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ORIGINAL PAPER

The association of *GABRB2* SNPs with cognitive function in schizophrenia

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Abstract

Cognitive impairment is one of the core symptoms of schizophrenia. Multiple domains of cognition are affected in patients with schizophrenia, which has a major effect on the functional outcome. Recent studies indicate that SNPs in the gamma-aminobutyric acid type A receptor beta 2 subunit (*GABRB2*) gene are associated with the risk of schizophrenia, however, the effect of these SNPs on cognitive function in patients with schizophrenia has not been explored. In this study, we first performed a case–control analysis of three SNPs (rs187269 allele A vs. G, rs252944 allele C vs. G, and rs194072 allele A vs. G) in 100 patients and 90 controls, then conducted a meta-analysis and found the SNP rs194072 was associated with schizophrenia (OR = 0.86, $P = 0.0119$), and survived after Bonferroni correction. The haplotype analysis suggested that the haplotype ACA, comprising the three SNPs (rs187269, rs252944 and rs194072) was also significantly associated with schizophrenia ($P = 0.049$).Then, we performed an association analysis of three SNPs (rs187269, rs252944 and rs194072) in *GABRB2* gene with cognitive performance in patients with first episode schizophrenia. We found that the allele G of rs187269 in the *GABRB2* gene was significantly associated with better cognitive flexibility ($P = 0.005$), a major aspect of executive function, in patients with first episode schizophrenia. The haplotype ACA was significantly associated with cognitive flexibility in patients with schizophrenia ($P = 0.023$). Our study showed that SNPs in *GABRB2* may have a significant effect on cognitive function in patients with schizophrenia, suggesting that modulating *GABRB2* may have therapeutic potential to improve cognitive function of patients with schizophrenia.

Keywords *GABRB2* · SNPs · Schizophrenia · Cognitive function

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Introduction

Schizophrenia is a severe mental disorder commonly characterized with distortions in cognition, perception, emotions, language, sense of self and behavior. The prevalence of schizophrenia is about 1% worldwide [1]. According to the World Health Organization (WHO) statistics in 2016, schizophrenia affects more than 21 million people worldwide, causing a heavy burden to the family and society. Cognitive impairment is one of the core symptoms of schizophrenia, approximately affecting 85% patients with schizophrenia [2]. Multiple domains of cognition are significantly affected in schizophrenia, including cognitive flexibility, attention, working memory, information processing speed, social cognition, etc. Recently, cognitive deficits in schizophrenia have received more attention, as they are persistent throughout the course of schizophrenia, even during the remission, which significantly impairs functional outcome and quality of life, such as a return to employment [3].

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter and $GABA_A$ receptors, which are highly expressed in the central neural system, mediate its inhibitory effect in the brain. Dysregulation of the GABAergic system plays an important role in the pathogenesis of schizophrenia [4]. Genetic linkage studies found that a schizophrenia-associated loci is located in the vicinity of multiple $GABA_A$ receptor genes, *GABRA1, GABRB2, GABRG2* and *GABRP* encoding α1, β2, γ2 and π subunits of $GABA_A$ receptor, respectively. Genetic variants of *GABRB2* were identified to be associated with psychosis [5]. Gabrb2-knockout mice were found to display schizophrenia-like and comorbid phenotypes with interneuron–astrocyte–microglia dysregulation [6]. In addition, Lo et al. reported that the single-nucleotide polymorphisms (SNPs), rs187269, rs194072, rs252944 in the *GABRB2* gene, but not SNPs in other genes, are associated with schizophrenia in the Chinese population [7]. Consistently, this association has been demonstrated in Japanese, German and Portuguese populations in multiple independent studies [8–11]. A meta-analysis also suggested the association between *GABRB2* and schizophrenia [12–14]. Moreover, a reduction of *GABRB2* mRNA and altered expression of GABRB2 isoforms were observed in patients with schizophrenia [15, 16]. However, the association between GABRB2 and cognitive deficits in patients with schizophrenia has not been explored.

In this study, we first conducted a meta-analysis and found the SNP rs194072 was associated with schizophrenia (OR = 0.86, $P = 0.0119$), and survived after Bonferroni correction. The haplotype analysis suggested that the haplotype ACA, comprising the three SNPs (rs187269, rs194072, and rs252944) was also significantly associated with schizophrenia ($P = 0.049$).Then, we performed an association analysis of three SNPs (rs187269, rs194072, rs252944) in *GABRB2* gene with cognitive performance in patients with first episode schizophrenia. We found that the allele G of rs187269 in *GABRB2* gene was significantly associated with better cognitive flexibility ($P = 0.005$), a major aspect of executive function, in patients with first episode schizophrenia. The haplotype ACA was significantly associated with cognitive flexibility in patients with schizophrenia ($P = 0.023$). Our study showed that SNPs in *GABRB2* may have a significant effect on cognitive function in patients with schizophrenia, suggesting that modulating *GABRB2* may have therapeutic potential to improve cognitive function of patients with schizophrenia.

Methods and materials

Subjects

We recruited 100 patients (47 females and 53 males) with first episode schizophrenia from the second Affiliated Hospital of Jining Medical University. Patients with schizophrenia were diagnosed according to ICD-10. The average age and education levels of the patients were 28.00 ± 7.50 years and 10.62 ± 0.86 years, respectively. Meanwhile, 90 healthy controls (41 females and 49 males) were recruited from Jining area (Shandong province, China). The average age and education levels of the normal controls were 27.51 ± 7.45 years and 11.20 ± 0.71 years, respectively. Cognitive function of patients was evaluated using Wisconsin Card Sorting Test (WCST) [17], Attention Network Test (ANT) [18], Trail Making Test (TMT) [19] and N-Back test [20], respectively. Informed consent was obtained from both the patients or their families and controls. This study was approved by the Ethical Committee of Jining Medical University.

Genotyping of SNP

The whole blood was collected into the EDTA tubes and the genomic DNA was extracted using the TIANamp Blood DNA Kit (Tiangen DP348). Two sequences of three SNPs in *GABRB2* gene were amplified using the primers of 5′-TGTTGCAAATATCATCTTCTAAGC-3′/5′-GCCTTGCACATATACCACTTATC-3′(rs187269) and 5′-GTGAGGACAGTTGTGATTCC-3′/5′-TAATTTTAAGTTCAAACTC-3′(rs252944 and rs194072), respectively, and the SNPs were identified by sequencing.

Statistical analysis

The case–control association analyses and haplotype analysis were performed using PLINK version 1.07. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the effects of different alleles. Bonferroni corrections were applied to correct the *P* values of alleles (corrected $\alpha = 0.05/3 = 0.017$), to control inflation of the Type I error rate. The pairwise LD analysis was applied to detect inter-marker relationships using the r^2 value. All of the tests were two-tailed, with statistical significance of $P < 0.05$. The meta-analysis was performed using R package 'metafor', and heterogeneity across the two samples was evaluated using the Cochran Q statistic to determine the heterogeneity statistic (I^2) and *P* value. We assessed the associations between the SNP genotype and cognitive performance using one-way ANOVA and Student's *t* test implemented in GraphPad Prism v7.0.

Results

The SNP rs194072 is associated with schizophrenia

First, to determine the association of *GABRB2* SNPs with schizophrenia, the *GABRB2* SNPs (rs187269, rs194072 and rs252944) were detected in 100 patients with first episode schizophrenia and 90 healthy controls. The samples with excellent signals were included in this study. Allelic and genotypic comparisons were made between the control and schizophrenia groups. There was no significant correlation between the three SNPs with schizophrenia (Table 1). Moreover, it should be pointed out that all the three SNPs did not deviate from Hardy–Weinberg equilibrium in either the control or the patient group (Table S1) and the age, gender and educational duration of the participants generated no inaccuracy to the association analysis of *GABRB2* SNPs with schizophrenia (Table S2).

Then, we searched the previous genetic association studies between *GABRB2* gene and schizophrenia in the schizophrenia gene database (http://www.szgene.org/), and combined them with our results using a meta-analysis (Fig. 1). The SNP rs194072 was significantly associated with schizophrenia (OR = 0.86, $P = 0.0119$), and survived after Bonferroni correction ($P < 0.17$).

Haplotype results of the entire block for the case–control association studies

Linkage disequilibrium was computed between every two SNPs to further analyze the haplotype structure. The r^2 value of each combination was > 0.8 using the combined case and control group. Therefore, we used the LD block that consisted of these three inner markers in the haplotype analysis (Table 2). Haplotypes ACA showed nominal differences between the patient and control groups. ACA is a risk haplotype that is highly associated with schizophrenia ($P = 0.049$). However, this result was not significant after the 1000-time permutation tests.

Allele G of rs187269 is associated with better cognitive flexibility in schizophrenics

To investigate the association between *GABRB2* SNPs and cognitive function in patients with schizophrenia, four cognitive tests, WCST, ANT, TMT and N-BACK, were performed in patients. The majority of the patients participated in the cognitive tests except that several cases did not cooperate. In the TMT tests, no difference was detected in task A, including time of task A (ART) and error numbers in task A (A-EN). However, allele G of rs187269 was significantly associated with reduced time of task B (BRT) and reduced difference between BRT and ART (BRT-ART),

Table 1 Chi square analysis for *GABRB2* genotypes/alleles with schizophrenia

SNPs	Sample	Genotypes/alleles (*N*/frequency)		χ^2	*P*
rs187269	Control	Genotype	AA (45/56.25%) AG (25/31.25%) GG (10/12.50%)	3.654	0.161
	Patients		AA (59/62.11%) AG (31/32.63%) GG (5/5.26%)		
	Control	Allele	A (115/71.88%) G (45/28.12%)	3.146	0.080
	Patients		A (149/78.42%) G (41/21.58%)		
rs252944	Control	Genotype	CC (47/60.26%) CG (25/32.05%) GG (6/7.69%)	0.909	0.635
	Patients		CC (58/65.17%) CG (27/30.34%) GG (4/4.49%)		
	Control	Allele	C (119/76.28%) G (37/23.72%)	1.059	0.349
	Patients		C (143/80.34%) G (35/19.66%)		
rs194072	Control	Genotype	AA (48/61.54%) AG (25/32.05%) GG (5/6.41%)	0.893	0.640
	Patients		AA (58/65.17%) AG (28/31.46%) GG (3/3.37%)		
	Control	Allele	A (177/77.56%) G (35/22.44%)	0.564	0.499
	Patients		A (144/80.90%) G (34/19.10%)		

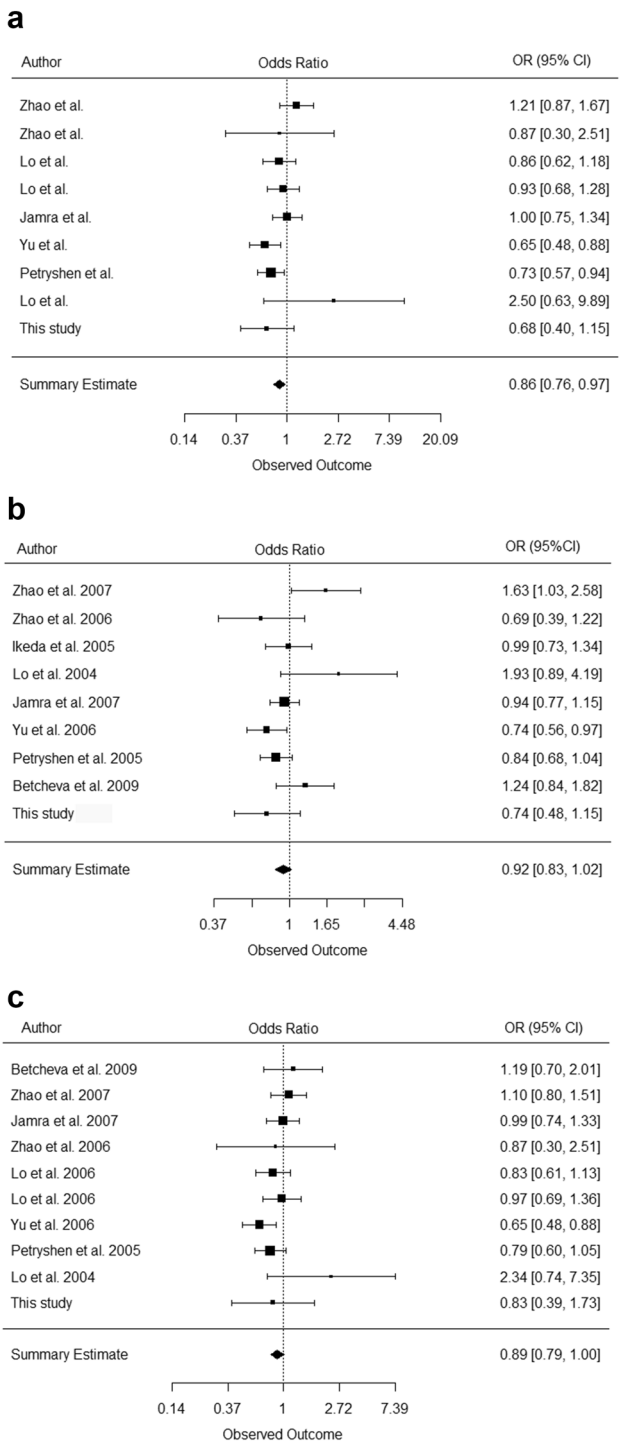

Fig. 1 Meta-analysis of the association between *GABRB2* SNPs and schizophrenia. **a** rs194072; **b** rs187269; **c** rs252944

122.32 ± 9.89 s vs. 151.85 ± 8.99 s ($P = 0.042$) and 74.18 ± 6.32 s vs. 103.00 ± 7.81 s ($P = 0.005$), respectively (Table 3). No difference of error numbers in task B (B-EN) was detected. These results indicated that patients carrying allele G of rs187269 may have a better cognitive flexibility (switch of attention between tasks), a major aspect of executive function [21].

Table 2 Haplotype results of the entire block for the case–control association studies

Haplotype	F_A[a]	F_U[b]	χ^2	*P*
GGG	0.04457	0.0666	0.7774	0.3779
AGG	0.005682	0.01568	0.8079	0.3687
GCG	0.1145	0.1161	0.002136	0.9631
ACG	0.01705	0.04842	2.654	0.1033
GGA	0.02929	0.004001	3.128	0.07696
AGA	0.005682	0.01499	0.7221	0.3955
GCA	0.1696	0.2271	1.744	0.1866
ACA	0.6136	0.5071	3.844	0.049

[a]Frequencies of cases

[b]Frequencies of controls

rs187269, rs194072 and rs252944 had no significant effect on cognitive performance in WCST tests, including responses achieved (RA), catergories completed (CC), rate of errors (RE) and rate of perseverative errors (RPE) (Table 4), indicating that the SNPs had no effect on concept formation in the patients. In addition, no significant difference was detected in ANT tests, including reaction time (RT) and the rate of errors (RE) (Table 5), indicating that the three SNPs had no significant effect on attention. In the N-Back tests (0-back, 1-back and 2-back), the reaction time (0-RT, 1-RT and 2-RT) gradually decreased while the rate of errors (0-RE, 1-RE and 2-RE) markedly increased from 0-back to 2-back in each group (Table 6). However, rs187269, rs194072 and rs252944 had no significant effect on the reaction time and rate of errors in 0-, 1- and 2-back tests, indicating that the three SNPs had no effect on the working memory in patients with schizophrenia.

Then, we used the LD block that consisted of these three SNPs in the haplotype analysis. Haplotypes ACA showed nominal association with N-back performance ($P = 0.023$). ACA is a risk haplotype that is highly associated with schizophrenia. Detailed information of haplotype results including mean, and SEM are listed in Supplemental materials (Tables S1–S4).

Discussion

GABRB2 is a schizophrenia candidate gene and minor alleles of SNPs, rs187269, rs194072 and rs252944, in the *GABRB2* gene are associated with increased risk of schizophrenia in various populations from different regions such as south China, Japan, and Germany [7–11]. In this study, we identified *GABRB2* variations and haplotypes that were associated with cognitive flexibility in patients with

Table 3 The association of *GABRB2* SNPs with TMT performance in schizophrenia

	rs187269 (mean + SEM)			rs252944 (mean + SEM)			rs194072 (mean + SEM)		
	AA (*N* = 41)	AG (*N* = 22)	*P*	CC (*N* = 42)	CG (*N* = 19)	*P*	AA (*N* = 42)	AG (*N* = 20)	*P*
ART (s)	51.333 ± 2.926	47.087 ± 5.076	0.440	50.565 ± 2.867	48.579 ± 6.057	0.738	50.565 ± 2.867	47.800 ± 5.799	0.634
A-EN	0.067 ± 0.038	0.174 ± 0.081	0.174	0.065 ± 0.037	0.263 ± 0.104	0.086	0.0652 ± 0.0368	0.250 ± 0.993	0.094
BRT (s)	151.850 ± 8.993	122.318 ± 9.887	0.042*	146.000 ± 9.065	131.842 ± 10.650	0.468	146.000 ± 9.065	131.400 ± 10.674	0.337
B-EN	4.286 ± 1.210	2.455 ± 1.124	0.329	4.309 ± 1.212	3.000 ± 1.280	0.515	4.114 ± 1.164	2.900 ± 1.218	0.529
BRT-ART (s)	103.±7.811	74.182 ± 6.317	0.005*	97.1901 ± 7.784	86.263 ± 7.494	0.319	97.190 ± 7.784	83.600 ± 7.592	0.217

Values are mean ± SEM

ART time of task A, *A-EN* error numbers in task A, *BRT* time of task B, *B-EN* error numbers in task B

*$P < 0.05$ by Student's *t* test

Table 4 The association of *GABRB2* SNPs with WSCT performance

	rs187269 (mean + SEM)			rs252944 (mean + SEM)			rs194072 (mean + SEM)		
	AA (*N* = 45)	AG (*N* = 23)	*P*	CC (*N* = 46)	CG (*N* = 19)	*P*	AA (*N* = 46)	AG (*N* = 20)	*P*
RA	121.844 ± 2.193	117.667 ± 3.964	0.426	121.870 ± 2.308	118.158 ± 4.085	0.407	121.870 ± 2.308	115.900 ± 4.485	0.197
CC	3.044 ± 0.298	3.273 ± 0.519	0.684	2.833 ± 0.304	2.810 ± 0.537	0.967	2.833 ± 0.304	2.955 ± 0.532	0.843
RE (%)	42.392 ± 2.571	41.334 ± 4.508	0.827	44.774 ± 2.464	43.031 ± 4.601	0.718	44.774 ± 2.463	43.853 ± 4.256	0.844
RPE (%)	81.596 ± 2.510	89.367 ± 8.473	0.269	80.437 ± 2.663	93.889 ± 9.742	0.076	80.437 ± 2.663	92.945 ± 9.290	0.091

RA responses achieved, *CC* categories completed, *RE* rate of errors, *RPE* rate of perseverative errors

Table 5 The association of *GABRB2* SNPs with ANT performance

	rs187269 (mean + SEM)			rs252944 (mean + SEM)			rs194072 (mean + SEM)		
	AA (*N* = 43)	AG (*N* = 21)	*P*	CC (*N* = 44)	CG (*N* = 17)	*P*	AA (*N* = 44)	AG (*N* = 18)	*P*
RT (ms)	727.686 ± 16.320	773.230 ± 25.587	0.126	745.957 ± 16.380	756.727 ± 30.998	0.724	745.957 ± 16.380	750.873 ± 29.806	0.878
ANTE (%)	7.868 ± 2.132	13.396 ± 4.826	0.227	9.006 ± 2.154	12.644 ± 2.858	0.47	9.006 ± 2.154	12.098 ± 5.550	0.528

RT reaction time, *RE* rate of errors

Table 6 The association of *GABRB2* SNPs with N-BACK performance

	rs187269 (mean + SEM)			rs252944 (mean + SEM)			rs194072 (mean + SEM)		
	AA (*N* = 40)	AG (*N* = 20)	*P*	CC (*N* = 39)	CG (*N* = 19)	*P*	AA (*N* = 41)	AG (*N* = 17)	*P*
0-RT (ms)	573.514 ± 17.282	587.155 ± 29.258	0.671	583.364 ± 18.332	556.0.26 ± 26.282	0.420	583.364 ± 18.332	558.738 ± 24.837	0.454
1-RT (ms)	457.894 ± 34.051	397.599 ± 33.932	0.256	446.450 ± 35.012	375.550 ± 34.049	0.228	446.450 ± 35.012	382.201 ± 32.538	0.260
2-RT (ms)	335.721 ± 27.454	311.334 ± 37.070	0.612	342.196 ± 28.462	290.541 ± 42.928	0.328	342.196 ± 28.462	301.178 ± 28.462	0.424
F value	22.774	15.327		20.148	15.745		20.148	16.185	
P	5.296E−09*	7.121E−06*		3.749E−08*	7.899E−06*		3.749E−08*	5.062E−06*	
0-RE (%)	8.387 ± 1.418	8.871 ± 2.584	0.859	9.520 ± 1.644	8.871 ± 2.365	0.831	9.520 ± 1.644	9.489 ± 2.306	0.991
1- RE (%)	60.277 ± 4.689	47.850 ± 7.667	0.151	61.198 ± 4.908	44.301 ± 8.230	0.449	61.198 ± 4.908	44.960 ± 7.727	0.075
2-RE (%)	75.760 ± 2.514	76.694 ± 4.205	0.843	74.668 ± 2.972	77.281 ± 3.670	0.618	74.668 ± 2.972	77.505 ± 3.423	0.575
F value	147.975	36.014		114.931	40.871		114.931	45.658	
P	4.852E−32*	3.284E−10*		1.791E−27*	1.397E−10*		1.791E−27*	1.479E−11*	

Values are mean ± SEM

0 0-back, *1* 1-back, *2* 2-back, *RT* reaction time, *RE* rate of errors

*$P < 0.05$ by One-way ANOVA

schizophrenia. As far as we know, cognitive deficit, one of the core symptoms of schizophrenia, plays a key role in the functional outcome of patients with schizophrenia. However, the association of these SNPs with cognitive function in the patients has not been explored. The cognitive flexibility, a major aspect of executive function, was examined in the patients by TMT test. We found that the allele G of rs187269 in *GABRB2* gene was significantly associated with better cognitive flexibility in patients with first episode schizophrenia. Although the minor alleles of rs194072 and rs252944 displayed the same trend as that of allele G of rs187269 did, i.e., reduced reaction time of task B (BRT) and reduced difference between BRT and ART (BRRT), they were not significant. Therefore, it needs to be examined in a larger sample size in a future study.

Furthermore, the associations of the three SNPs with schizophrenia were investigated in Jining, Shandong, an area in north China. We found that these SNPs were not associated with schizophrenia (Table 1), which might be due to the regional characteristic of the Han populations in Shandong region. In addition, the sample size of this study was smaller than that in Lo's study, 100 vs. 130 in control group and 90 vs. 137 in schizophrenic group, respectively, which might also contribute to the different results. We combined our results with schizophrenia gene database using meta-analysis and found the SNP rs194072 was significantly associated with schizophrenia and survived after Bonferroni correction. However, the associations between the three SNPs and schizophrenia in Psychiatric Genomics Consortium GWAS database were not significant. Therefore, the association needs to be further confirmed by increasing the sample size [7].

Cognitive deficit, one of the core symptoms of schizophrenia, plays a key role in the functional outcome of patients with schizophrenia. However, the association of these SNPs with cognitive function in the patients has not been explored. The cognitive flexibility, a major aspect of executive function, was examined in the patients by TMT test. We found that the allele G of rs187269 in *GABRB2* gene was significantly associated with better cognitive flexibility in patients with first episode schizophrenia. Although the minor alleles of rs194072 and rs252944 displayed same trend as allele G of rs187269 did, i.e., reduced reaction time of task B (BRT) and reduced difference between BRT and ART (BRRT), they were not significant. Therefore, it needs to be examined in a larger sample size in future study.

Although all SNPs had no significant effect on concept formation measured by WCST tests, attention measured by ANT tests and working memory measured by N-Back tests, several issues need to be considered. First, rs187269, rs194072 and rs252944 had no significant effect on the reaction time and proportion of errors in 0-, 1- and 2-back tests. It has to be noted that both 1-RT and 1-RE were reduced in patients carrying minor allele of rs187269, rs194072 and rs252944, respectively, although they did not reach significance. It suggested that a parameter should be developed to consider both RT and RE in the task, which may precisely reflect the function of work memory. Moreover, further investigation needs to be done in a larger sample size. In addition, 0-RT and 2-RT, and 0-RE and 2-RE were similar in two genotypes of the SNPs. It suggested that low load (0-back) and high load (2-back) might not be optimal tasks for measuring the difference of working memory in the patients. Therefore, 1-back task might be sufficient to detect the difference of working memory in schizophrenic patients, which will be more feasible for clinical application.

Previous studies suggested that these cognitive dimensions were impaired in schizophrenia patients, including Wisconsin Card Sorting Test (WCST), Attention Network Test (ANT), Trail Making Test (TMT) and N-Back test. In the present study, the sample size was relatively small, so we only identified that the *GABRB2* polymorphisms were associated with cognitive flexibility. However, the *GABRB2* polymorphisms might also be associated with other cognitive dimensions. Cognitive flexibility is also impaired in patients with other psychiatric disorders, including depression [22] and bipolar disorder [23].

Our study had several limitations. First, the sample size was relatively small and may be underpowered to detect true effects with moderate effect sizes. Therefore, the sample size should be amplified in the future. Second, the *GABRB2* associations were performed in samples of Han Chinese ancestry. These identified variants might not be associated with cognitive performances in other ethnic groups. Validation studies in other populations are necessary, to investigate whether the identified loci can be generalized to the other ethnicities but also to identify new susceptibility loci for cognitive deficit.

In summary, we have identified *GABRB2* SNPs to be associated with cognitive deficit in patients with schizophrenia. Future research should extend these findings to larger samples and different populations to confirm their associations.

Author contributions QZ, XZ, SS and HH performed the cognitive test in patients and collected the blood samples; QZ and XW performed DNA extraction and amplification experiments; HY, SW and XZ analyzed the data; QZ, HY, and SW wrote the paper. GL and YW conceived the experiments and wrote the paper. All authors reviewed the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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