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The *GABRB1* gene is associated with thalamus volume and modulates the association between thalamus volume and intelligence

Bi Zhu [a,b,*], Chuansheng Chen [c,**], Gui Xue [a,b], Xuemei Lei [a,b], Jin Li [a,b], Robert K. Moyzis [d], Qi Dong [a,b], Chongde Lin [a,b]

[a] State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, China
[b] Center for Collaboration and Innovation in Brain and Learning Sciences, Beijing Normal University, Beijing, China
[c] Department of Psychology and Social Behavior, University of California, Irvine, CA, USA
[d] Department of Biological Chemistry and Institute of Genomics and Bioinformatics, University of California, Irvine, CA, USA

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ABSTRACT

The *GABRB1* gene encodes the beta 1 subunit of the gamma-aminobutyric acid A receptor (GABA A receptor), which is responsible for mediating inhibitory neurotransmission in the thalamus. Potential relationships between the *GABRB1* gene, thalamus volume, and intelligence have been suggested by previous clinical studies, but have not been directly examined among nonclinical samples. The current study collected structural MRI, genetic, and behavioral data from 316 healthy Chinese adults (including 187 females and 129 males), and examined associations between *GABRB1* variants, thalamus volume, and intelligence (measured by the Wechsler Adult Intelligence Scale Revised). After controlling for intracranial volume, sex, and age, *GABRB1* genetic polymorphism at the SNP rs7435958 had the strongest association with thalamus volume ($p = 0.002$ and 0.00008 for left and right thalamus volumes, respectively), with GG homozygotes having smaller bilateral thalamus volumes than the other genotypes. Furthermore, there were positive correlations between bilateral thalamus volumes and intelligence, especially for *GABRB1* rs7435958 GG female homozygotes (r's $= 0.31$ and 0.29, $p < 0.01$, for the correlations of intelligence with left and right thalamus volumes, respectively). This study provides the first evidence for the involvement of the *GABRB1* gene in the thalamus structure and their interactive effects on intelligence. Future studies of the thalamus–intelligence associations should consider genetic factors as potential moderators.

Introduction

The thalamus, situated between the cerebral cortex and the midbrain, serves as a central relay station of the brain by filtering and gating sensory and motor signals to the cerebral cortex (Van der Werf et al., 2000). Several recent twin studies have suggested that thalamus volume has high heritability (i.e., about 80%) (Bohlken et al., 2014; den Braber et al., 2013). In terms of specific genes likely to be involved in the thalamus structure and function, *GABRB1* (i.e., gamma-aminobutyric acid receptor subunit beta-1) is a good candidate. *GABRB1* encodes the beta 1 subunit of GABA A receptors, which mediates most of the fast inhibitory synaptic transmission in the mammalian brain. This gene's expression has been found to influence the fast inhibitory postsynaptic current in the thalamus (Huntsman and Huguenard, 2006), because GABAergic neurons accounted for about 30% of the neurons in human thalamus (Letinic and Rakic, 2001).

Potential associations between *GABRB1* and thalamus volume have been suggested by several previous studies of clinical samples, including patients with alcohol dependence, neuropathic pain, bipolar disorder, autism, and schizophrenia. First, *GABRB1* was associated with alcohol dependence (Porjesz et al., 2002; Song et al., 2003), and such patients showed reduced thalamus volume (Jernigan et al., 1991; Sullivan et al., 2003). Second, a common haplotype in the *GABRB1* gene was associated with movement limitation in patients with neuropathic pain (Mishra et al., 2007), and such patients showed significantly reduced thalamus volume and lower GABA level within the thalamus (Henderson et al., 2013). Third, *GABRB1* genetic polymorphisms were associated with bipolar disorder based on a genome-wide association study (Hamshere et al., 2009), and GABRB1 protein was significantly reduced in the brain of bipolar disorder patients (Fatemi et al., 2013). Moreover, bipolar disorder patients not treated with lithium had smaller right thalamus volume (Radenbach et al., 2010). Fourth, *GABRB1* genetic variants were associated with autism in families with a positive history for seizures (Collins et al., 2006), and autism was associated with the gene–gene interaction between *GABRB1* and *GABRA4* (Ma et al., 2005). Researchers also

* Correspondence to: B. Zhu, State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, China. Fax: +86 10 58808470.
** Correspondence to: C. Chen, Psychology and Social Behavior; 4201 Social & Behavioral Sciences Gateway, University of California, Irvine; Irvine, CA 92697-7085, USA. Fax: +1 949 824 3002.
E-mail addresses: psyzhubi@gmail.com (B. Zhu), cschen@uci.edu (C. Chen).

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suggested that autism patients showed altered *GABRB1* expression in the brain (Fatemi et al., 2010). In addition, the reduction of thalamus volume was reported in autism patients (Tamura et al., 2010; Tsatsanis et al., 2003) and in children with complex partial seizures (Lin et al., 2013). Finally, schizophrenia was found to be associated with a set of genes including *GABRB1* based on a gene expression profiling analysis in a Han Chinese sample (Yu et al., 2014). Moreover, schizophrenia patients had significantly reduced expression of GABRB1 protein in the brain (Fatemi et al., 2013), and reduced thalamus volume (Adriano et al., 2010), especially in antipsychotic-naive schizophrenia patients (Haijma et al., 2013). In general, the *GABRB1* gene has been associated with many neuropsychological diseases as mentioned above, and patients with these diseases usually have abnormal thalamus volume.

The thalamus, due to its essential role in corticocortical interactions, is involved with many processes underlying intellectual ability in healthy and clinical samples (Bohlken et al., 2014; Xie et al., 2012). First, several studies suggested that thalamus volume was positively correlated with intelligence in healthy subjects (Bohlken et al., 2014; Raznahan et al., 2014). Specifically, Bohlken et al. (2014) suggested that, among all subcortical volumes, only thalamus volume was positively correlated with intelligence in healthy adults. The other studies showed that thalamus volume was positively correlated with general intelligence measured by Wechsler Intelligence Scales in healthy youth aged between 5 and 25 years old (Raznahan et al., 2014), verbal intelligence in healthy children and adolescents (Xie et al., 2012), performance on cognitive speed tasks in young and middle-aged healthy subjects (Van Der Werf et al., 2001), and verbal memory in healthy adults (Philp et al., 2014). Second, consistent with the data from healthy subjects, positive associations between thalamus volume and intelligence have also been revealed when examining clinical samples and/or when comparing them with healthy samples. For example, extremely preterm adolescents were found to have smaller thalamus volume and lower intelligence than control subjects, while within each sample there was a positive correlation between thalamus volume and intelligence (Cheong et al., 2013). Bjuland et al. (2014) further found that, among all subcortical volumes, thalamus volume had the highest positive correlation with intelligence measured by Wechsler Adult Intelligence Scales in young adults born preterm with very low birth weight. Subjects with intellectual disabilities (IQ < 70) also showed smaller left thalamus than did normal controls (Mannerkoski et al., 2009). In addition, reduced thalamus volume was found to be correlated with various poor intellectual performance in patients with alcohol-dependence, schizophrenia, complex partial seizures, sickle cell anemia, tuberous sclerosis complex, and periventricular leukomalacia (Chanraud et al., 2007; Coscia et al., 2009; Lin et al., 2013; Mackin et al., 2014; Ridler et al., 2007; Zubiaurre-Elorza et al., 2012).

However, not all studies found positive associations between thalamus volume and intelligence (Crespo-Facorro et al., 2007; Hartberg et al., 2011). Some studies reported no correlation between thalamus volume and intelligence in healthy samples or clinical samples, and some even reported negative correlations in clinical samples. For example, a previous study reported that there were no significant correlations between thalamus volume and intelligence in either healthy middle-aged adults or patients with schizophrenia or bipolar disorder (Hartberg et al., 2011). Another study reported a significant negative association between thalamus volume and cognitive function in patients with first-episode non-affective psychosis when controlling for intracranial volume (ICV), but the correlation was not significant in a small sample of healthy young adults (Crespo-Facorro et al., 2007). Sex differences were also reported in the correlations between structural brain variation and intelligence (Deary et al., 2010). For example, gray matter in the thalamus pulvinar area was found to be positively correlated with verbal intelligence in healthy adult females but not in males (Haier et al., 2005). Females had smaller thalamus volume than males, but females had a greater ratio of thalamus to grey matter than males (Xie et al., 2012). A recent study showed that females attained peak thalamus volume significantly earlier than males, and the positive correlation between thalamus volume and intelligence disappeared after correcting for total brain volume in healthy children and adolescents (Raznahan et al., 2014). One possible reason for such discrepant results is that the association between thalamus volume and intelligence might be modulated by age, sex, ICV, and genetic factors (especially genes related to the thalamus). Indeed, a recent twin study found a positive correlation between thalamus volume and intelligence, but this correlation was higher among monozygotic twins than among dizygotic twins, suggesting that genetic factors influence the association between thalamus volume and intelligence (Bohlken et al., 2014). Molecular genetics research is needed to identify specific genes that moderate the relationship between thalamus volume and intelligence.

In sum, evidence from separate lines of research has suggested potential relationships among the *GABRB1* gene, thalamus volume, and intelligence, but these variables have not been studied together in the same study. Such studies are necessary in order to examine gene–brain interaction effect on behavior (Green et al., 2008; Schmidt et al., 2009). In the present study, we first performed an association study of thalamus volume and single nucleotide polymorphisms (SNPs) within the *GABRB1* gene in a sample of healthy Han Chinese adults. Based on the association results, we then selected the *GABRB1* genetic polymorphism most significantly associated with thalamus volume and examined the potential effects of this genetic variant and thalamus volume as well as their interaction on intelligence.

Materials and methods

Participants

Participants were 316 healthy Han Chinese college students (mean age = 20.41 years, *SD* = 0.89, range 18–22 years old; 59% female, 98.4% right handed). All participants had valid brain imaging, genotype, and behavioral data. They had normal or corrected-to-normal vision and had no history of psychiatric or neurological diseases, head injuries, or stroke/seizure. Individuals in this sample were all unrelated to one another. Written consent was obtained from each participant after a full explanation of the study procedure. This study was approved by the Institutional Review Board (IRB) of Beijing Normal University, China. Handedness did not influence any result in the current study; therefore, we included all subjects in the analysis.

MRI data collection and analysis

MRI scans were performed on a 3.0T Siemens Magnetom Trio scanner equipped with a standard head coil at the Beijing Normal University Brain Imaging Center. Structural MRI data were acquired with the T1-weighted, three-dimensional, MPRAGE pulse sequence, using the following imaging parameters: TE = 3.75 ms, TR = 2530 ms, flip angle = 7°; FOV = 256 mm × 256 mm, voxel size = 1 × 1 × 1.33 mm^3, number of partitions = 128. To extract volumetric measures of regions of interest, MRI data were analyzed automatically with atlas-based FreeSurfer segmentation software (http://surfer.nmr.mgh.harvard.edu, version 5.0.0) (Fischl et al., 2002). Volumes of bilateral thalami were generated according to the standard FreeSurfer segmentation and parcellation procedures, relying upon variations in voxel signal intensities, probabilistic atlas location, and local spatial relationships between the structures (Fischl et al., 2002). Previous research provided strong evidence for the reliability of thalamus volume estimation using FreeSurfer (Keller et al., 2012). See Supplemental Materials Fig. S1 for Freesurfer subcortical segmentation of the thalamus for two extreme examples from this study. Intracranial volume (ICV), including brain tissues and other biological materials such as meninges and cerebrospinal fluid, was taken from the standard output of FreeSurfer analysis as well. Quality control of scan images and segmentation was assured by visual inspection of the whole cortex of each subject.

Any inaccuracies in Talairach-transformation, skull stripping, and segmentation were manually corrected, and re-inspected.

Genotyping and quality control

A 4 ml venous blood sample was collected from each subject. Genomic DNA was extracted according to standard methods within two weeks after the blood sample was collected. All samples were genotyped using the standard Affymetrix genotyping protocol (Affymetrix, Inc). As described in Supplemental Materials Table S1, 49 SNPs within the *GABRB1* gene on chromosome 4 were selected, and the allele frequencies in our sample were very similar to those of the Chinese sample in the HapMap dataset. These SNPs covered most of the linkage disequilibrium (LD) blocks in this gene, as defined for the Chinese samples included in the HapMap Project (http://www.hapmap.org [phase 3], also see Supplemental Materials Figs. S2–S5 for the LD plots of the *GABRB1* gene in different populations). The *GABRB1* gene contains 9 exons and 8 introns. All SNPs met the following criteria: minor allele frequency (MAF) > 0.10, Hardy–Weinberg equilibrium (HWE) $p > 0.05$, and genotype call rate > 0.95.

Behavioral assessment

To assess general intelligence, all subjects were tested with the Chinese adaptation of the Wechsler Adult Intelligence Scale—Revised (city version) (i.e., WAIS-R), which includes six subtests (three verbal and three performance tests). This test was individually administered for about 30 min. The three verbal tests assessed general knowledge (tapping general information acquired from one's culture), similarities (abstract verbal reasoning), and digit span (attention and concentration). The three performance tests assessed picture completion (ability to quickly perceive visual details), symbol digit coding (visual–motor coordination and motor and mental speed), and block design (spatial perception, visual abstract processing, and problem solving). This test had good reliability and validity in China (the test–retest reliability was 0.89) (Gong, 1992). The full scale intelligence score was used as the measure of intelligence in the current study.

Statistical analysis

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 thalamus volume. Linear regression models were used to detect the associations between each SNP and thalamus volume in each hemisphere. Additive genetic models (i.e., additive effects of allele dosage) were used, with sex, age, and ICV included as covariates. In order to test genotype group differences in thalamus volumes, MANCOVA and the Fisher's least significant difference (LSD) post hoc tests were performed with sex, age, and ICV as covariates in SPSS 16.0. Next, we selected the SNP with the strongest association with thalamus volume for further analysis.

We then obtained partial correlations between intelligence and thalamus volume after partialling out sex, age, and ICV in one analysis, and after partialling out age and ICV in another analysis that was run for female and male subjects separately.

In order to test the effects of thalamus volume and the genotype of the identified SNP as well as their interactive effect on intelligence, linear regression models were performed in SPSS 16.0. The score of intelligence was the dependent variable, and independent variables included thalamus volumes (left and right thalamus volumes separately), the genotype of this SNP (i.e., using this genotype as a continuous [dosage] variable), and their interaction term (which was created by multiplying the two independent variables after they were de-meaned or centered to control for multi-collinearity [Aiken et al., 1991]). Age and ICV were also included as covariates of no-interest. As suggested by a previous study (Haier et al., 2005), due to sex differences in the correlation between thalamus and intelligence (and confirmed by our own results, see below), the linear regression models were performed for female and male subjects separately. Potential interactions were further examined by obtaining partial correlations between intelligence and thalamus volume for each genotype of this SNP (i.e., major allele homozygotes, heterozygotes, and minor allele homozygotes) with age and ICV as covariates.

Results

The means and standard deviations of left and right thalamus volumes, intracranial volume (ICV), and intelligence score, as well as correlations among these variables are shown in Table 1 (also see Supplemental Materials Fig. S6 for detailed distributions of these variables). Females had significantly smaller bilateral thalamus volumes and ICV than did males ($t = -10.49$, -11.20 and -12.77, $p < 0.001$, for the left and right thalamus volumes and ICV, respectively). There was no sex difference in intelligence score ($t = -0.22$, $p > 0.05$). Age had a small but statistically significant negative correlation with intelligence score ($r = -0.13$, $p < 0.05$), but not with bilateral thalamus volumes or ICV ($r = 0.04$, 0.05, and 0.06, $p > 0.05$, for the left and right thalamus volumes and ICV, respectively). Age, sex, and ICV were used as covariates in the subsequent analyses.

As presented in Fig. 1 and Supplemental Materials Table S2, genetic association analysis using Plink showed that a SNP (rs7435958) within the *GABRB1* gene had the strongest association with thalamus volume ($\beta = 142.20$ and 173.20, $t = 3.19$ and 4.01, $p = 0.002$ and 0.00008 for the left and right thalamus volumes, respectively), with age, sex, and ICV as covariates. The G allele was associated with smaller left and right thalamus volumes. In order to test genotype group differences in thalamus volume, MANCOVA and the Fisher's least significant difference (LSD) post hoc test were also performed with age, sex, and ICV as covariates. After controlling for age, sex, and ICV, the *GABRB1* rs7435958 GG homozygotes had smaller bilateral thalamus volumes than CG heterozygotes ($p = 0.006$ and 0.0002 for the left and right thalamus volumes, respectively) and CC homozygotes ($p = 0.016$ and 0.005 and for the left and right thalamus volumes, respectively), but there were no significant differences between CG heterozygotes and CC homozygotes in bilateral thalamus volumes ($p = 0.43$ and 0.58 for the left and right thalamus volumes, respectively). Haplotype analysis of directly genotyped variants near rs7435958 in the current sample confirmed that the association was present across SNPs in the haplotype (see Supplemental Note 1 and Fig. S7 for details). After correcting for multiple testing by max(T) permutation approach in Plink (10000 permutation) for individual SNPs within the *GABRB1* gene, SNP rs7435958 remained significantly associated with thalamus volume (corrected empirical p-values [max(T) / familywise] = 0.029 and 0.002 for the left and right thalamus volumes, respectively). We selected the SNP rs7435958 for subsequent analysis, because it had the strongest association with bilateral thalamus volumes. In addition, complete results for the other SNPs within the *GABRB1* gene are shown in the Supplemental Materials Table S2 and a summary of gender differences is in Supplemental Note 2 (Additional analyses).

There were significant positive correlations between intelligence and bilateral thalamus volumes after controlling for age, sex, and ICV ($r = 0.16$ and 0.17, $p = 0.004$ and 0.002, for the correlations of intelligence with left and right thalamus volumes, respectively). For females, there were significant positive correlations between intelligence and bilateral thalamus volumes after controlling for age and ICV ($r = 0.21$ and 0.19, $p = 0.004$ and 0.008, for the correlations of intelligence with left and right thalamus volumes, respectively). For males, there was no significant correlation between intelligence and bilateral thalamus volumes after controlling for age and ICV ($r = 0.09$ and 0.14, $p = 0.304$ and 0.112, for the correlations of intelligence with left and right thalamus volumes, respectively).

Table 1
Descriptive statistics and correlations among phenotypic variables ($N = 316$).

	Mean	SD	Left thalamus volume	Right thalamus volume	ICV
Left thalamus volume	7031.74	698.66			
Right thalamus volume	7134.81	702.43	.92***		
ICV	1,463,759.81	227,597.56	.64***	.66***	
Intelligence	125.60	8.33	.18**	.18**	.10

Note: ** $p < .01$, *** $p < .001$; the unit of brain structural volume is mm^3. ICV: intracranial volume.

To explore the joint effect of *GABRB1* rs7435958 genotype and thalamus structure on intelligence, linear regression analyses were conducted for female and male subjects separately. Intelligence score was the dependent variable, with the *GABRB1* rs7435958 genotype, lateral thalamus volume, and their interaction as predictors, and age and ICV as control variables. For females, the *GABRB1* rs7435958 genotype had significant interactions with lateral thalamus volume on intelligence ($t = -2.42$ and -2.24, $p = 0.017$ and 0.026 for its interactions with left and right thalamus volumes, respectively). However, for males, the *GABRB1* rs7435958 genotype did not have significant interactions with lateral thalamus volume on intelligence ($t = -0.84$ and 0.29, $p = 0.401$ and 0.774 for its interactions with left and right thalamus volumes, respectively).

We further examined the associations between bilateral thalamus volumes and intelligence for the three *GABRB1* rs7435958 genotypes separately (GG homozygotes, CG heterozygotes, and CC homozygotes, as well as combined CG and CC groups to form the C carrier group) in female and male subjects, respectively. Although this analysis was taxing the statistical power, it should be suggestive in terms of which subgroups of subjects contributed the most to the associations among the

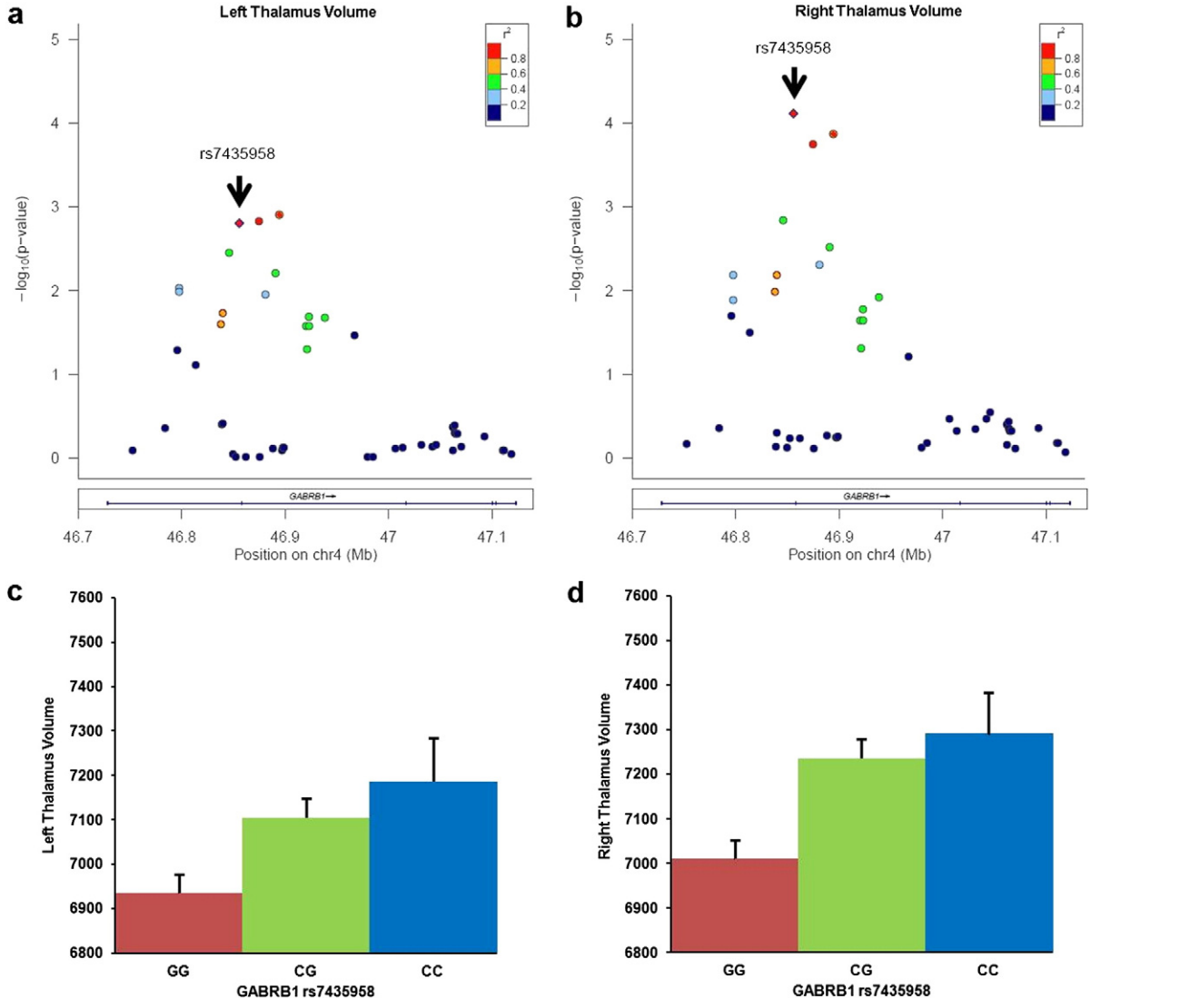

Fig. 1. Associations between 49 SNPs within the *GABRB1* gene and bilateral thalamus volumes with sex, age and ICV as covariates (a and b at the top) and diagrams of allele-specific thalamus volumes (means and standard errors) in rs7435958 GG homozygotes, CG heterozygotes, and CC homozygotes within the *GABRB1* gene (c and d at the bottom) with sex, age and ICV as covariates. For a and b, all SNPs are plotted with their *p* values against their genomic position. The strongest association with right thalamus volume was found for rs7435958. Genotyped SNPs are plotted as dots, with the color indicating the degree of pairwise LD between the leading SNP rs7435958 and neighboring SNPs. Red indicates strong pairwise LD, with $r^2 > 0.8$; dark blue indicates no LD, with $r^2 < 0.2$. For c and d, mean thalamus volumes are plotted as a function of genotype after controlling for age, sex, and ICV.

GABRB1 gene, thalamus volume, and intelligence. Age and ICV were used as covariates again. Only for the female *GABRB1* rs7435958GG homozygotes ($N = 86$), did we find significant positive correlations between bilateral thalamus volumes and intelligence ($r = 0.31$ and 0.29, $p = 0.004$ and 0.008 for left and right thalamus volumes, respectively) (see Table 2 and Fig. 2). There was no significant correlation between bilateral thalamus volumes and intelligence for the other two genotype groups or their combined group in females, and no significant correlation between bilateral thalamus volumes and intelligence in males (p's > 0.05, actual p values and other details can be seen in Table 2).

Additional analyses were conducted to examine potential confounding variables such as mental health-related factors (e.g., depression, anxiety, alcohol and smoking). Results reported above were not changed when these variables were considered. Detailed results can be seen in the Supplemental Materials (Supplemental Note 2).

Discussion

In the present study, we investigated whether the *GABRB1* gene was associated with thalamus volume and whether this gene and thalamus volume were associated with intelligence as measured by WAIS-R in healthy Chinese adults. We identified a SNP (rs7435958) within the *GABRB1* gene that was significantly associated with thalamus volume; *GABRB1* rs7435958 GG homozygotes had smaller thalamus volume than other genotypes. We also found a significant positive correlation between thalamus volume and intelligence, which appeared to be driven mostly by *GABRB1* rs7435958 GG female homozygotes. These effects were independent of subjects' age, sex, ICV, and mental health-related covariates that might have been related to thalamus volumes (see Supplementary Materials, Note 2). These results demonstrated the critical role of the *GABRB1* gene in the thalamus structure and its moderating effect on the relation between the thalamus and intelligence (especially for females).

The SNP rs7435958, located in the third intron of the *GABRB1* gene, is very close to the fourth exon (about 2 kb away) of the gene. It serves as a marker for a number of polymorphisms in the haplotype block. Any of these SNPs in the haplotype block may have functional consequences on the amount of GABRB1 protein synthesized. As presented in the supplemental Fig. S8, the *GABRB1* rs7435958 had relatively high LD with a nearby SNP rs2351299 ($r^2 = 0.75$ in the current sample and $r^2 = 0.79$ and in the Han Chinese sample based on the HapMap data; see Table S2 for our results on SNP rs2351299). Previous studies suggested the *GABRB1* rs2351299 was associated with autism in families with a positive history for seizures (Collins et al., 2006), and its interaction with rs1912960 in the *GABRA4* gene was also associated with autism (Ma et al., 2005), while autism was associated with smaller thalamus volume (Tamura et al., 2010; Tsatsanis et al., 2003). In other words, the *GABRB1* rs2351299 GG (i.e., a plausible risk genotype for autism) had relatively high LD with the *GABRB1* rs7435958 GG genotype (i.e., a genotype associated with smaller thalamus volume). Therefore, future studies should explore potential associations between the *GABRB1* rs7435958 genotype and thalamus volume of individuals with autism.

As a relay between different subcortical areas and the cerebral cortex, the thalamus plays an important role in cognition (Eyler et al., 2011). We found a positive correlation between thalamus volume and intelligence in healthy subjects, which was consistent with many previous studies (Bohlken et al., 2014; Raznahan et al., 2014), but not others (Crespo-Facorro et al., 2007; Hartberg et al., 2011) as reviewed in the introduction section. The conflicting results in the literature might have been due to different samples with the confounding factors like sex, age, ICV, and genetic variants. Indeed, our finding of an interaction between *GABRB1* genetic variants and thalamus volume on intelligence in females may provide an explanation for these inconsistencies.

Our results integrate and expand several lines of research. First, previous research has suggested possible links between *GABRB1*, thalamus and cognition. For example, *GABRB1* was found to be related to the beta oscillation in the human brain (Porjesz et al., 2002), while inhibition of mediodorsal thalamus disrupted thalamofrontal beta oscillatory synchrony and cognition in mice (Parnaudeau et al., 2013). A previous pharmacological study also found that injection of a GABA-agonist (e.g., muscimol) or GABA-antagonist (e.g., bicuculline) into the thalamus altered visual spatial attention in monkeys (Petersen et al., 1987).

Second, genetic factors as possible moderators for the thalamus–intelligence association in females have been documented with other genes. For example, the fragile X syndrome provides a model for understanding how specific genetic factors can influence female thalamus volume and IQ–brain volume correlation. Previous studies suggested females with the *FMR-1* gene mutation (i.e., fragile X) had larger thalamus volume than healthy females (Reiss et al., 1995), and the correlation between brain volume and intelligence was different for children with fragile X and typically developing children (Eliez et al., 2001). As for the current study, using a healthy young adult sample, we found that females with the *GABRB1* rs7435958 GG genotype had smaller thalamus volume than the CG and CC genotype groups, and that the positive correlation between thalamus volume and intelligence was higher for females with *GABRB1* rs7435958 GG genotypes than other groups (see Table 2), which would account for the significant interaction between genotype and thalamus volume on intelligence in females.

Third, previous research has shown sex differences in the correlations between thalamus volume and intelligence. A meta-analysis based on 37 samples ($N = 1530$) found that the positive correlation between brain volume and intelligence was higher for females than males (McDaniel, 2005). As indicated by Bohlken et al. (2014), it is important to examine the correlations between thalamus volume and intelligence for males and females separately. Based on their sample of twins and siblings (i.e., 54 females and 78 males), the phenotypic correlations between thalamus volume and intelligence were 0.27 for females and 0.21 for males, and the genetic correlations between thalamus volume and intelligence were 0.37 for females and 0.20 for males (Bohlken et al., 2014). But differences in these correlations did not reach statistical significance, perhaps due to their small sample sizes. In addition, previous

Table 2
Thalamus volumes and their correlations with intelligence for three genotypes of SNP rs7435958 within the *GABRB1* gene in female and male subjects.

	GABRB1 gene rs7435958 genotype	*N*	Left thalamus volume (LTHV)		Right thalamus volume (RTHV)		Correlations between thalamus volumes and intelligence (IQ) controlling for age and ICV	
Subjects			Mean	SD	Mean	SD	LTHV-IQ	RTHV-IQ
Females	GG	86	6626.41	625.45	6726.07	581.43	**$r = .31$ ($p = .004$)**	**$r = .29$ ($p = .008$)**
	CG	88	6819.74	596.85	6904.26	587.52	$r = .15$ ($p = .179$)	$r = .14$ ($p = .208$)
	CC	13	6903.69	524.62	6895.62	472.19	$r = -.31$ ($p = .347$)	$r = -.24$ ($p = .478$)
	CG + CC	101	6830.54	586.31	6903.15	571.90	$r = .08$ ($p = .430$)	$r = .08$ ($p = .406$)
Males	GG	64	7387.94	567.59	7433.48	557.42	$r = .15$ ($p = .244$)	$r = .09$ ($p = .489$)
	CG	48	7489.44	635.11	7702.63	624.78	$r = .03$ ($p = .826$)	$r = .11$ ($p = .475$)
	CC	17	7644.35	506.62	7851.18	630.64	$r = -.17$ ($p = .540$)	$r = .06$ ($p = .823$)
	CG + CC	65	7529.95	604.23	7741.50	624.84	$r = .01$ ($p = .950$)	$r = .14$ ($p = .266$)

Note: Significant correlations are shown in bold. The unit of brain structural volume is mm^3. ICV: intracranial volume.

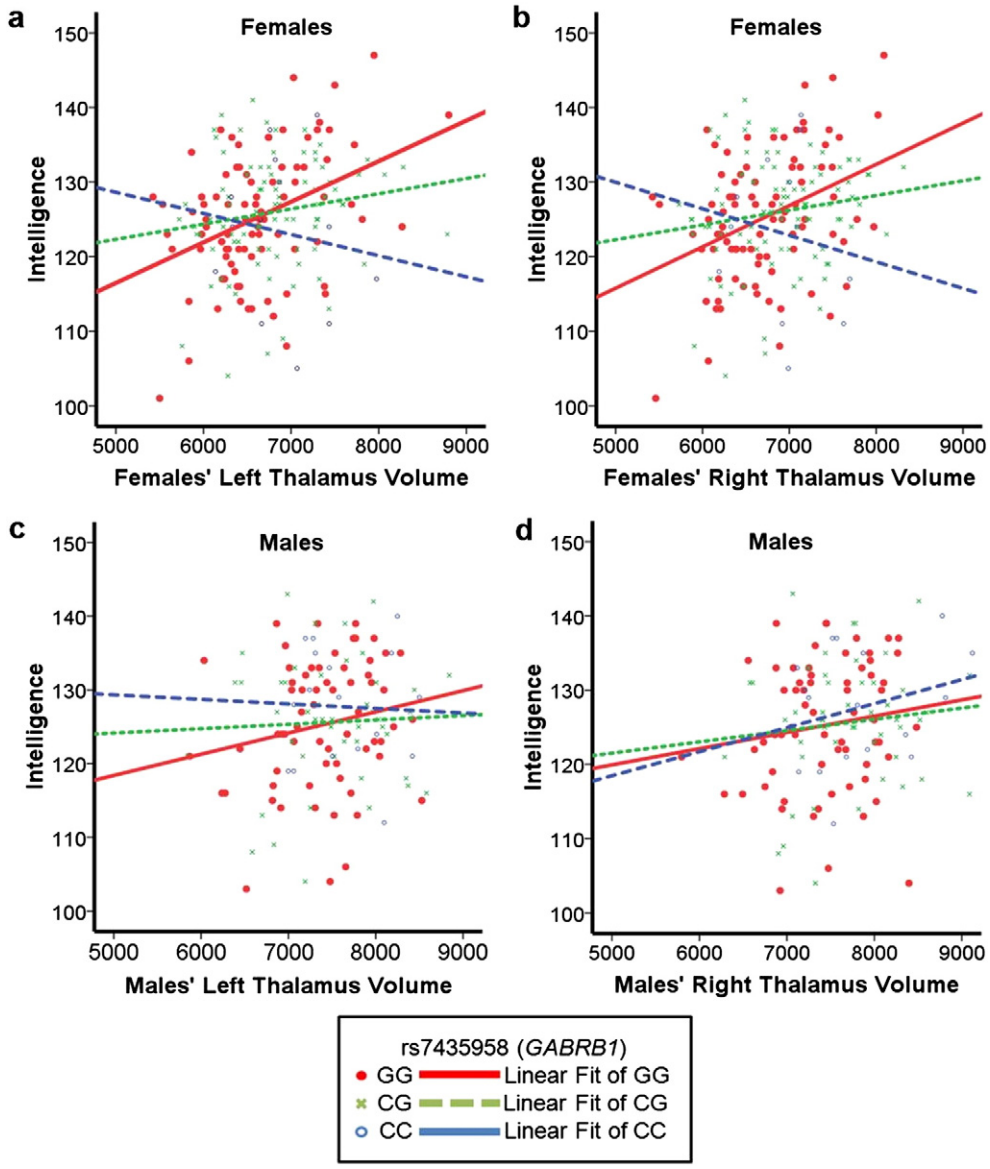

Fig. 2. Scatter plots and regression lines showing the relationship between thalamus volume and intelligence (raw scores) in rs7435958 GG homozygotes (filled circles, solid red regression line), CG heterozygotes (cross, short-dashed green regression line), and CC homozygotes (open circles, long-dashed blue regression line) within the *GABRB1* gene in females (a and b at the top) and males (c and d at the bottom).

studies also reported sex differences in the relationship between thalamus volume and other behavioral indices. For example, smaller thalamus volumes and poorer memory were found in alcoholic boys compared to non-drinking boys, but larger thalamus volumes and poorer memory were found in alcoholic girls compared to non-drinking girls (Fein et al., 2013). In the current study, a significant positive correlation between thalamus and intelligence was found for females but not for males, although Fisher *r* to *z* transformation test did not find the sex difference to be statistically significant (*p*'s > 0.05).

Several limitations of this study and directions for future research need to be noted. First, additional molecular functional studies are needed to investigate the detailed biochemical mechanisms of the genetic effects found in this study. As identified in a recent genetic study, duplication of a cluster of four GABA A receptor genes located on chromosome 4p12 (i.e., *GABRB1*, *GABRA4*, *GABRA2*, *GABRG1*) was associated with neurodevelopment disorders (Polan et al., 2014). Due to the implications of *GABRB1* in clinical samples characterized by reduced thalamus volume and abnormal intellectual performance, future research should explore potential associations between these GABA A receptor genes and thalamus volume and their interaction effect on intelligence in clinical samples, such as those with alcohol dependence, bipolar disorder, and schizophrenia. Second, it should be noted that other structural indices of the thalamus were also found to be related with intelligence. For example, researchers reported positive correlations between grey matter density in the thalamus and intelligence in healthy youth (Frangou et al., 2004). Moreover, the local efficiency (i.e., an index of the fault tolerance of the brain network) of the thalamus was correlated with general intelligence measured by WAIS-R in normal Chinese adults (Li et al., 2009). A recent study also found that shape variability of the right thalamus was correlated with spatial intelligence after controlling for sex and age in young healthy adults (Burgaleta et al., 2014). In addition, regional cerebral blood flow in the thalamus was positively related to intelligence in patients with Parkinson's disease (Wakamori et al., 2014). Therefore, these indices of the thalamus should also be considered in future studies. Third, it should be noted that the current study was based on a healthy Han Chinese college sample. College students on average have higher scores on intelligence tests than community samples. Finally, the SNPs within the *GABRB1* gene have different minor allele frequencies (MAF) and constructed different LD blocks in different ethnic populations based on the HapMap Data (www.

hapmap.org, see Table S1 and Figs. S2 to S5). For example, the identified SNP rs7435958 in the current study had different allele frequencies in different ethnic groups (e.g., the frequency of G allele [i.e., major allele] of SNP rs7435958 was lower in Chinese population than European population). Further, whole genome scans for evidence of recent adaptive selection have identified *GABRB1* as a strong potential target of selection in Han Chinese (Hawks et al., 2007; Wang et al., 2006). In order to obtain confirmatory evidence, the association found in the current study should be explored in future studies using different ethnic samples.

Conclusions

In conclusion, this study provided the first evidence of an association between the *GABRB1* gene and thalamus volume in healthy Chinese individuals, with *GABRB1* rs7435958 GG homozygotes having smaller thalamus volume. There was a significant positive correlation between thalamus volume and intelligence, especially for *GABRB1* rs7435958 GG female homozygotes. Our findings suggested that future studies of the thalamus–intelligence association should consider genetic modulation.

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.08.048.

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