

# Variations in 5-HT<sub>2A</sub> Influence Spatial Cognitive Abilities and Working Memory

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**ABSTRACT: Background:** 5-hydroxytryptamine receptor 2A (5-HT<sub>2A</sub>) participates in diverse psychiatric disorders by regulating the activity of serotonin. Some previous studies have also suggested that the receptor is involved in cognitive abilities of disease groups. We hypothesize that some functional genetic variants in 5-HT<sub>2A</sub> have certain specific influences on cognitive abilities in a normal population. **Method:** To confirm this hypothesis, two polymorphisms (rs6313 and rs4941573) in 5-HT<sub>2A</sub> were selected, and a population-based study was performed in a young healthy Chinese Han cohort. **Results:** The results indicated that the rs6313 and rs4941573 were associated with touching blocks and mental rotation-3D error ratio in males, and the rs4941573 was associated with visuo-spatial working memory in the whole cohort. **Conclusion:** All the findings suggest that 5-HT<sub>2A</sub> participates in human spatial cognitive abilities and spatial working memory.

**RÉSUMÉ: Des variations du 5-HT<sub>2A</sub> influencent les habiletés nécessaires à la cognition spatiale et la mémoire à court terme. Contexte :** Le récepteur 2A de la 5-hydroxytryptamine (5-HT<sub>2A</sub>) est impliqué dans la pathogenèse de différentes maladies psychiatriques à cause de son activité sur la sérotonine. Selon certaines études antérieures, il est possible que le récepteur influence les habiletés cognitives dans certains groupes de maladies. Nous avons émis l'hypothèse que des variantes génétiques fonctionnelles du 5-HT<sub>2A</sub> aient des influences spécifiques sur les habiletés cognitives dans la population normale. **Méthode :** Deux polymorphismes situés dans le gène 5-HT<sub>2A</sub>, rs6313 et rs4941573, ont été choisis. Nous avons effectué une étude de population chez une cohorte de jeunes Chinois Han en bonne santé afin de confirmer cette hypothèse. **Résultats :** Les résultats indiquent que ces deux polymorphismes sont associés aux taux d'erreurs de la reconnaissance par le toucher et de la rotation mentale 3D chez les hommes et que le polymorphisme rs4941573 est associé à la mémoire visuo-spatiale à court terme dans l'ensemble de la cohorte. **Conclusion :** Selon ces observations, 5-HT<sub>2A</sub> participerait aux habiletés nécessaires à la cognition spatiale chez l'humain et à la mémoire spatiale à court terme.

Can J Neurol Sci. 2011; 38: 303-308

5-hydroxytryptamine (5-HT) was described as a modulator interacting with other neurotransmitter systems. The neurotransmitter exerts diverse physiological and pharmacological effects through acting on its multiple receptors. 5-hydroxytryptamine receptor 2A (5-HT<sub>2A</sub>), a member of the 5-HT receptors, has received considerable attention for its implications in mental diseases and cognitive abilities<sup>1</sup>. The receptor is one of the G protein-coupled serotonin receptors in cerebral cortex<sup>2</sup>. It is involved in the processes of phosphoinositide hydrolysis, which regulates a variety of intracellular signals and controls the differentiation of cells<sup>3</sup>. 5-hydroxytryptamine receptor 2A is expressed at high levels in cerebral cortical areas and at intermediate levels in the hippocampus, nucleus accumbens and the hypothalamus<sup>4</sup>. The postsynaptic activations of receptor in those brain structures may increase during the process of memory<sup>5,6</sup>. The 5-HT<sub>2A</sub> gene is located 13q14.2. The gene has been considered as one of the antipsychotic drugs targets. Some studies have demonstrated that the gene is associated with schizophrenia, Alzheimer's disease and personality traits<sup>7-9</sup>.

Recently, direct genetic analyses have identified some functional variants in the gene. The rs6313 was the one of most

investigated variants within the gene. This single-nucleotide polymorphism (SNP) is located at exon I of the gene. Some researches have indicated rs6313 is related to brain functions and glucose metabolism in brain although it is a synonymous substitution which is involved in coding the 34th amino acid as serine. Evidence from human brain tissue has indicated that the individuals with the C/C genotype have lower total levels of receptor messenger ribonucleic acid (mRNA), protein and receptor binding than the ones with the T/T genotype<sup>7,10</sup>. A recent report has also shown the SNP affects N100 amplitude of event-related potentials which are mediated by both frontal and

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RECEIVED JUNE 21, 2010. FINAL REVISIONS SUBMITTED SEPTEMBER 17, 2010.  
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temporal networks<sup>11</sup>. So far, some studies have found the SNP is associated with memory, executive functions, attention and verbal fluency<sup>12,13</sup>. His452Tyr is another functional variant in 5-HT2A. Studies have shown the variant is associated with the consolidation of episodic memory and the performance of verbal memory in human<sup>14,15</sup>. The carriers with His/Tyr had poor word memory performance compared to carriers with His/His. In the present study, it is unnecessary to analyze the association between the variant and cognition because it had too rare polymorphisms in Chinese Han population. (<http://www.ncbi.nlm.nih.gov/projects/SNP>). Furthermore, rs4941573 is one of the concerned common variants in 5-HT2A. The SNP is located at intron III of the gene. Recently, a reported has shown rs4941573 plays a role in personality traits, and the A allele of the SNP is associated with a higher extraversion score<sup>16</sup> although the role of the SNP is still unclear. In the study, we selected rs6313 and rs4941573 as candidate genetic variations based on the importance of functions and roles above.

Previous studies have demonstrated 5-HT2A is related to episodic memory, word memory, executive functions, attention and verbal fluency. Taking into account these reasons, we analyzed the influence of 5-HT2A on working memory and spatial cognitive ability in the study. Firstly, working memory in our study was a form of short-term memory while the episodic memory and word memory in the previous studies<sup>14,15</sup> were some forms of long-term memory. The working memory denotes an ability to remember and manipulate information for a short-time. Evidence has shown working memory is connected with the activity of the prefrontal cortex<sup>17,18</sup>. Furthermore, in neuropsychological sense, the executive functions, attention and verbal fluency were essential to the specific cognitive ability<sup>19</sup>. However, no reports have shown 5-HT2A was associated with working memory in human although a report has shown the receptor had a role in working memory of monkeys by performing a delayed-response task<sup>6</sup>. Secondly, there was no report that definitely showed 5-HT2A was related to human spatial cognitive ability. For these reasons, influences of 5-HT2A on working memory and spatial cognitive ability were examined in this study.

Most of the previous results on the association between 5-HT2A and human cognition were drawn from case-control studies, in which the patients had schizophrenia, Alzheimer's disease or attention deficit<sup>20-22</sup>. To investigate the relationship between 5-HT2A and working memory and spatial cognitive ability in a healthy cohort, we conducted a preliminary population-based study in a large healthy Chinese population.

## MATERIALS AND METHODS

### Participants

The study was performed following the guidelines of the Declaration of Helsinki which was revised by the World Medical Association in 2000. The volunteers were recruited from the Northwest University of China according to their roll numbers. They were all freshmen with a 12.5 years education level. The ethnicity was assessed with a self-report questionnaire by asking for first language and ethnicity of the subject and their parents. All volunteers were unrelated Chinese Han individuals who came from different provinces of China. The participants comprised 295 females and 347 males with an average age of 22

(20 ± 2.4). All of them were in good physical health without alcohol dependence, drug abuse or dependence, which were determined by physical examination and laboratory tests including liver, renal and urinalysis. They gave standard informed consents, which were reviewed and approved by the Ethical Committee of the National Human Genome Center, after explanation of the study. Oral mucosa exfoliative cells were collected after informed consents were obtained from all the participants.

### Cognitive testing

The subjects were administered a battery of standardized cognitive measures. The assessments were carried out by trained psychologists using standardized batteries. These testing programs were compiled with the DMDX display software. The software is a display system that is widely used in psychological laboratories to measure reaction time (RT) of visual and auditory stimuli with millisecond (ms) accuracy<sup>23</sup>. The DMDX display software is a Windows 32-based display system, and it gives the Windows programmer better access to the actual hardware which is essential to accurate timing. It is generally believed that the display program has high accuracy. The standard deviation of the timing accuracy is no more than 2 or 3 ms<sup>24</sup>. In our study, the display software (version number: 3.2.6.4) was set up on the computers with video card at 640×480 with 8 bits per pixel in Windows XP system.

### Visuo-Spatial Working memory

Visuo-spatial working memory was measured by means of Hegarty's paradigm<sup>17</sup>. The working memory span and reaction time were the two dependent variables in the task. In the task, a dot-matrix question and a 3×3 checkerboard with a black spot were presented in a white screen. The dot-matrix question was in line with the principles of addition or subtraction while the spot was generated in any lattice check of checkerboard randomly. The answer of the question was given, then the participants were asked to judge the correction of the formula and report the position of the spot in the checkerboard. The span levels ranged from 2 to 7, and each span level included three sub-tests. Once the participant made two mistakes in a certain span level, the test was stopped.

### Spatial cognitive ability batteries

Spatial cognitive ability tests administered were part of the cognitive laterality battery<sup>25</sup>. The measurement instruments consist of four parts (localization, mental rotation-3D, touching blocks and picture detection) and can detect differences in spatial abilities. The localization, mental rotation-3D and touching blocks each contain 24 items, and Gestalt picture includes nine items. In the localization test, a black rectangular box and a stimulus ('x') in the box were presented on a white screen for two seconds, followed by a black screen for three seconds. During this time, the participants were required to mark the position of the 'x' in a rectangular box on their answer sheets. In the mental rotation-3D test, two three-dimensional graphs combined with several small cubes were presented in a black screen as stimulus for 90 seconds. The two three-dimensional graphs might be in overlap or symmetrical mirror

**Table 1: The differences of cognitive abilities performance between male and female**

Cognitive assessments		whole group	male	female	$\chi^2$	<i>p</i>
VSWM	WMS	4.21±0.06	4.39±0.09	4.07±0.08	6.16	<b>0.013</b>
	RT (ms)	1368.38±17.94	1347.27±26.56	1377.41±24.31	0.69	0.406
	SL	0.51±0.01	0.49±0.01	0.52±0.02	0.26	0.610
VSP	BT	19.92±0.13	21.18±0.14	18.88±0.19	90.05	<b>2.322E-21</b>
	PD	13.45±0.19	13.61±0.28	13.31±0.26	0.53	0.466
	MR3D ER	0.25±0.01	0.22±0.01	0.28±0.01	29.42	<b>5.827E-08</b>
	MR3D RT (ms)	9187.62±173.06	8717.65±216.93	9584.69±259.88	3.28	0.070

Abbreviations: Reaction Time-RT; Error rate-ER; Visuo-Spatial Working Memory- VSWM; Working Memory span -WMS; Visuo-Spatial Perception-VSP; Spatial Localization-SL; Block touching – BT; Picture Detection-PD; Mental Rotation3D Reaction Time- MR3DRT; millisecond-ms; Centimeter-cm. Bold font indicates there was a significant difference of performance between male and female.

by rotating movement. The participants were asked to judge the relationship of the stimulus graphs as quickly as possible.

### Genotyping

Genomic DNA was extracted from oral mucosa exfoliative cell samples using the Chelex-100 method. The rs6313 gene was amplified to produce a 242 bp product using the upstream primer, 5'-AACTACGAACTCCCTAA-3' and the downstream primer, 5'-GTATGTTTCCAGCAAAT-3'. Cycling conditions consisted of an initial denaturation at 94°C lasting for 4 minutes, followed by 30 cycles with denaturation at 94°C for 30 seconds, an annealing at 52.5°C for 30 seconds and an extension at 72°C for 45 seconds. Finally, an extension at 72°C was conducted for 5 minutes. Genotyping was performed by single strand conformation polymorphism(SSCP) method. On genotyping, six of the samples, which were selected randomly from three the genotypes, were sequenced to determine the allele of the genotyping results. For the rs4941573 polymorphism, a 149 bp DNA fragment was amplified with upstream primer, 5'-AAGCCTGAATGAGATGGG-3' and the downstream primer, 5'-GCAGAGGGAGCAAAT GAA-3'. Cycling conditions consisted of an initial denaturation at 94°C lasting for 3 minutes, followed by 35 cycles with denaturation at 94°C for 30 seconds, an annealing at 63°C for 45 seconds and an extension at 72°C for 1 minute. Finally, an extension period at 72°C was conducted for 10 minutes. The method of genotyping was the same as the one used for rs6313.

### Statistical analysis

Microsoft Visual FoxPro 6.0 software was used for preparing the preliminary data. Hardy-Weinberg equilibrium tests were carried out with Finetti. The performance differences of cognitive abilities between males and females were analyzed using the Kruskal–Wallis test. The effects of the genotypes on the cognitive variables were analyzed using the Kruskal–Wallis

test for males and females respectively when gender had a significant effect on the cognitive variables (In the present study, the performance of working memory and spatial cognitive ability in the male or female groups was not in normal distribution nor in homogeneity of variance. In this case, the method of non-parametric test was better than the multivariate analysis of variance.). The analysis of variance was performed using SPSS 15.0 software for windows (SPSS, Chicago). Corrections for multiple tests were conducted by Benjamini-Hochberg FDR-controlling method. A power analysis was implemented by the G\*Power program which was based on Cohen's method.

### RESULTS

On genotyping, we detected there were 171 with TT, 338 with TC and 133 with CC at rs6313, 148 with AA, 305 with AG and 158 with GG at rs4941573 polymorphism. There were no significant differences in frequencies of the genotypes between males and females ( $\chi^2=3.68$ ,  $p = 0.16$ ;  $\chi^2=0.83$ ,  $p = 0.67$ ), and genotype frequencies of the two genetic variants showed no deviations from Hardy–Weinberg equilibrium in the group ( $p = 0.15$ ,  $p = 0.97$ ).

We found there were significant differences in the average performance of working memory span, touching blocks and mental rotation-3D error ratio between males and females ( $\chi^2 > 3.84$ ,  $p < 0.05$ ). The average performance of working memory and spatial cognitive ability was listed in Table 1. The effects of 5-HT2A on the cognitive performance without gender difference and with gender difference are displayed in Table 2 and Table 3, respectively. Since greater than 20 comparisons were made in the study, the multi-test correction  $0.05*4/20=0.01$  according to the Benjamini-Hochberg FDR-controlling method was made<sup>26</sup>. After correcting for multiple tests, we still observed there were some significant associations. Firstly, rs6313 was associated with touching blocks and mental rotation-3D error ratio ( $\chi^2 =$

**Table 2: Effects of the SNPs in 5-HT2A on the performance of some cognitive abilities without gender difference**

		rs6313					rs4941573				
		Means±S.E			$\chi^2$	<i>p</i>	Means±S.E			$\chi^2$	<i>p</i>
		TT	TC	CC			AA	AG	GG		
Frequency		120	269	85			104	261	119		
VSWM	RT(ms)	3049.71±64.83	3060.48±38.16	2939.04±69.71	2.51	0.285	2856.32±65.98	3055.13±39.53	3125.97±55.75	9.56	<b>0.008</b>
Frequency		160	322	123			137	305	154		
VSP	SL(cm)	0.50±0.01	0.50±0.01	0.53±0.03	2.87	0.238	0.54±0.04	0.50±0.01	0.50±0.01	2.29	0.318
	PD	13.43±0.40	13.96±0.28	12.48±0.49	7.71	0.021	12.66±0.43	13.59±0.27	13.82±0.39	4.53	0.104
	MR3DRT(ms)	9576.66±388.75	8932.66±220.61	9057.96±438.92	1.13	0.568	9150.86±387.08	9151.72±249.03	9726.84±365.09	1.57	0.456

Bold font indicates significantly associated statistic after correction for multi-test by Benjamini-Hochberg FDR-controlling method.

9.59,  $p = 0.008$ ;  $\chi^2 = 9.53$ ,  $p = 0.009$ ) in males. The individuals with TT genotype had better performance of touching blocks and mental rotation-3D error ratio than the ones with CC genotype. Secondly, rs4941573 was associated with mental rotation-3D error ratio in males ( $\chi^2 = 16.63$ ,  $p = 0.0003$ ) and visuo-spatial working memory reaction time in the whole cohort ( $\chi^2 = 9.56$ ,  $p = 0.008$ ). The individuals with AA genotype had better performance of visuo-spatial working memory and worse performance of mental rotation-3D than the ones with GG genotype.

The sample size of the study had more than 95% power for the detection of significant associations ( $p < 0.05$ ), when the tested variations had a small to medium genetic effect, under an effect size index of 0.25.

## DISCUSSION

Increasing evidence that documented that the 5-HT2A receptor gene plays a role in human cognitive abilities. In the present study, we found 5-HT2A was associated with building block and mental rotation-3D error ratio in the male group and visuo-spatial working memory in the whole cohort. The sample of our study had a number of advantages compared with the population in other studies given that age and education were known to have significant impacts on cognition. The participants were all freshmen who had equal educational levels and ages. The study benefited from these analogical backgrounds. Furthermore, these participants were unrelated individuals coming from different regions, which ensured the randomization of the sample.

**Table 3: Effects of the SNPs in 5-HT2A on the performance of some cognitive abilities with gender difference**

		Male					Female				
		Means±SE			$\chi^2$	<i>p</i>	Means±SE			$\chi^2$	<i>p</i>
		TT	TC	CC			TT	TC	CC		
rs6313	Frequency	87	155	53			84	183	80		
VSWM	WMS	4.46±0.19	4.45±0.14	4.00±0.23	2.96	0.227	4.01±0.17	4.06±0.13	4.36±0.20	1.91	0.385
VSP	BT	21.39±0.34	21.39±0.18	20.18±0.43	9.59	<b>0.008</b>	18.89±0.43	18.84±0.29	19.12±0.45	0.94	0.625
	MR3DER	0.21±0.01	0.22±0.01	0.27±0.02	9.53	<b>0.0085</b>	0.29±0.02	0.28±0.01	0.27±0.02	1.22	0.543
rs4941573	Frequency	59	141	75			80	164	83		
VSWM	WMS	4.15±0.23	4.44±0.14	4.54±0.18	2.04	0.361	4.29±0.19	4.01±0.11	4.04±0.16	1.25	0.535
VSP	BT	20.30±0.40	21.31±0.20	21.38±0.30	7.53	0.023	19.17±0.41	18.79±0.27	18.72±0.40	1.39	0.499
	MR3DER	0.28±0.02	0.20±0.01	0.21±0.01	16.39	<b>0.0003</b>	0.26±0.01	0.28±0.01	0.29±0.01	2.43	0.297

Bold font indicates significantly associated statistic after correction for multi-test by Benjamini-Hochberg FDR-controlling method.

In the research, we detected the TT genotype of rs6313 was associated with better performance of spatial cognitive abilities. The result possibly indicated the higher levels of *5-HT2A* receptor messenger ribonucleic acid (mRNA) and protein were possibly related to better spatial cognitive abilities because previous studies have revealed the TT genotype was related to higher levels of receptor messenger ribonucleic acid (mRNA) and protein of *5-HT2A*. We also found the individuals with AA genotype of rs4941573 had better performance of visuo-spatial working memory and worse performance of mental rotation-3D. It was an interesting result that the AA genotype had opposite influences on different cognitive abilities although it was still unclear about the specific effect of the SNP on the function or the expression of the receptor. Not only visuo-spatial working memory but also mental rotation-3D were related to spatial cognitive abilities. However, different spatial cognitive abilities were assessed in the two tests. Spatial memory and spatial observation ability are required in visuo-spatial working memory while spatial visualization was tested in mental rotation-3D test. We speculated the spatial memory component in visuo-spatial working memory had no significant mediate effect on the mental rotation-3D test.

5-hydroxytryptamine receptor 2A is expressed widely in several brain regions such as the cerebral cortical areas, nucleus accumbens and the hypothalamus. Those areas contain the brain regions which are related to mental rotation and working memory. That may be a potential reason why *5-HT2A* is associated with working memory and visual spatial cognitive abilities. Some previous studies have indicated the activities of the superior parietal lobule, dorsolateral premotor areas, anterior neostriatum and lateral frontal cortical areas were significantly increased during the process of mental rotation tasks<sup>27-30</sup>. Evidence from fMRI has shown prefrontal cortex, including left and right dorsolateral prefrontal cortex, left ventrolateral prefrontal left premotor cortex, and left and right posterior parietal cortex, plays an important role in working memory<sup>31,32</sup>.

It was still difficult to explain why *5-HT2A* showed a gender difference in visual spatial cognitive abilities although we have gotten some exciting results in the study. We speculated that the estrogen level was an underlying cause in the a gender difference of *5-HT2A* affecting on visual spatial cognitive abilities. Not only the genotypes of *5-HT2A* but also the level of estrogen could influence the density and protein of the receptor in female brain. Some studies have indicated that the brain serotonergic system is affected by estrogen, and the hormone can increase the density and mRNA level of *5-HT2A* receptors in several brain areas<sup>33,34</sup>. It is generally believed that the level of estrogen is significant higher in females. It is significant that estrogen influences the density and mRNA levels of *5-HT2A* receptors in females. However, the influence of estrogen on *5-HT2A* may show cyclical fluctuations in young females due to the menstrual cycle. In our study, we did not investigate the menstrual cycles of the female participants during the cognitive ability assessments. The different stages of the menstrual cycles may be an important interference factor in young females. The right brain is the dominant hemisphere in visual spatial cognitive abilities, and males have the advantage over females. Studies have shown mental rotation-3D was more dependent on right hemisphere, and there was significant difference in the activity in

frontal and parietal areas between men and women during the process of mental rotation tasks<sup>35</sup>. Males and females employed different neural mechanisms in the task<sup>36</sup>. We supposed there was a gender difference in the regulating of *5-HT2A* to the neural mechanisms of mental rotation-3D task. However, this is speculation, and more work is needed to confirm the views.

## CONCLUSION

Taken together, the present study suggests that certain variations in *5-HT2A* influences on spatial working memory and plays a role in visual spatial cognitive abilities in male group. These results will provide a new insight into the potential contributions of the receptor to the individual differences in cognition.

## ACKNOWLEDGEMENTS

The authors thank all the participants and researchers in this study. This work was supported by Special Prophase Project on Basic Research of the National Department of Science and Technology (2007CB516702), National Natural Science Foundation of China (No. 30970967) and Graduate Innovative Education Program of Northwest University (09YJC34).

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