieval of information, whereas false memory refers to the memory distortion in which people develop recollections of things that were not experienced (Roediger & McDermott, 1995; Schacter & Loftus, 2013). Specifically, in the DRM test, subjects are presented with lists of words, and each list contains words that are semantically associated with a critical lure (but the lure is not presented in the studied word list). Five minutes after word presentation, subjects are asked to recall or recognize the list of words that they just learned. Subjects frequently report having seen the critical lure in the list of words studied. For example, after viewing a list that includes words like "tired", "rest", "awake", "nap", and "yawn", many subjects later incorrectly remember seeing the critical lure "sleep". Put another way, many subjects recall or recognize that the critical lure was presented as part of the word list. To explain this finding, researchers have suggested that the critical lure shares semantic features with the studied words and these common features make the critical lure seem familiar or make subjects believe that they just saw the lure (Gallo, 2010).

True and false memories are expressed as the endorsement rates for studied words and critical lures separately. False memory in the DRM test mainly reflects semantic memory (because there is no contextual information available for unpresented words; and it is based on pre-existing knowledge of the shared semantic features among the studied words), whereas true memory in the DRM test reflects both semantic and episodic memory (because not only it is specific to the experimental context, but also knowing the theme of the word list allows accurate retrieval of studied words) (Payne et al., 2009). Consistent with the general findings based on recent neuroimaging studies, true memory involves more episodic memory components (i.e., retrieval with greater perceptual and contextual-specific details of the events) than false memory (Schacter & Loftus, 2013). As addressed earlier, previous studies suggested that the *HTR2A* gene was associated with episodic memory (Wagner et al., 2008). Thus, we hypothesized that true memory would be more likely to be associated with the *HTR2A* gene than false memory in the DRM test.

To date, no study has examined possible associations between *HTR2A* genetic variants and both true and false memories. Given that the previously reported *HTR2A* SNPs have different MAF in different ethnic populations, it is unclear if other SNPs within the *HTR2A* gene may be associated with memory performance. In the current study, we analyzed 30 single nucleotide polymorphisms (SNPs) selected to cover the whole *HTR2A* gene, in order to explore whether the *HTR2A* gene is associated with true and false memories in Chinese subjects.

2. Material and methods

2.1. Participants

336 healthy undergraduates were recruited (mean age = 20.41 - years, *SD* = 0.89, range 18–22 years old; 58% female) from Beijing Normal University (BNU) in China. All subjects were Han Chinese with no neurological or psychiatric history based on their self-report. Individuals in this sample were all unrelated to one another. They all signed written informed consent. This study was approved by the Institutional Review Board (IRB) of BNU, China.

2.2. Genotyping

A 4 ml venous blood sample was collected from each subject. Genomic DNA was extracted according to the standard method within 2 weeks after the blood sample was collected. These subjects were genotyped using the standard Affymetrix genotyping protocol (Affymetrix, Inc.). The *HTR2A* gene contains 3 exons and 2 introns. As described in Table S1, thirty SNPs within the *HTR2A* gene were selected to cover most of the linkage disequilibrium (LD) blocks in *HTR2A*, as defined for the samples of Chinese included in the HapMap Project (http://www.hapmap.org [phase 3]). All 30 SNPs met the following criteria: MAF > 0.1, Hardy–Weinberg equilibrium (HWE) $p > 0.0001$, and genotype call rate >0.95. The allele frequencies of genotyped SNPs in our sample were very similar to those of the Chinese in the HapMap dataset (see Table S2). Figs. S1–S5 presents the LD plots of the *HTR2A* gene in different populations.

2.3. Behavioral assessment

All subjects completed the DRM memory test. Ten word lists were used and they were from the Chinese DRM test adapted by Zhou, Yang, and Qin (2007) based on the original word lists used in previous research (Roediger & McDermott, 1995). Each list contained 12 words that are semantically associated to a critical lure. For example, one studied list includes words such as "sugar", "honey", "candy", "cake", and "soda", while the unstudied critical lure was "sweet". Each word was presented for 2000 ms and the inter-word intervals were 500 ms. After working on a filler task (the Iowa Gambling Task) for about 5 min, subjects took a recognition test. They made a Yes (studied) or No (unstudied) judgment for 60 words (30 studied words, 10 critical lures, and 20 unstudied unrelated words). The endorsement rates for the studied words, critical lures, and unstudied unrelated represented the "true memory", "false memory", and "foil", respectively. In addition, data from the attention network test (Fan et al., 2002; also see Zhu et al., 2013 for a description of this test as used in the current study) were used to investigate whether genetic correlates of memories would also be linked to attention and executive function.

2.4. Data analyses

Quantitative trait genetic association analysis was carried out by using Plink v1.07 (Purcell et al., 2007), including allelic association tests between individual SNPs and behavioral measures, and associations between haplotype and behavioral measures. Pairwise LD (i.e., correlations among neighboring alleles, reflecting 'haplotypes' descended from single, ancestral chromosomes) between all SNPs was assessed using the Haploview 4.2 program (Barrett, Fry, Maller, & Daly, 2005). Analysis for behavioral indices, such as descriptive analysis, correlations, and *t*-tests were performed in SPSS 17.0. True memory and false memory were analyzed separately. All significant associations were corrected for multiple testing by the max(*T*) permutation approach in Plink (1000 permutation) for individual SNP analysis and haplotype-based association analysis, considering all tests for all behavioral traits.

3. Results

The means and standard deviations of the indices in the DRM memory test were 0.78 ($SD = 0.13$) for true memory, 0.66 ($SD = 0.20$) for false memory, 0.12 ($SD = 0.18$) for foil. The mean endorsement rate of studied words (i.e., 78%) indicates a high level of true memory. Meanwhile, the strong semantic connections between the studied words and the critical lures resulted in a high level of false memory (i.e., 66%). In comparison, the mean endorsement rate for unstudied unrelated items (foil) was only 12%. These results were similar to those obtained in previous studies of non-clinical samples (Roediger & McDermott, 1995). False memory was significantly higher than foil, $t(335) = 50.28$, $p < 0.001$. These results suggest that the DRM paradigm reliably created false memory. The correlation between true and false memories in DRM was .41 ($p < 0.001$). Males had slightly higher false memory ($M = 0.69$, $SD = 0.19$) than did females ($M = 0.64$, $SD = 0.20$), $F(1, 334) = 5.86$, $p < 0.05$. Age had a small but statistically significant negative correlation with false memory ($r = -.13$, $p < 0.05$). Therefore, sex and age were used as covariates in all subsequent analyses.

Individual SNP analysis using Plink revealed 11 significant associations with true memory: rs17068986, rs9567735, rs6561333, rs9567736, rs1923888, rs1745837, rs9567739, rs3742279, rs655888, rs655854, and rs2296972 ($p = 0.000076–0.043$, see Fig. 1 and Table S1 for details). The associations between true memory and seven adjacent SNPs (i.e., rs1923888, rs1745837, rs9567739, rs3742279, rs655888, rs655854, and rs2296972) remained significant after correcting for multiple testing by max(T) permutation. Corrected empirical *p*-values (max(*T*)/familywise) were 0.001 for rs2296972, 0.002 for rs9567739, rs3742279, rs655888, rs655854, 0.003 for rs1745837, and 0.01 for rs1923888. As shown in Fig. 2, a haplotype block across *HTR2A* was revealed from the linkage disequilibrium (LD) data for these seven SNPs, which covered 4 kb. The mean pair-wise r^2 value of these seven SNPs within *HTR2A* was .96. Haplotype-based association analysis was performed for different combinations of SNPs within *HTR2A* in the current sample. As shown in Table 1, we found a major haplotype A-C-C-G-C-T-A (with a frequency of 53%) for rs1923888–rs1745837–rs9567739–rs3742279–rs655888–rs655854–rs2296972 that showed a significant positive association with true memory ($p = 0.000075$). The haplotype G-T-G-A-T-C-C for these same SNPs (with a frequency of 45%) showed a significant inverse association with true memory ($p = 0.00081$). Only the first haplotype-based association remained significant after correcting for multiple testing by max(*T*) permutation. Corrected empirical *p*-values (max(*T*)/familywise) were 0.015 and 0.079. However, only one SNP rs655854 was associated with false memory ($p = 0.023$), but it did not survive the permutation.

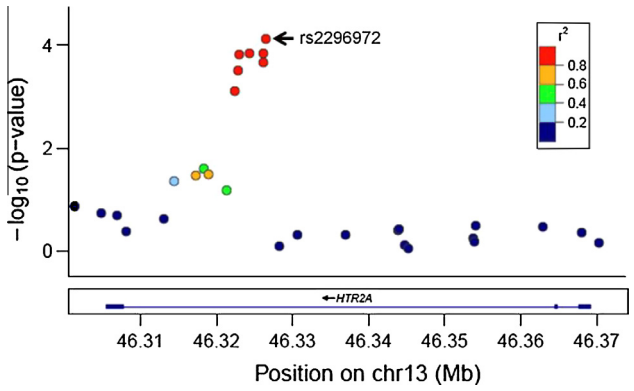

Fig. 1. Association scatter plot for the SNPs within the *HTR2A* gene and true memory in DRM after controlling for age and sex. Seven SNPs as shown in red dots were significant after correction for multiple comparisons. The strongest association with true memory was found for rs2296972. Genotyped SNPs are plotted as dots, with the color indicating the degree of pairwise LD between the leading SNP rs2296972 and neighboring SNPs. Red indicates strong pairwise LD, with $r^2 > 0.8$; dark blue indicates no LD, with $r^2 < 0.2$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

To control for possible response biases in the recognition memory tests (Snodgrass & Corwin, 1988), we also calculated the discriminability index (d') for true and false memories separately: For DRM true memory, $d'_{true\ memory} = Z$ (true memory) $- Z$ (foil); for DRM false memory, $d'_{false\ memory} = Z$ (false memory) $- Z$ (foil). They were positively correlated with the original memory indices ($r = 0.54$, $p < 0.05$, for true memory; and $r = 0.64$, $p < 0.05$, for false memory). Using the same data analytical method as for the original memory indices, we examined the association between the *HTR2A* gene and the discriminability indices. The results were very similar to those using the original memory indices, with the same directions of the significant *HTR2A* genetic associations and very similar *p* values. Specifically, individual SNP analysis using Plink revealed 11 significant associations with the discriminability index (d') for true memory: rs9567735, rs6561333, rs9567736, rs1923886, rs1923888, rs1745837, rs9567739, rs3742279, rs655888, rs655854, and rs2296972 ($p = 0.000084–0.009$, see Table S3 for details). The associations between the discriminability index (d') for true memory and eight adjacent SNPs (i.e., rs1923886, rs1923888, rs1745837, rs9567739, rs3742279, rs655888, rs655854, and rs2296972) remained significant after correcting for multiple testing by max(*T*) permutation. Corrected empirical *p*-values (max(*T*)/familywise) were 0.002 for rs2296972, 0.003 for rs9567739 and rs3742279, 0.005 for rs1745837 and rs655888, 0.006 for rs1923888 and rs655854, and 0.016 for rs1923886. Haplotype-based association analysis showed the major haplotype A-C-C-G-C-T-A for rs1923888–rs1745837–rs9567739–rs3742279–rs655888–rs655854–rs2296972 (with a frequency of 53%) had a significant positive association with the discriminability index (d') for true memory ($p = 0.0001$), and the haplotype G-T-G-A-T-C-C for these same SNPs (with a frequency of 45%) showed a significant inverse association with true memory ($p = 0.0004$). Only the first haplotype-based association remained significant after correcting for multiple testing by max(*T*) permutation. Corrected empirical *p*-values (max(*T*)/familywise) were 0.032 and 0.068. Moreover, SNP rs9567739, rs3742279, rs655854, rs2770293, rs582854, and rs9526245 were associated with the discriminability index (d') for false memory ($p = 0.026–0.49$), but none of them survived the permutation.

In addition, consistent with the findings of Wagner et al. (2008), the *HTR2A* gene was related to true memory specifically, but not to

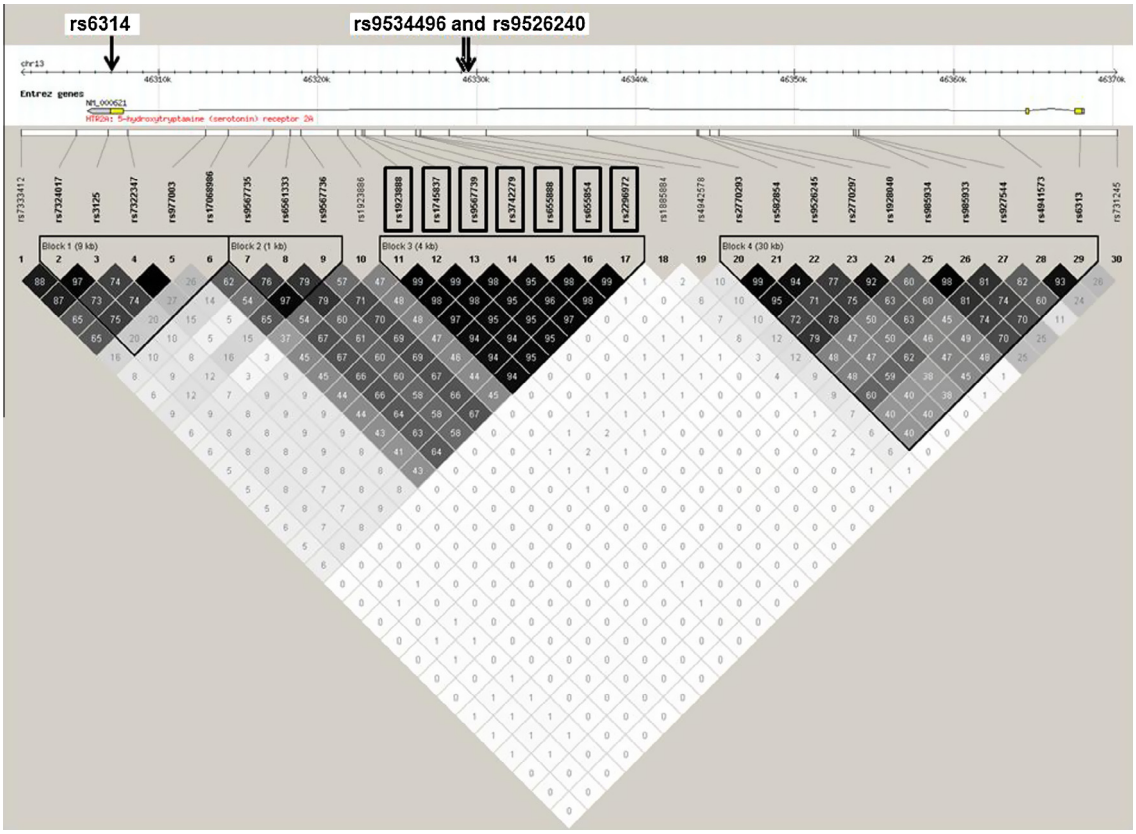

Fig. 2. Schematic representation of the *HTR2A* gene and linkage disequilibrium map of the 30 SNPs used in the current sample. The position of previously reported SNPs rs6314, rs9534496, and rs95626240 associated with memory are noted (de Quervain et al., 2003; Sigmund et al., 2008). Regions of high LD are shown in dark gray. Markers with lower LD are shown in light gray with the intensity decreasing with decreased r^2 value. Regions of low LD are shown in white. The numbers indicate the r^2 statistic value between the corresponding two SNPs. The haplotype associated with true memory in the current study consisted of the seven boxed SNPs.

attention and executive function in the current study. Attention and executive function in the current study were measured by the attention network test (Fan, McCandliss, Sommer, Raz, & Posner, 2002). There was no significant association between *HTR2A* genetic variants and the indices of alerting, orienting, and executive function measured by the attention network test (all p's > .05).

4. Discussion

In the present study, we chose multiple SNPs in the *HTR2A* gene to investigate their associations with true and false memories using the DRM test in a Han Chinese sample. We found that seven adjacent SNPs (i.e., rs1923888, rs1745837, rs9567739, rs3742279, rs655888, rs655854, and rs2296972) were significantly associated with true memory after multiple testing corrections. Furthermore, we found that the haplotype A-C-C-G-C-T-A (frequency of 53%) for these SNPs (rs1923888–rs1745837–rs9567739–rs3742279–rs655888–rs655854–rs2296972) was linked to high scores on true memory. This haplotype association was still significant after multiple testing corrections. However, the association between the *HTR2A* gene and false memory was not significant after multiple testing corrections. These effects were independent of subjects' age and sex. In addition, these significant genetic associations were the same when discriminability indices were used. These results suggest a critical role of *HTR2A* variation in true memory rather than in false memory.

Consistent with our hypothesis, *HTR2A* genetic variants were more likely to be associated with true than false memories in healthy subjects. These results were in line with the previous finding that the *HTR2A* gene is specifically associated with episodic memory (de Quervain et al., 2003; Wagner et al., 2008), which is a more important component for true memory than for false memory in the DRM test (Payne et al., 2009). It is worth noting that, although there was no significant association between false memory and SNPs within the *HTR2A* gene after multiple testing corrections, SNPs related to true memory had similar albeit much weaker associations with DRM false memory in the current study. This observation is consistent with previous studies that suggested both differences and similarities between true and false memories

Table 1
Associations between the major haplotypes of the *HTR2A* gene and true memory after controlling for age and sex.

rs1923888–rs1745837–rs9567739–rs3742279–rs655888–rs655854–rs2296972 Haplotype	Frequency	t	p
A-C-C-G-C-T-A	.53	16.1	0.000075
G-T-G-A-T-C-C	.45	−11.4	0.00081

(Gallo, 2010). For example, a previous study showed that both DRM true and false memories were influenced by the semantic interconnections between studied words (McEvoy, Nelson, & Komatsu, 1999).

In the current study, we identified seven *HTR2A*SNPs (rs1923888, rs1745837, rs9567739, rs3742279, rs655888, rs655854, and rs2296972 located within intron 2) and a corresponding seven-marker haplotype of A-C-C-G-C-T-A that were significantly associated with high scores on true memory measured by DRM test in healthy Chinese. As shown in Fig. 2, the physical positions of these seven significant markers were very close to those SNPs (i.e., rs9526240 and rs9534496) also located within intron 2 as identified in the study of Sigmund et al. (2008). The distance was only about 2.6 kb between these previously identified SNP rs9534496 and the most significant SNP rs2296972 found in our study. In their study, the major allele homozygotes had better memory than other minor allele carriers for those two identified SNPs in Europeans. However, these previously indentified SNPs had much lower MAFs in Asians (i.e., MAFs < 3%) than those in Europeans (i.e., MAFs ≈ 22%) based on the HapMap Data. In addition, the MAF of SNPs rs6314, which was located within exon 3 and identified in the study of de Quervain et al. (2003), was less than 1% in Asians. So it is unlikely to find the association between these low MAF SNPs and behavioral phenotype in Chinese samples. The SNP rs3125, which is also located within exon 3 and 0.2 kb from rs6314, was not associated with memory performance in our study. Therefore, it appears that *HTR2A* genetic variants were related to verbal delayed true memory in different ethnic samples, but the associated SNPs of *HTR2A* might be different across populations. It should be noted that, like the previously identified SNPs, the SNPs used in this study have different allele frequencies in different ethnic populations based on the HapMap Data (www.hapmap.org [phase 3], see Table S2). The alleles positively associated with DRM true memory in our study had relatively higher allele frequencies in Asian samples (i.e., about 50% on average) than in non-Asian samples (e.g., about 30% in Europeans and 20% in Africans on average). In order to obtain confirmatory evidence, these associations should be explored in future studies using different ethnic samples.

The current findings can also be integrated with multiple lines of human and animal research (including genetic, biochemical, pharmacological, and neuroimaging studies) on the *HTR2A* gene and memory performance. *HTR2A* encodes one of the receptors of serotonin, which plays an important role in learning and memory (McEntee & Crook, 1991; Weingartner, Rudorfer, Buchsbaum, & Linnoila, 1983). Interestingly, HTR2A is internalized in response to both agonists and antagonists (Raymond et al., 2001), which had influence on memory in rats and human. Using the HTR2A agonist TCB-2 and antagonist MDL 11,939 in mice, one previous study suggested that the stimulation of HTR2A facilitated memory, while blocking the HTR2A impaired memory (Zhang et al., 2013). Using an HTR2A antagonist (i.e., ketanserin) in healthy human volunteers pretreated with a selective serotonin reuptake inhibitor led to the blockade of HTR2A and impaired memory (Wingen, Kuypers, & Ramaekers, 2007). In addition, using a different HTR2A antagonist (i.e., [^{18}F]altanserin), a positron emission tomography (PET) study found *in vivo* changes of the serotoninergic system at the HTR2A in the orbitofrontal cortex in humans while performing a memory task (Hautzel, Muller, Herzog, & Grandt, 2011). Recently, several researchers had already explored the effects of drug and substance on true and false memories. For example, caffeine appears to enhance both true and false memories as measured with the DRM test (Capek & Guenther, 2009). Another group of researchers used two psychoactive drugs, one with memory-enhancing properties (dextroamphetamine; AMP), and the other with memory-impairing properties (Δ^9-tetrahydrocannabinol; THC), and they found that drug-induced changes in true memory were positively correlated with changes in false memory for both drugs (Ballard, Gallo, & de Wit, 2012). In the current study, we found that *HTR2A* genetic variants were more likely to be associated with true memory than with false memory. Therefore, future neuropsychopharmacological studies might explore whether these HTR2A antagonists' and agonists' effects are specific to true memory only.

What factors may explain the significant associations between the *HTR2A* gene and true memory rather than false memory? First, we can reasonably exclude a possible speculation about the reliability of false memory, because several previous studies suggested that DRM false memory is as much a reliable measure as DRM true memory (Blair, Lenton, & Hastie, 2002; Roediger, Watson, McDermott, & Gallo, 2001). Second, it is plausible that false memory is less heritable than true memory. No study has compared the heritability of DRM true and false memories, but the heritability of episodic memory (about 60%) is a little higher than that for semantic memory (about 50%) (Wilson et al., 2011). DRM true memory involves both episodic and semantic memories, whereas DRM false memory seems to rely solely on semantic memory (Payne et al., 2009). Therefore, DRM false memory might be a little less heritable than true memory. Future twin and family studies should directly compare the heritability of DRM true and false memories. Third, DRM false memory might be related to other genes, given that various genes have been found to be associated with different kinds of memories (Gong et al., 2012).

Several limitations of this study need to be noted. First, the biochemical and physiological functions of the identified SNPs within the *HTR2A* gene were not directly explored in the present study. The associated SNPs are located on the second intron of the *HTR2A* gene. It is possible that intron variants can also regulate mRNA expression and slicing (Zhang et al., 2007). Therefore, additional molecular functional studies are needed to investigate the detailed biochemical mechanisms of these associations. Moreover, 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 in China, future research should employ an objective systematic tool to assess such disorders. Finally, future neuroimaging studies should also examine the interrelationship between the *HTR2A* gene, brain structure or activation, and true and false memories. A previous study showed that the effects of rs6314 within the *HTR2A* gene on explicit memory performance may be mediated by alterations of hippocampal novelty processing (Schott et al., 2011). Specifically, Tyr carriers showed reduced hippocampal response to novel stimuli and more false alarms during delayed recognition, as compared to His homozygotes. Moreover, there was a negative correlation between hippocampal novelty response and false alarm rate during delayed recognition. Therefore, it is possible that the association between the *HTR2A* gene and memory might be modulated by the hippocampus.

In conclusion, the current study showed that the *HTR2A* gene was significantly associated with true but not false memory in the DRM test, perhaps because episodic memory is a more important component for true memory than for false memory in the DRM test.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nlm.2013.09.004.

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