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

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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.

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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.