Neuropsychopharmacology (2012) 37, 1572–1578

www.neuropsychopharmacology.org

Evidence of IQ-Modulated Association Between *ZNF804A* Gene Polymorphism and Cognitive Function in Schizophrenia Patients

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ZNF804A gene polymorphism rs1344706 has been suggested as the most compelling case of a candidate gene for schizophrenia by a genome-wide association study and several replication studies. The current study of 570 schizophrenia patients and 448 controls again found significantly different genotype frequencies of rs1344706 between patients and controls. More important, we found that this association was modulated by IQ, with a stronger association among individuals with relatively high IQ, which replicated results of Walters *et al*, 2010. We further examined whether this IQ-modulated association also existed between the SNP and the intermediate phenotypes (working memory and executive functions) of schizophrenia. Data were available from an N-back task (366 patients and 414 controls) and the attention network task (361 patients and 416 controls). We found that the SNP and IQ had significant interaction effects on the intermediate phenotypes for patients, but not for controls. The disease risk allele was associated with poorer cognitive function in patients with high IQ, but better cognitive function in patients with low IQ. Together, these results indicated that IQ may modulate the role of rs1344706 in the etiology of both schizophrenia and its cognitive impairments, and pointed to the necessity of considering general cognitive function as indexed by IQ in the future studies of genetic bases of schizophrenia.
Neuropsychopharmacology (2012) **37,** 1572–1578; doi:10.1038/npp.2012.1; published online 29 February 2012

Keywords: schizophrenia; ZNF804A; working memory; executive function; polymorphism

INTRODUCTION

The zinc-finger protein 804A (*ZNF804A*) gene has a zinc finger domain at its N-terminal end and can thus bind DNA and regulate the expression of multiple genes. Recently, an intronic SNP in this gene, rs1344706, has been found to be one of the most compelling candidate SNPs for schizophrenia. As shown by a recent whole genome study (O'Donovan *et al*, 2008) and several follow-up replications (Riley *et al*, 2010; Williams *et al*, 2011; Steinberg *et al*, 2011), there is a strong association between this SNP and schizophrenia with the A allele being the risk allele. This association has also been replicated among Han Chinese population in two studies (Zhang *et al*, 2011; Xiao *et al*, 2011) but not a third one (Li *et al*, 2011).

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Received 14 September 2011; revised 21 December 2011; accepted 24 December 2011

Using cognitive intermediate phenotypes or other related neurobiological intermediate phenotypes such as functional MRI or structural MRI data, many studies found that the risk allele was associated with low cognitive functions (Balog *et al*, 2011; Hashimoto *et al*, 2010) and altered cortical activity (Esslinger *et al*, 2011; Esslinger *et al*, 2009; Walter *et al*, 2011) or volumes (Voineskos *et al*, 2011). By contrast, two studies in schizophrenia patients found different results (Walters *et al*, 2010; Donohoe *et al*, 2011). Walters *et al* (2010) assessed multiple cognitive functions in two samples (an Irish sample and a German sample) and found consistent results that the risk allele was significantly associated with better cognitive functions in multiple areas such as working memory and episodic memory in a dose-dependent pattern. Subsequently, their imaging study found relatively larger gray matter volumes in patients homozygous with the risk allele (Donohoe *et al*, 2011).

To further examine their counterintuitive results, Walters *et al*, 2010 tested the hypothesis that the role of rs1344706 may depend on patients' IQ. Indeed, they found that the higher the IQ, the stronger the association between rs1344706 and schizophrenia. However, Walters *et al* (2010) did not

examine whether IQ modulated the association between rs1344706 and cognitive functions of patients. This was perhaps because of the relatively small sample sizes of patients with high IQ levels (only 68 patients in the Irish sample and 126 in the German sample had IQ scores $\geqslant 100$).

The current study aimed to replicate results of Walters *et al* (2010) with a Chinese sample and extended their results by exploring the potential modulating effect of IQ on the role of rs1344706 in the cognitive intermediate phenotypes of schizophrenia. First, we aimed to replicate results of Walters *et al* (2010) that IQ may modulate the association between rs1344706 and schizophrenia. Then, we explored whether IQ may also modulate the association between rs1344706 and cognitive functions, especially in schizophrenia patients. We enrolled both patients and controls and included two specific cognitive functions, *viz.* spatial working memory measured by an N-back task and executive function measured by the attention network task (ANT). Both tasks or similar ones had been used in previous studies (Walters *et al,* 2010; Balog *et al*, 2011) and had been suggested to be associated with this SNP. We expected to replicate Walters *et al* (2010) results of IQ-modulated association between rs1344706 and schizophrenia (ie, stronger associations in patients with higher IQ). Because poor cognitive functions are the intermediate phenotypes of schizophrenia, we further hypothesized that, in patients with higher IQ (for whom the A allele is likely to be a risk allele), the A allele would be associated with poorer cognitive functions than would the C allele. For subjects with lower IQ, the A allele seemed to pose less a risk or no risk for schizophrenia; thus, we hypothesized that it would not be associated with poorer cognitive functions.

MATERIALS AND METHODS

Subjects

The sample consisted of 570 patients with schizophrenia (SCZ) and 448 healthy controls. All subjects were Han Chinese. The patients were recruited from the inpatients of the Ankang Hospital in Shangdong province, a division of the Jining Medical College, from August 2008 to July 2011. All patients had been hospitalized for <1 month and fulfilled the ICD-10 criteria for SCZ on the basis of diagnostic consensus of two experienced psychiatrists using the Mini International Neuropsychiatric Interview (MINI). This scale has a Chinese version with high reliability and validity (Si *et al*, 2009). Subjects were excluded if one of the psychiatrists was uncertain about a given patient's diagnosis. The general recruitment procedure was that a clinician first judged whether the patient satisfied the inclusion and the exclusion criteria (see below). The clinician and the psychologist then together explained the study to the patient, including drawing of blood and cognitive tests, and answered all questions. Subjects then signed informed consent document. Afterwards, the blood was drawn and the psychologist asked the patient to perform the cognitive tasks.

The positive and negative syndrome scale (PANSS) was used to assess each SCZ patient's positive (SAPS) and negative (SANS) symptoms at the time of the administration of the cognitive tests. The mean score of the patients' SAPS was 19.04 ± 6.48 and the mean SANS score was 17.33 ± 7.28. The mean duration of illness was 5.36 ± 7.83 years, and the mean number of previous hospitalizations was 1.99 ± 3.47. All patients were undergoing monotherapy with atypical antipsychotics and had been treated for >2 weeks. The mean chlorpromazine equivalent dose (CPZE) was 586.71 ± 426.15. Exclusion criteria for the patients included a history of other psychiatric disorders, a history of severe head injury (including any closed or open head injuries that may be related to current symptoms or impact cognitive functions), currently having acute psychotic episodes, current substance abuse, and failure to cooperate during the cognitive tests. Subjects were deemed by the experimenter as 'fail to cooperate' when they abruptly stopped performing tasks in the middle of the experiment, when they pressed keys only when prompted by the experimenter, and when they failed to cooperate to complete the practice trials of a test to reach an acceptable threshold of accuracy after multiple attempts.

The healthy controls were from the same geographical region as the patients and were interviewed by experienced psychiatrists to screen for any personal or family history of psychiatric disorders. Additional demographic information for both patients and the healthy controls is shown in Table 1. This study was approved by the Institutional Review Board of the Institute of Cognitive Neuroscience and Learning at Beijing Normal University, and all subjects gave written informed consent for this study.

Cognitive Tasks

Among all the subjects, 531 patients and 442 controls completed the Wechsler Adult Intelligence Scale-Revised (WAIS-RC). Both the N-back task and the ANT task were completed by almost all healthy controls (414 finished the N-back task and 416 finished the ANT task), but by only a subsample of the patients (366 finished the N-back task and 361 finished the ANT task) because these tasks were added later to data collection from the patients.

The N-back task was similar to the version introduced by Callicott *et al* (1998). In this task, a white circle was presented randomly at one of the four corners of a gray diamond-shaped square in a white background on an IBM 14-inch screen notebook. The four response buttons were arranged also in a diamond shape similar to the configuration of the white circles presented on the screen. Subjects used their right index or middle finger to press one of the four buttons to match the target stimulus. There were three task conditions: 0-, 1-, and 2-back. In the 0-back task, the

Table 1 Differences in the Demographic Data Among all Patients with SCZ and all Healthy Controls

	SCZ	Controls	F or χ^2	*P* value
Male, %	61.54	65.10	1.314	0.252
Age (years)	28.21 ± 7.84	22.96 ± 7.00	119.369	<0.001**
Education (years)	10.01 ± 2.88	10.68 ± 2.83	13.235	<0.001**
IQ[a,b]	97.09 ± 14.72	109.50 ± 11.88	207.029	<0.001**

[a]Age, gender, and education were used as covariates.
[b]Data were available from 531 patients and 442 controls.
**P value <0.05.

subjects were instructed to press the button whose position was the same as the white circle on the screen at the current trial. In the 1-back task, the subjects pressed the button corresponding to the position of the white circle presented one trial before the current one. In the 2-back task, the subjects pressed the button corresponding to the position of the white circle presented two trials before the current one. Each condition (performed in one block) included 48 trials. All subjects followed the order of 0-, 1-, and 2-back conditions. The stimulus presentation time was 200 ms and the inter-stimulus interval was 800 ms. Following Blokland *et al*, 2008's twin study, the current study used error rate (percentage of wrong responses) to index performance.

The ANT uses arrows pointing to the left or the right as stimuli, so it is believed to reflect the spatial conflict effect (Fan *et al*, 2003). More detailed descriptions of the design of this task can be found elsewhere (Fan *et al*, 2002). The current study used the short version of this test, which contained 144 trials and can be freely downloaded from Fan's web page (http://www.sacklerinstitute.org/users/jin.fan/). This version omitted the double cue conditions and the neutral target conditions, which were irrelevant to the calculation of the conflict effect. The conflict effect was calculated by subtracting the mean reaction time (RT) of all correct trials for the congruent target condition from the mean RT of correct trials for the incongruent target condition. Following the suggestion of Fan *et al* (2001), ratios of conflict effect were also calculated (conflict effect/mean RT) to take into account the direct or indirect effects of overall mean RT.

SNPs Genotyping

Rs1344706 was genotyped using Taqman allele-specific assays on the 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). The sample success rate for this SNP was 100% (ie, no failures across participants to 'call' the polymorphism) and the reproducibility of the genotyping was 100% according to a duplicate analysis of at least 2% of the genotypes.

Analysis

The Hardy-Weinberg test of the SNP was done by using the PLINK program (Purcell *et al*, 2007). All other analyses were done by using SPSS version 13.0. Non-genetic factors, including age, gender, IQ, and years of education among genotypic groups or between patients and controls were compared using either ANOVA or the χ^2 test. Firstly, following the procedure used by Walters *et al* (2010), the association between rs1344706 and schizophrenia was analyzed by χ^2 tests at different IQ levels. Secondly, hierarchical linear regression was used to examine the association between genotype and performance on the N-back and the ANT tasks. These analyses were done in patients and controls separately. Score for each cognitive task was entered as dependent variable. Genotype, IQ, and all the demographic factors were entered as independent variables. To explore the potential interaction between genotype and IQ, an interaction term was created by multiplying de-meaned IQ and genotype, and entered into the regression as an independent variable. Lastly, if significant interaction effects between genotype and IQ were found, further regression analyses of the effects of genotype were conducted in subjects with high and low IQ separately. In this analysis, genotype, IQ, and all demographic factors were entered as independent variables.

RESULTS

There were significant differences in mean age, education years, and IQ between SCZ patients and controls (all P values <0.05, see Table 1). After controlling for IQ and all the demographic factors, patients showed significantly higher error rates on the N-back task and stronger conflict effects of ANT than did the controls (all P values <0.001).

No deviation from Hardy-Weinberg equilibrium was found in the total samples ($P>0.05$). There were no significant differences in all demographic and clinical factors across genotypes in patients (all P values >0.05, see Supplementary Table S1). After controlling for all the demographic factors, there was no difference in IQ across genotypes in patients ($F=0.818$, $P=0.416$). As for controls, age ($F=4.664$, $P=0.010$) differed significantly across genotypes, whereas other demographic factors did not. After controlling for these demographic factors, IQ showed no difference across genotypes in controls ($F=1.961$, $P=0.142$) (see Supplementary Table S1).

Following the procedure used by Walters *et al* (2010), we progressively restricted both patients and controls by IQ scores, and tested whether rs1344706 had a more important role for the subgroup of schizophrenia patients with high IQ scores. Stronger associations emerged in samples with high IQ scores: $\chi^2=13.179$, $P=0.001$, for those with IQ of $\geqslant 100$ and $\chi^2=15.502$, $P=0.0004$, for those with IQ of $\geqslant 110$ (see Table 2).

Table 2 Associations Between rs1344706 and Schizophrenia According to IQ

IQ cutoff value	Sample	Number	Genotypes			χ_2	*P* value
			AA	AC	CC		
All	SCZ	570	179	285	106	6.536	0.038**
	Controls	448	116	223	109		
With IQ[a]	SCZ	531	165	266	100	5.986	0.050**
	Controls	442	115	218	109		
$\geqslant 70$	SCZ	510	159	254	97	5.682	0.058*
	Controls	442	115	218	109		
$\geqslant 80$	SCZ	461	143	232	86	5.273	0.072*
	Controls	440	115	218	107		
$\geqslant 90$	SCZ	375	116	187	72	5.691	0.058*
	Controls	414	103	207	104		
$\geqslant 100$	SCZ	238	80	123	35	13.179	0.001**
	Controls	352	87	172	93		
$\geqslant 110$	SCZ	115	43	58	14	15.502	<0.001**
	Controls	239	55	114	70		

[a]Subjects whose IQ were assessed.
*$P\leqslant 0.1$; **$P\leqslant 0.05$.

Table 3 Cogntive Analysis by rs1344706 and IQ in Patients and Controls

	Number	Mean ± SD			IQ Effect	Genotype Effect	Interaction Effect
		AA	AC	CC	Beta (*P* value)	Beta (*P* value)	Beta (*P* value)
Patients							
Error rate at 1-back	366	0.35 ± 0.22 (123)	0.37 ± 0.24 (189)	0.37 ± 0.25 (54)	−0.394 (<0.001)**	−0.022 (0.655)	−0.154 (0.008)**
Error rate at 2-back	366	0.67 ± 0.20 (123)	0.65 ± 0.19 (189)	0.69 ± 0.20 (54)	−0.408 (<0.001)**	0.035 (0.477)	−0.120 (0.034)**
Conflict effect	361	90.80 ± 69.60 (123)	96.38 ± 64.37 (185)	99.17 ± 92.74 (53)	−0.156 (0.015)**	−0.006 (0.914)	−0.179 (0.004)**
Conflict effect ratios	361	0.12 ± 0.08 (123)	0.13 ± 0.08 (185)	0.13 ± 0.12 (53)	−0.056 (0.386)	0.006 (0.905)	−0.154 (0.014)**
Controls							
Error rate at 1-back	414	0.14 ± 0.15 (110)	0.17 ± 0.17 (203)	0.16 ± 0.14 (101)	−0.165 (0.003)**	0.005 (0.932)	−0.001 (0.991)
Error rate at 2-back	414	0.39 ± 0.26 (110)	0.41 ± 0.25 (203)	0.38 ± 0.25 (101)	−0.246 (<0.001)**	0.005 (0.931)	−0.029 (0.604)
Conflict effect	416	89.95 ± 38.25 (106)	86.26 ± 39.01 (207)	85.09 ± 35.88 (103)	−0.208 (<0.001)**	0.004 (0.948)	−0.042 (0.475)
Conflict effect ratios	416	0.15 ± 0.05 (106)	0.15 ± 0.06 (207)	0.14 ± 0.15 (103)	−0.099 (0.096)	−0.016 (0.794)	−0.043 (0.473)

**$P \leqslant 0.05$.

The linear regression analysis of the effects of genotype and IQ on cognitive measures among patients showed no main effects of genotype (all $P > 0.05$, (See Table 3 for details), but significant main effects of IQ (all $P < 0.05$) and significant interactions between genotype and IQ for all measures of the two tasks (for the error rate of 1-back, $P = 0.008$; for the error rate of 2-back, $P = 0.034$; for the conflict effect of ANT, $P = 0.004$; and for the conflict ratio of ANT, $P = 0.014$). For controls, there were a significant main effect of IQ, but the main effect of genotypes (all $P > 0.05$) and the interaction (all $P > 0.05$) were not significant.

We then divided the patients into two separate subgroups: those with high IQ (scores $\geqslant 100$) and those with low IQ (scores < 100). In the low-IQ subgroup, compared with the CC genotype, the AA and AC genotypes showed lower error rates in both measures of the N-back task (for the error rate of 1-back, $P = 0.037$; and for the error rate of 2-back, $P = 0.017$) and smaller conflict effects in the ANT task (for the conflict effect, $P = 0.046$; and for the conflict ratio, $P = 0.034$). However, in the high-IQ subgroup, the direction of the associations was reversed. Compared with the CC genotype, the AA and AC genotypes showed higher error rates in the 1-back task (for the error rate of 1-back, $P = 0.050$) and larger conflict effects in the ANT task (for the conflict effect, $P = 0.026$; and for the conflict ratio, $P = 0.038$) (see Figure 1). The result for the 2-back task was not significant ($P = 0.929$). To further investigate whether our results could have been due to confounding factors, we added the onset age, duration of disease, CPZE dose, SAPS, and SANS as additional independent factors in the above analyses. Results showed that the association patterns did not change (see Supplementary Tables S4 and S5).

DISCUSSION

Consistent with previous studies (Riley *et al*, 2010; Williams *et al*, 2011; Steinberg *et al*, 2011; Zhang *et al*, 2011; Xiao *et al*, 2011, see Li *et al*, 2011, for an exception), the current study found evidence for the association between rs1344706 and schizophrenia. In addition, we replicated results of Walters *et al* (2010) that the association between rs1344706 and schizophrenia became stronger when the samples were limited to those with relatively high IQ. In other words, this SNP poses more risk to high-IQ patients. Moreover, we found consistent interaction effects between rs1344706 and IQ on patients' cognitive functions. As we hypothesized, in patients with higher IQ, the risk allele was associated with poorer cognitive functions (higher error rates on the N-back task and larger conflict effects on the ANT task) but in patients with lower IQ, the risk allele was associated with better cognitive functions.

The SNP rs1344706 was firstly suggested as a candidate SNP for schizophrenia by a large multicenter cooperation study (O'Donovan *et al*, 2008) that used the whole genome scan technique on several independent samples and also by a meta-analysis of combined samples. This finding has been replicated by other studies of various ethnic groups. Including our study, there have been three studies showing the association between rs1344706 and schizophrenia in Han Chinese population (Zhang *et al*, 2011; Xiao *et al*, 2011). All these studies had sample sizes of about 500 pairs of patients and controls, and consistently found the A allele of this SNP to be the risk allele for schizophrenia. However, using almost the same sample size, Li *et al* (2011) did not replicate this association in two independent samples. It is noteworthy that the allele frequencies were somewhat different across these studies. There appears to be a north–south difference. Control samples from northern China showed a higher A allele frequency (0.52 in the HapMap database from Beijing, 0.54 in Xiao *et al* (2011) from Beijing also, and 0.51 in the current study from Shandong Province) than did a southern Chinese sample (0.46 in Zhang *et al* (2012) from Sichuan province and 0.49 in Li *et al* (2011) from Yunnan province). For patients, the frequency of the A allele in Zhang *et al*'s study was 0.527, a frequency similar to that of controls from northern China, was also quite different from those of patients in northern China in both Xiao *et al*'s (2011) and our study. This discrepancy may reflect variations within Chinese population (Li *et al*, 2010), and thus is worth noting as a reference for future studies. Moreover, as suggested

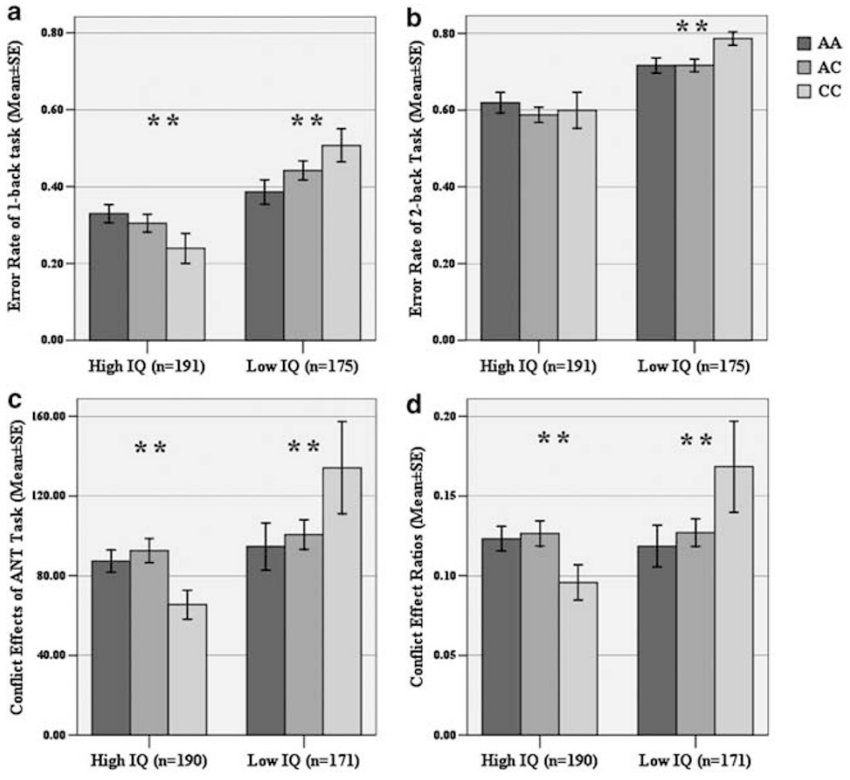

Figure 1 Cognitive functions by rs1344706 genotype and IQ in schizophrenia patients. For patients with higher IQ, compared with CC genotype, the clinical risk allele (a) homozygotes and the heterozygotes made more errors at the 1-back task (the left panel-a) and stronger conflict effect of the ANT task (the left panel-c and d). By contrast, for patients with lower IQ, the clinical risk allele (a) homozygotes and the heterozygotes made fewer errors at both the 1-back (the right panel-a) and 2-back task (the right panel-b) and weaker conflict effect of the ANT task (the right panel-c and d).

by the study of Walters *et al* (2010) and as replicated by our current results, rs1344706 may have a special role in the subgroup of patients with relatively high IQ. It appears that different demographic characteristics across studies may also have contributed to the discrepant results. For example, studies that included more patients with a chronic course, older age, or other characteristics that may impair IQ (Seidman *et al*, 2006) may end up with a weaker association between rs1344706 and schizophrenia.

The most important contribution of the current study may be that we found significant interaction effects between rs1344706 and IQ on patients' cognitive impairments. In patients with an IQ of $\geqslant 100$, we found that the A allele was linked to a poorer cognitive function, but the effect was reversed in patients with an IQ <100. Our results can be used to reconcile previous inconsistent results about schizophrenia patients between Walters *et al* (2010) and Hashimoto *et al* (2010) studies. In the study of Walters *et al* (2010), most patients (about 220 out of 288 patients in the Irish sample) had an IQ of <100 and the directions of the associations were consistent with our results in patients with lower IQ. By contrast, although no IQ data were available in Hashimoto *et al* (2010), their patients had a high level of education with a mean of >14 years and a SD of about 2 years, who as a group were likely to have above average IQ because of the high correlation between IQ and education levels (Petrill *et al* (2010)). Hashimoto *et al* (2010) found a link between A allele and poorer cognitive function, which is similar to our results in patients with relatively high IQ.

As for the role of this SNP in controls, the results have been mixed. Four studies including ours (Donohoe *et al*, 2011; Walters *et al*, 2010; Hashimoto *et al*, 2010) that enrolled both patients and controls consistently found no significant contributions of this SNP to cognitive function in controls, although they all found significant results in patients. Interestingly, there are at least six studies that enrolled controls only and found significant results (Lencz *et al*, 2010; Balog *et al*, 2011; Esslinger *et al*, 2009; Esslinger *et al*, 2011; Voineskos *et al*, 2011; Walter *et al*, 2011). Five of these studies, however, were imaging genetic studies using intermediate phenotypes. Using almost the same N-back task as the current study, the two fMRI studies by Esslinger *et al* (2009, 2011) did not find significant differences at the dorsolateral prefrontal cortex and hippocampus cortex, but found significant results in connectivity within or between these cortexes. Perhaps the effect of this SNP in controls is subtler than in schizophrenia patients, and can only be detected with sensitive imaging measures (sometimes indirect measures). In other words, our behavioral measures might not have been sensitive enough, and thus yielded negative results in controls.

Another finding that needs discussion is that, in the patients with high IQ, we found significant results for the 1-back task but not for the 2-back task. This pattern seems similar to our previous results about the association between rs1006737 and the same tasks (Zhang *et al*, 2012). As we argued in the other article, compared with the 2-back task, the 1-back task is simpler and may involve fewer

neural and cognitive components, and is consequently a better intermediate phenotype of schizophrenia.

Some limitations of the current study need to be mentioned. First, the mean IQs of both patients and controls were higher than the theoretical mean of 100. There are two explanations for this finding. The current study used the only existing full WAIS-RC (Gong and Caitai, 1993), which was based on the older WAIS and was standardized and normalized with data collected in the 1980s. Therefore, the Flynn effect (Flynn, 1987), coupled with the rapid urbanization and development of secondary and higher education in China, would have contributed to the higher mean IQs of this study's subjects. The second reason for the higher IQs of our samples is that subjects with low IQs were more likely to fail the practice trials especially on the computerized cognitive tasks, thus had to be excluded. An updated IQ test and easier cognitive tasks are needed in future research to overcome this limitation.

Second, patients in this study seemed to have lower scores of both negative and positive symptoms than some previous studies (eg, Darwish *et al*, 2011; Majadas *et al*, 2012; Rabany *et al*, 2011). The most likely explanation is that patients who were severely impaired could not perform the computerized tasks. Consistent with this explanation, none of the studies cited above for higher symptoms used cognitive tasks. In contrast, other genetic studies that used cognitive measures as intermediate phenotypes (eg, Hashimoto *et al*, 2010; Quednow *et al*, 2011; Opgen-Rhein *et al*, 2008; Ehlis *et al*, 2007) had similar PANSS scores as the current study. In any case, however, it should be cautioned that results from studies that used cognitive tasks might not be generalized to low-functioning patients.

Lastly, some demographic factors were not well-matched across the genotypic groups (see Supplementary Tables S1, S2, and S3). Although these demographic factors were included as covariates in all the analyses on the associations between genotype and cognitive measures, better-matched samples through targeted sampling should yield more convincing results. Moreover, although the exact function of ZNF804A is unknown, the zinc-finger domain of ZNF804A made it possible to interact with many other RNA and protein molecules. However, the current study did not control for these molecular factors or other genes such as COMT (Stokes *et al*, 2011) and DARPP-32 (Houlihan *et al*, 2009) that are known to modulate cognitive functions. Future research should study interactions among these genes.

In conclusion, the current study found a possible modulating effect of IQ on the roles of rs1344706 for the etiology of schizophrenia and its cognitive impairments. The directions of the associations between this SNP and cognitive function were opposite in patients with high as opposed to low IQ. All these results indicated that this SNP may be a risk factor for a subgroup of schizophrenia with relatively unimpaired cognitive functions, which deepened our current understanding on the role of this SNP and highlighted the necessity to consider IQ in future studies of genetic bases of schizophrenia.

ACKNOWLEDGEMENTS

This work was supported by the Natural Science Foundation of China. (30800294), the Medical Science and Technology Plan of Shandong Province (2009QZ003), and the Fundamental Research Funds for the Central Universities.

DISCLOSURE

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)