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The impact of the CACNB2 Rs11013860 polymorphism on grey matter volume and brain function in bipolar disorder

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Abstract

Background Recent genome-wide association studies have linked voltage-gated calcium channel genes to bipolar disorder (BD), in which CACNB2 gene rs11013860 is respectively reported. Less is known, though, about how precisely its polymorphism affects both the structure and function of the brain.

Methods 173 BD patients and 207 healthy controls (HCs) were underwent structural and functional magnetic resonance imaging scan and genotyped for CACNB2 rs11013860. Grey matter volume (GMV), regional homogeneity (ReHo) and degree centrality (DC) were used to examine the brain structure, functional activity and connectivity of these participants.

Results The emotional circuits in BD patients, such as cerebellum, insula, cingulate gyrus, fusiform gyrus, superior frontal gyrus, superior / middle temporal gyrus, middle occipital gyrus, lingual gyrus, precuneus, putamen, hippocampus and parahippocampal gyrus, were the main areas where GMV, ReHo, and DC differed from HCs. And the right anterior and posterior cerebellar lobes, parahippocampal gyrus as well as lingual gyrus showed an interaction between CACNB2 rs11013860 genotypes and diagnoses in GMV. In addition, there was a significant stepwise increase of GMV with decreased dosage of the A risk allele in HCs, but this pattern of relationship was absent in BD patients. No interaction between BD and CACNB2 rs11013860 was found in ReHo and DC.

Conclusions These results suggest that the polymorphism of CACNB2 rs11013860 in BD patients may be associated with brain structural abnormalities in cerebellar, limbic system and other brain regions, perhaps contributing to the disease.

Keywords Bipolar disorder (BD), CACNB2 Rs11013860, Grey matter volume (GMV), ReHo, Degree centrality (DC)

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Introduction

Bipolar disorder (BD), characterized by recurrent episodes of mania/hypomania and depression, is one of the most severe mental disorders with high prevalence, morbidity and mortality [1]. Though the etiology remains largely unclear [2], the heritability of BD was estimated to be as high as 85% according to previous research [3]. Numerous investigations have demonstrated the complexity of the genetic underpinnings of BD, including several genes and gene-gene interactions. Even though there have been several documented correlations between risk variations and BD, the consistency and repeatability of the results are frequently lacking. One of the most notable genetic pathways, however, is the aberration of voltage-gated calcium channels (Ca_v) gene, which has good repeatability in BD studies [4, 5, 6].

In one genome-wide association (GWA) investigation, CACNB2 rs11013860 in the Han Chinese population was linked to BD in 409 BD-I patients and 1000 controls [7] (OR = 1.36, $P = 5.15 \times 10^{-5}$). Not by coincidence, another study reinforced the role of CACNB2 rs11013860 in the pathogenesis of BD-I by combining data with independent replication samples [8]. Rs11013860 is located on the intronic region of calcium channel, voltage-dependent, β-2 subunit (CACNB2) gene. As an auxiliary subunit, β modulate the trafficking and biophysical properties of principle α1 subunit [9]. The CACNB2 gene has been found to express in thalamus, cerebellar Purkinje neurons and hippocampal pyramidal neurons [10], supporting biological plausibility of the involvement of Ca_v in the etiological pathways of BD. However, how the neuropathological process of bipolar illness is affected by the expression of CACNB2 rs11013860 remains unclear, thus emerging studies have concentrated on the relationship between rs11013860 and brain structure/function of BD patients.

Prior evidence has shown that BD patients with the CACNB2 rs11013860 AA/CA genotype (A as the risk allele) may exhibit altered hippocampal-cortical connectivity [11]. Furthermore, another study raises the possibility that CACNB2 rs11013860 is linked to a thicker prefrontal cortex (PFC) in individuals suffering from first-episode mania from a structural standpoint [12]. To uncover the genetic influence of CACNB2 rs11013860 on pathophysiological mechanism of BD, both morphologically and functionally, more extensive evidence is necessary. Gray matter volume (GMV) variations can be assessed using voxel-based morphometry (VBM) in order to quantify the structural deficits of grey matter. Moreover, regional brain function as well as functional connectivity, which is respectively measured by the value of ReHo and degree centrality (DC), can be evaluated using resting-state functional magnetic resonance imaging (rs-fMRI). ReHo reflects the regional consistency and synchronization of neural activity between adjacent voxels [13]. Furthermore, DC is an index of the degree of connection of many brain spatial units (voxels in fMRI), and it is the most direct measure of node centrality in network analysis [14]. Based on the level of voxel, GMV, ReHo and DC illustrate brain structural and functional characteristics and show a comprehensive lens that allows for more sensitive identification of regional brain abnormalities.

In present study, we used structural and rs-fMRI to investigate the impact of CACNB2 rs11013860 polymorphism on brain morphological structure (GMV) as well as function (ReHo and DC) in BD patients.

Participants and methods

Participants

173 BD patients and 207 age, gender matched healthy controls (HCs) were enrolled in the study. A minimum of two psychiatrists used the Structured Clinical Interview (SCID-I/P) for the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) to determine the diagnosis for all BD patients, who were either inpatient or outpatients at the Mental Health Center of West China Hospital of Sichuan University. Patients' emotional symptoms were measured with the 17-item Hamilton Depression Rating Scale (HDRS) [15] and Young Mania Rating Scale (YMRS) [16], while their psychiatric symptoms with the Positive and Negative Syndrome Scale (PANSS) [17]. Patients diagnosed with schizophrenia, mental retardation or any other mental disorders in DSM-IV were excluded in this study. Additional exclusion criteria including a history of unconsciousness and electroconvulsive therapy within 6 months. Meanwhile, the HCs were recruited locally through advertising and confirmed for a lifetime absence of psychiatric illness using the Non-Patient Edition of SCID for DSM-IV. HCs with psychiatric illness in their first-degree relatives and a history of psychotic substances intake were excluded. Participants who had contraindications for MRI, showed evidence of organic brain disorders, neurological illness, alcohol or drug abuse (including sedative, cannabis, stimulant, opioid, cocaine, hallucinogen, phencyclidine but not nicotine), or any other severe physical illness such as brain tumor or epilepsy were also excluded from the study. All participants were ethnic Han Chinese and right-handed. This study was approved by The Ethics Committee of Sichuan University West China Hospital (Reference No. 2021(943)), which is in line with the Declaration of Helsinki. All subjects signed informed consent prior to participation in the study.

Genotyping

DNA samples were extracted from blood cells using phenol-chloroform method. ImLDRTM multiple SNP typing kit was used to genotype for CACNB2 rs11013860 and GeneMapper 4.1 for the genotype results. All of the subjects were split into three groups: an AA-allele group, an AC-allele group, and a CC-allele group as the secondary allele of rs11013860 is A allele. Minor allele frequencies were 0.42% and genotype frequencies were consistent with Hardy-Weinberg equilibrium (HWE) expectations ($\chi^2 = 0.06$, $P = 0.75$) (Supplementary Table 1).

Image Acquisition

All images were acquired on a 3.0 T MR scanner (Achieva X-series, Philips Medical Systems, Best, Netherlands). Participants were demanded to lie on their backs, close their eyes, keep heads fixed and stay awake during scanning without thinking about anything specific (confirmed by subjects immediately after the experiment). Head movement and scanner noise were reduced with the use of foam padding and earplugs. The scanning parameters are as follows:

High-resolution T1 images were acquired by 3D magnetization-prepared rapid gradient-echo sequence as follows: repetition time 8.1 ms, echo time 3.7 ms, flip angle 7°, in-plane matrix resolution 256 × 256, field of view 256 × 256 cm ^{2}, voxel size 1 × 1 × 1 mm ^{3}, slice thickness 1 mm and number of slices 188.

A total of 240 volumes of echo-planar images were obtained axially with a gradient-echo planar imaging sequence with the following parameters: repetition time 2000 ms, echo time 30 ms, flip angle 90°, field of view 240 × 240 mm ^{2}, and 38 axial slices.

After excluding subjects with missing image data, a total of 380 subjects were included in the study, of which 173 were BD patients and 207 were HCs.

Image pre-processing

T1-weighted images were processed using Statistical Parameter Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/). Firstly, T1-weighted images were realigned manually according to the anterior commissure-posterior commissure line and midsagittal plane. Secondly, images were segmented into probability maps of gray matter (GM), white matter (WM) and cerebrospinal fluid. The resulting GM probability maps were automatically rigidly aligned to Montreal Neurological Institute (MNI) space. Thirdly, correct the deviation of GM image in MNI space to generate modulated gray matter volume image. Finally, use 6 mm full-width at halfmaximum isotropic Gaussian kernel to get smoothed, modulated and spatially normalized GM in MNI space and GMV was retained for subsequent statistical analysis.

Rs-fMRI image processing was carried out using SPM12 and Data Processing Assistant for Rs-fMRI (DPARSF) according to the following steps: The first 10 time points were removed to allow the fMRI signal to reach steady state. Raw rs-fMRI images were first slice time corrected, realigned and subsequently unwrapped to correct for susceptibility-by-movement interaction. The data were scrubbed based on a measure of average framewise displacement (FD) with (FD ≤ 0.5 mm) using a nearest neighbor interpolation approach to further correct for movement artifacts. Each image volume was spatially normalized using T1 image of DATEL segment, and nuisance covariates including Friston 24 motion parameters, cerebrospinal fluid (CSF), and white matter signals were regressed out. All images were linearly detrended and bandpass-filtered (0.01–0.10 Hz) to eliminate high-frequency physiological noise. The head motion and rotation of all the subjects (maximal motion between volumes in each direction, and rotation about each axis) are < 2 mm and < 2°.

ReHo and DC calculation

Calculating the Kendall's coefficient of concordance (KCC) of the time series of a given voxel and its nearest neighbor (27 voxels) in a voxel-wise way to generate a single ReHo map. For standardization, the ReHo value of every voxel was divided by the global mean ReHo of each individual. DC was calculated using DPARSF. For each voxel, the BOLD time course was extracted and correlated with every other voxel in the brain. In line with previous studies, the correlation matrix was binarized by thresholding at $r > 0.25$ before counting the number of connections to generate voxelwise DC. For each subject, a map with DC values for every voxel was obtained. These maps were normalized to z maps using the mean value and standard deviation within the whole gray matter mask. Finally, the resulting ReHo and DC maps were smoothed with a Gaussian kernel (full-width half maximum = 6 mm) to enable group comparisons.

Statistical analyses

Statistical analyses were conducted using the Statistical Package for Social Science version 18.0 (SPSS 18.0). Independent two-sample t tests (continuous variables) or χ^2 tests (categorical variables) were used to evaluate differences in demographic and clinical characteristics between BD patients and HCs.

A full factorial model was used to obtain the main effects of diagnosis as well as diagnosis-by-genotype (D×G) interaction in GMV, ReHo and DC, controlling age, sex, years of education and total intracranial volume (TIV) as covariates. Statistical inferences were made with $p < 0.005$ uncorrected for multiple comparisons at the voxel level, and then a significance threshold level was set

at $p < 0.05$ corrected for topological FDR (false discovery rate). Then, significant region-of-interest (ROI) masks of brain regions were obtained from the results of main effects or D×G interaction analysis of the GMV, ReHo and DC. The masks were extracted using Xjview (https://www.alivelearn.net/xjview/).

Results

Demographic characteristics and clinical information

The demographic characteristics of the study subjects are shown in Table 1. There were significant differences in age, gender and education between 173 BD patients and 207 HCs ($P < 0.05$). The distribution of the CACNB2 rs11013860 polymorphism didn't deviate from Hardy-Weinberg expectation in HCs ($P = 0.75$). The genotype distributions and allelic frequencies are presented in supplementary (Supplementary Table 1). There were no significant differences in the frequencies of genotypes and alleles between BD patients and HCs.

Main effects of diagnosis on GMV, ReHo, DC

Main effects of diagnosis on GMV

Compared with HCs, the BD group revealed smaller GMV compared with HCs in the left cerebellar summit and hillside, left anterior and posterior cerebellar lobes, left fusiform gyrus, left parahippocampal gyrus, left suboccipital gyrus (T = 5.66, $P < 0.001$), right anterior/posterior cerebellar lobe, right fusiform gyrus, right parahippocampal gyrus, right lingual gyrus (T = 4.58, $P = 0.002$), bilateral anterior cingulate gyrus and parascingulate gyrus, bilateral superior frontal gyrus, left anterior cuneiform lobe (T = 7.54, $P < 0.001$), left lingual gyrus and left superior temporal gyrus (T = 6.59, $P = 0.007$), right insula and right central tegmental regions (T = 7.15, $P = 0.005$) (Fig. 1; Table 2). No significant increased GMV was found in BD.

Table 1 Demographic characteristics and clinical information of BD and HC groups

Variables	BD patients (*N* = 173)	HC (*N* = 207)	T /χ^2	*P* value
Age (years)	25.55 ± 8.74	27.33 ± 8.58	-2.00	0.047*
Gender (M/F)	77/96	66/141	6.40	0.01*
BMI (kg/m^2)	22.10 ± 3.46	21.13 ± 3.05	3.06	0.081
Education (years)	13.50 ± 3.06	15.07 ± 3.33	-4.73	0.001*
Course (years)	12.14 ± 3.83	N	N	N
BD-I / BD-II	39/134	N	N	N
Medication, n (%)	108 (62.42%)	N	N	N
Mood stabilizers	91 (84.26%)	N	N	N
Antidepressants	64 (59.25%)	N	N	N
Antipsychotics	76 (70.37%)	N	N	N
HDRS	12.42 ± 5.86	N	N	N
YMRS	10.49 ± 4.50	N	N	N
TIV	1511.19 ± 153.43	1462.17 ± 142.07	3.23	0.001*
GMV	677.35 ± 68.89	677.47 ± 63.04	-0.19	0.99
WMV	530.85 ± 60.43	525.32 ± 58.7	0.90	0.37

Note: Unless otherwise indicated, data are means ± SD; BD, bipolar disorder; HC, healthy control; M, male; F, female; BMI, Body Mass Index; N, not applicable; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; TIV, total intracranial volume; GMV, grey matter volume; WMV, white matter volume; *$P < 0.05$

Main effects of diagnosis on ReHo

BD patients revealed different ReHo compared with HCs (Fig. 2A and B; Table 3). In BD group, decreased ReHo was found to locate in the bilateral superior frontal gyrus, left anterior cingulate gyrus and paracingulate gyrus (T = 5.17, $P < 0.001$), left insula, left superior temporal gyrus, left putamen (T = 4.35, $P = 0.034$), left middle occipital gyrus, left middle temporal gyrus, left angular gyrus (T = 4.74, $P = 0.003$), right superior temporal gyrus, right putamen (T = 3.74, $P = 0.025$), right middle temporal gyrus, right middle occipital gyrus (T = 4.85, $P = 0.025$), right suproccipital gyrus and bilateral calar fissure (T = 3.34, $P = 0.034$) (Fig. 2A). In addition, ReHo enhanced in bilateral thalamus, bilateral talar cleft, bilateral hippocampus, bilateral precuneus, left suproccipital gyrus, left parahippocampal gyrus in BD group (T = 5.03, $P < 0.001$) (Fig. 2B).

Main effects of diagnosis on DC

Compared with HCs, the BD group also revealed differences in DC (Fig. 2C and D; Table 4). The DC of the bilateral anterior cingulate gyrus, the bilateral paracingulate gyrus and the bilateral superior frontal gyrus (T = 6.45, $P < 0.001$, all results below are of the cluster level, FDR-corrected), left superior temporal gyrus (T = 5.63, $P = 0.007$), right superior temporal gyrus (T = 5.72, $P = 0.005$), the bilateral middle temporal gyrus, the bilateral middle occipital gyrus and the bilateral suproccipital gyrus (T = 6.97, $P < 0.001$) decreased in BD group (Fig. 2C). In BD group, the DC of the left middle frontal gyrus, left inferior frontal gyrus triangle (T = 4.88, $P = 0.01$), right middle frontal gyrus, right inferior frontal gyrus triangle and right insula lobe (T = 4.91, $P < 0.001$), bilateral precuneus, bilateral thalamus, bilateral caudate nucleus, bilateral hippocampus (T = 6.91, $P < 0.001$), the left middle temporal gyrus, left angular gyrus and left superior temporal gyrus (T = 5.95, $P = 0.042$) were enhanced (Fig. 2D) in comparison to HCs.

Diagnosis × genotype Interaction in GMV, ReHo, DC

Diagnosis × genotype Interaction in GMV

There was a significant interaction of genotype-by-diagnosis between the right anterior, posterior cerebellar lobes, right parahippocampal gyrus and right lingual gyrus (F = 10.37, $P = 0.022$) (Fig. 3A; Table 5).

We also found a significant step-wise decrease of GMV with increased dosage of the A risk allele in these brain regions of HCs ($P < 0.001$). However, BD patients

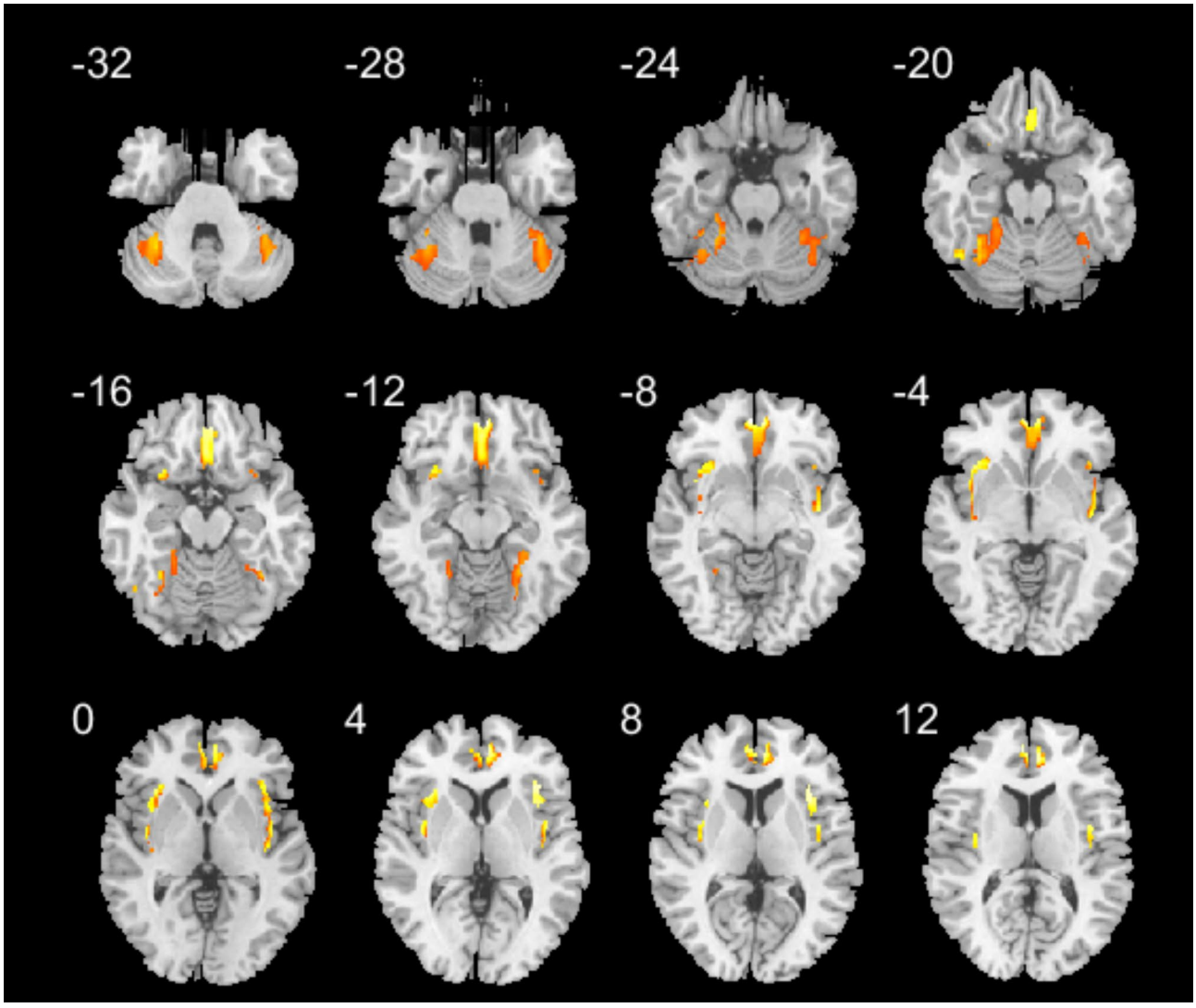

Fig. 1 Brain regions of BD group revealed smaller GMV compared with HCs

Table 2 Brain areas with differences in GMV between BD and HC groups

Cluster number	Brain area	voxel	MNI coordinates			T	*P*
			X	Y	Z		
BD < HC							
01	The hillside of the left cerebellar extends to the anterior cerebellar lobe, posterior cerebellar lobe, suboccipital lobe and parahippocampal gyrus	751	-33	-51	-16.5	5.66	< 0.001
02	The right anterior cerebellar lobe extends to the posterior cerebellar lobe, fusiform gyrus, parahippocampal gyrus, and lingual gyrus	1009	25.5	-49.5	-10.5	4.58	0.002
03	Bilateral superior frontal gyrus extends to anterior cingulate gyrus, paracingulate gyrus, anterior cuneus	4170	3	48	-13.5	7.54	< 0.001
04	The left lingual gyrus extends into the superior temporal gyrus	751	-33	19.5	6	6.59	0.007
05	The right insula extends to the central operculum	809	-3	24	6	7.15	0.005
BD > HC							
	None						

Note: BD, bipolar disorder; HC, healthy control; MNI, Montreal Neurological Institute

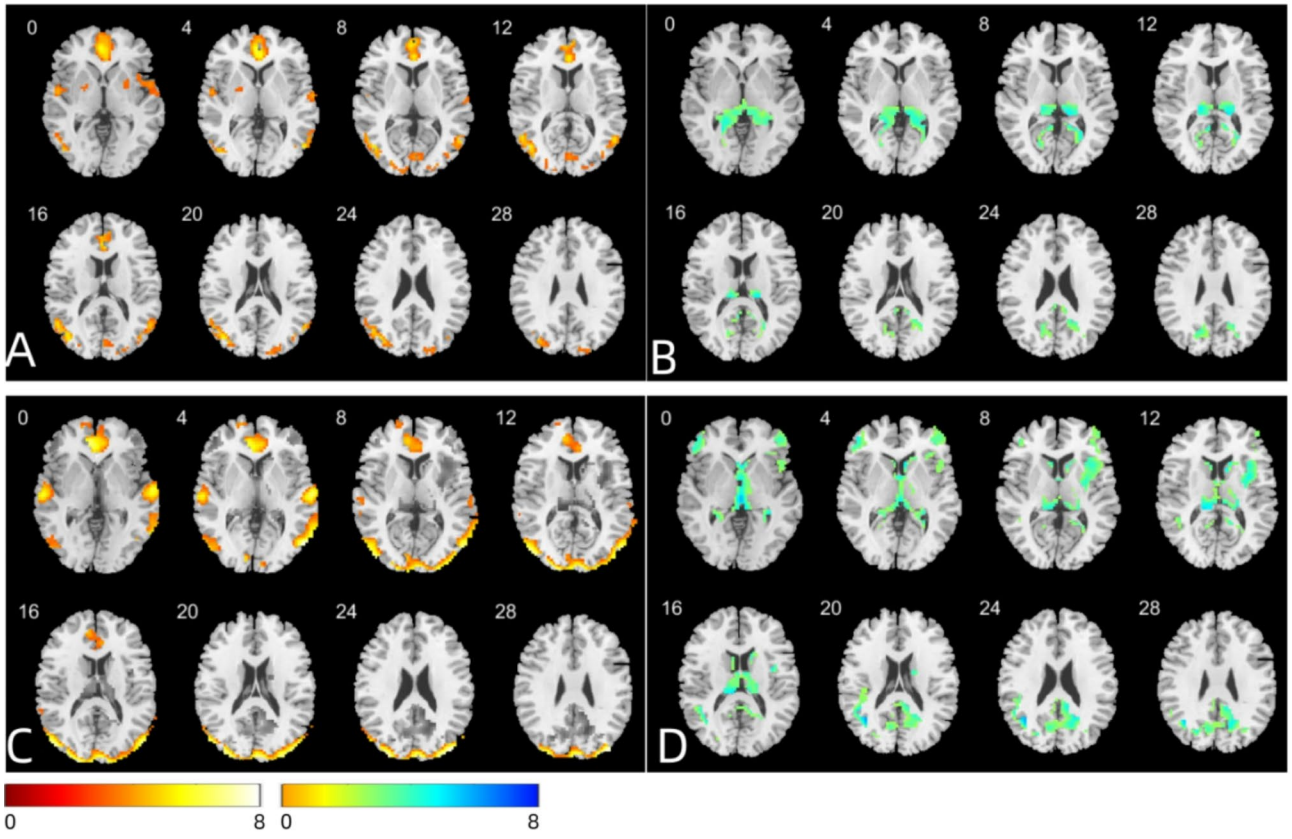

Fig. 2 Different ReHo/DC between BD and HC groups. (**A**): ReHo decreased in BD group. (**B**): ReHo enhanced in BD group. (**C**): DC decreased in BD group. (**D**): DC enhanced in the BD group

Table 3 Brain areas with differences in ReHo between BD and HC groups

Cluster number	Brain area	voxel	MNI coordinate			T	*P*
			X	Y	Z		
BD < HC							
01	The superior frontal gyrus extends to the anterior cingulate gyrus and the paracingulate gyrus	455	-3	57	-9	5.17	< 0.001
02	The right superior temporal gyrus extends into the putamen	127	54	3	-3	3.74	0.025
03	The left insula extends to superior temporal gyrus and putamen	101	-39	-3	-6	4.35	0.034
04	The left middle occipital gyrus extends to the middle temporal gyrus and the angular gyrus	247	-42	-72	18	4.74	0.003
05	The right medial temporal gyrus extends into the medial occipital gyrus	135	51	-69	3	4.85	0.025
06	The right suproccipital gyrus and bilateral calar fissure	104	12	-93	21	3.34	0.034
BD > HC							
01	The thalamus extends to the calar fissure, hippocampus, precuneus, posterior cingulate gyrus, supraspital gyrus, and parahippocampal gyrus	764	9	-33	6	5.03	< 0.001

Note: BD, bipolar disorder; HC, healthy control; MNI, Montreal Neurological Institute

showed a loss of relationship as the risk allele heterozygote AC group presented the smallest GMV among the three groups, whereas no significant differences in GMV was found between the risk allele homozygote AA and CC groups. Additionally, BD patients showed increased GMV compared with HCs in the AA group in these regions ($P < 0.001$) (Fig. 3B).

Diagnosis × genotype interaction in ReHo

No significant D×G interaction in ReHo was found.

Diagnosis × genotype interaction in DC

No significant D×G interaction in DC was found.

Table 4 Brain areas with differences in DC between BD and HC groups

Cluster number	Brain area	voxel	MNI coordinate			T	*P*
			X	Y	Z		
BD < HC							
01	Bilateral anterior cingulate gyrus extends to paracingulate gyrus and superior frontal gyrus	547	-6	42	-3	6.45	< 0.001
02	The left superior temporal gyrus extends into the middle temporal gyrus	179	-54	6	-9	5.63	0.007
03	The right superior temporal gyrus	210	63	-15	3	5.72	0.005
04	Bilateral medial temporal gyrus extends to medial occipital gyrus and suproccipital gyrus	937	39	-87	24	6.97	< 0.001
BD > HC							
01	The left orbital medial frontal gyrus extends to inferior frontal gyrus, triangular gyrus, and medial frontal gyrus	193	-48	48	3	4.88	0.01
02	The medial frontal gyrus extends to the triangle of the inferior frontal gyrus	512	42	45	-9	4.91	< 0.001
03	Bilateral precuneus extends to the bilateral thalamus, bilateral caudate nucleus, bilateral hippocampus	1127	0	-6	-12	6.91	< 0.001
04	The left middle temporal gyrus extends to the angular gyrus and superior temporal gyrus	118	-39	-57	21	5.95	0.042

Note: DC, degree centrality; BD, bipolar disorder; HC, healthy control; MNI, Montreal Neurological Institute

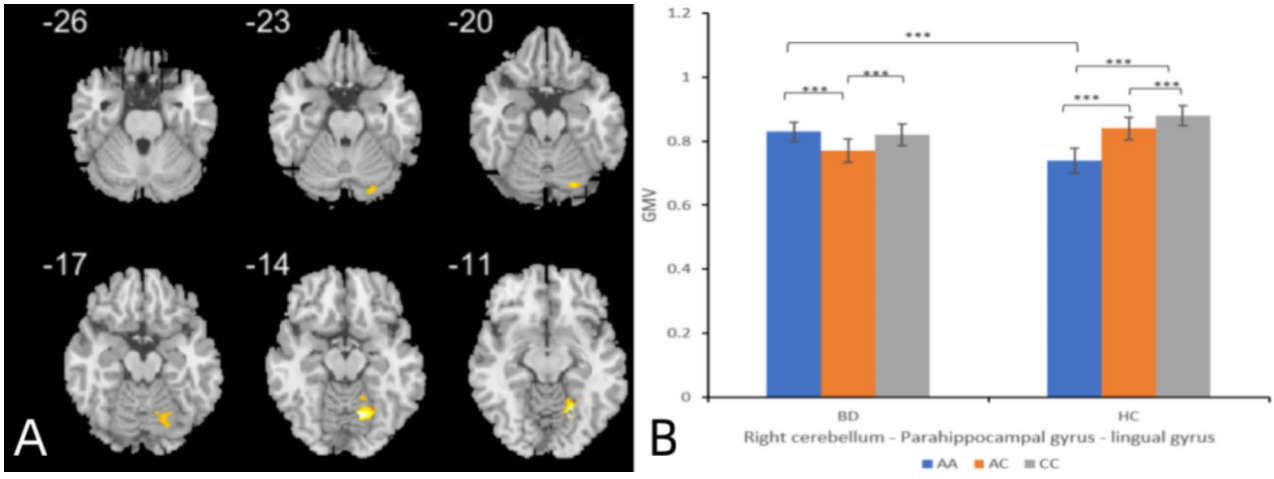

Fig. 3 Interaction effects between diagnosis and CACNB2 rs11013860 polymorphism in GMV. (**A**): Brain regions with statistical different GMV between CACNB2 rs11013860 genotype and diagnosis. (**B**): D×G interaction in the GMV of right cerebellum - parahippocampal gyrus - lingual gyrus. In BD group, the AC group presented the smallest GMV among the three subgroups, whereas no significant differences in GMV was found between the AA and CC groups. In HCs, GMV demonstrates a significant step-wise decrease with increased dosage of the A risk allele. For AA group, GMV was increased in BD patients compared to HCs. *Note*: GMV, grey matter volume; D×G: diagnosis-by-genotype; BD, bipolar disorder; HC, healthy control; AA, homozygote for the risk A-allele; AC, heterozygote for the risk A-allele; CC, homozygous for the non-risk C-allele

Table 5 Brain areas with interaction between CACNB2 rs11013860 genotype and diagnosis in GMV of BD patients and HCs

Cluster number	Brain area	voxel	MNI coordinate			F	*P*
			X	Y	Z		
01	The anterior and posterior lobes of the right cerebellum extend to the parahippocampal and lingual gyrus	425	16.5	-64.5	-10.5	10.37	0.022

Note: GMV, grey matter volume; BD, bipolar disorder; HCs, healthy controls; MNI, Montreal Neurological Institute

Discussion

This is the first study to investigate the impact of CACNB2 rs11013860 on whole-brain morphological characteristics and functional activity as well as connectivity in BD patients. We had two main findings: (1) Compared with HCs, the abnormalities of brain GMV, regional function and functional connectivity (FC) in BD patients were mainly located in the emotional circuits such as cerebellum, cingulate gyrus, superior

frontal and temporal gyrus, middle temporal and occipital gyrus, fusiform gyrus, lingual gyrus and precuneus as well as hippocampus, parahippocampal gyrus, insula and putamen. (2) A significant interaction between CACNB2 rs11013860 and the diagnosis of BD was observed in the gray matter of right anterior/posterior cerebellar lobes, parahippocampal gyrus and lingual gyrus. Moreover, BD patients displayed a loss of pattern of relationship between a significant step-wise increase of GMV and decreased dosage of the A risk allele found in HCs.

In BD group, we found significantly lower GMV in bilateral cerebellum, fusiform gyrus, cingulate gyrus, superior frontal gyrus, lingual gyrus, parahippocampal gyrus, left superior temporal gyrus (STG), anterior cuneus, right insula and central operculum compared to HCs. The findings not only corroborated but also added to the findings of the earlier study, which showed that BD patients had GM deficits in the medial orbitofrontal cortex (OFC), inferior temporal and fusiform regions, insular cortex, hippocampus and cerebellum [18]. A systematic analysis identified bilateral GM loss in the parahippocampal gyrus and STG, asymmetrical changes in the left inferior parietal lobule / inferior frontal gyrus and the right insula of BD [19]. Additionally, prior research on BD revealed reduced GM in the frontal and temporal regions, cerebellum and basal ganglia [20], dorsal anterior cingulate cortex (ACC) and bilateral insula [21], OFC, dorsolateral prefrontal cortex (dPFC), angular gyri and cingulate gyri [22], as well as right hippocampus [23]. Regarding subtypes of BD, some studies found less pronounced WMV alterations in BD-II compared with BD-I [24, 25], while others found no GMV differences between subtypes [26, 27]. According to our research, regions with GMV alterations in BD patients mainly located in frontal, temporal and limbic lobes, expanding to the fusiform gyrus, anterior cuneus and central operculum.

Lower ReHo in bilateral superior frontal gyrus, superior/middle temporal gyrus, putamen, middle occipital gyrus, left cingulate gyrus, angular gyrus, insula and right suproccipital gyrus were found in BD with higher ReHo in bilateral thalamus, talar fissure, hippocampus, precuneus, left suproccipital gyrus and parahippocampal gyrus. These findings are consistent with prior studies showing that ReHo increased in the BD striatum [28] and decreased in the insula [28, 29], right STG, superior parietal lobule, precental gyrus [29]. Moreover, increased ReHo in the left medial frontal gyrus and inferior parietal lobe were reported in bipolar depressed patients [30]. Nevertheless, another study found that BD-II depression patients showed significantly higher ReHo in bilateral middle occipital gyrus and lower ReHo in the left orbitofrontal cortex when compared to HCs [31]. The variations in the results could be attributed to mixed emotional states as well as subtypes of BD. It was found that BD-II manifested significantly higher dynamic amplitude of low-frequency fluctuation (dALFF) than those in BD-I in the right superior / middle temporal gyrus [32]. In terms of FC, we observed decreased DC in bilateral medial frontal gyrus, pars triangularis of inferior frontal gyrus, anterior cuneus, thalamus, caudatum and hippocampus with increased DC in the left STG, middle temporal gyrus, angular gyrus and posterior cingulum gyrus. These findings were in line with previous researches indicating that BD may be associated with decreased FC in bilateral anterior cingulate cortex, right angular gyrus, middle part of superior frontal gyrus and precuneus [33], left cingulate [34], as well as the prefrontal-striatal-pallidal-thalamic-limbic networks [35]. However, according to a previous study, BD patients' resting-state FC in the left middle frontal gyrus, right superior frontal gyrus, and left thalamus/caudate body was decreased, whereas the right STG - parahippocampal gyrus FC was increased than that of HCs [36]. The observed differences in the population of the studies, such as the length of illness and intensity of mood episodes, are likely to have an impact on regional brain function and could explain the diversity of these results [28]. In summary, the frontal-limbic circuit exhibited the majority of the structural and functional changes in the brains of BD patients.

Interestingly, we discovered overlaps between the brain regions in BD patients that exhibit altered brain structure (found in GMV) and impaired brain function (found in ReHo or DC), including bilateral cingulum gyrus, superior frontal gyrus, parahippocampal gyrus, left STG, anterior cuneus and insula. It implies that the functional and anatomical changes might alter simultaneously and dependently in these brain regions. Previous studies have reported that BD patients displayed aberrant brain resting-state functional activity and VBM in the insula [28, 37], altered fractional amplitude of low-frequency fluctuations and GMV in the left superior frontal gyrus [38], right fusiform gyrus as well as hippocampus [39], and decreased GMV along with decreased resting-state FC (rs-FC) within the frontal-cingulate network, particularly between the left ACC - orbitofrontal cortex [23]. The overlaps between structural and functional abnormalities may suggest that regional grey matter changes functionally influence local neurocircuits. However, certain regions with anatomical and functional changes were dissociated, such as cerebellum, fusiform gyrus, lingual gyrus and caudate nucleus. Although the exact cause of the phenomenon is unknown, one possible explanation is that various environmental, personal and illness factors may have varying degrees of impact on how the brain develops and how it plays a part in BD [38]. In such cases, the abnormality of brain structure may represent a relatively stable or slowly progressing process, whereas brain functional alterations are more likely to be an indicator of

the disease state in certain brain regions [40]. Otherwise, the overlaps we found mostly located in the forebrain, rather than posterior areas such as occipital lobe or cerebellum, which still require exploration.

In present study, an interaction between CACNB2 rs11013860 genotypes and diagnoses in GMV was found in the right anterior and posterior cerebellar lobes, parahippocampal gyrus as well as lingual gyrus. In these brain regions, we found a significant step-wise increase of GMV with decreased dosage of the A risk allele in HCs. In contrast, BD patients showed a loss of this pattern of relationship, as the risk allele heterozygote AC group presented the smallest GMV among the three subgroups. This implied that BD patients and HCs have different patterns of the CACNB2 rs11013860 polymorphism effecting the architecture of the right anterior/posterior cerebellar, parahippocampal gyrus and lingual gyrus. A study that investigated the influence of the CACNB2 rs11013860 on prefrontal cortex morphology in BD also discovered a different pattern of gray matter affected by A-allele between BD patients and HCs [11]. In addition, the patterns of brain function influenced by CACNB2 rs11013860 were also reported. In BD patients, the AA/CA group showed lower rs-FC between the hippocampus and right pars triangularis compared to the CC group; in contrast to HCs, AA/CA group exhibited higher rs-FC than that of the CC group [14]. However, we didn't find a diagnosis-by-genotype (D×G) interaction in GMV of the prefrontal cortex, while Chen et al. observed a thinner superior frontal thickness in CACNB2 rs11013860 BD A-allele carriers in comparison to HCs [11]. It could be partially explained by different neuroimaging analytical methods of two studies; whereas they primarily concentrate on the prefrontal cortex, we utilized voxel-based morphometry to examine changes in gray matter throughout the entire brain. The parameter of interest - we focused on GMV, while Chen et al. emphasized on cortex thickness - was another factor that might have contributed to the disparate outcomes. To our knowledge, the current study is the first to use the VBM approach to investigate the impact of CACNB2 rs11013860 on whole-brain morphological characteristics. Our findings suggest more extensive structural abnormalities related to the polymorphism of Ca_v gene CACNB2 rs11013860 in BD patients, which may lead to BD by affecting right anterior and posterior cerebellar lobes, parahippocampal gyrus as well as lingual gyrus.

The mechanism of CACNB2 rs11013860 risk A-allele may affect the morphology of brain in BD patients remains imprecise. According to Martins et al., miR-499-5p suppresses CACNB2 translation and lowers calcium influx, both of which are essential for dendritic growth, and is thus correlated with the GMV of BD patients [41]. CACNB2 impacts voltage-gated L-type calcium channels (LTCCs) activity by encoding its β2 subunit [42, 43]. LTCCs are extensively expressed in the central nervous system and are crucial for synaptic plasticity, since they regulate the amount of calcium that enters neurons and processes that rely on calcium [44, 45]. Given that CACNB2 r11013860 has been found to be expressed in the brain thalamic and cerebellar Purkinje cells [46, 47], the risk A-allele variation may implicate modifications in the expression and/or function of LTCCs, which could lead to aberrant neuronal plasticity in such areas and consequent variations in brain morphology. Notably, we discovered that in homozygous carriers of the risk A-allele (the AA group), the GMV of right cerebellum - parahippocampal gyrus - lingual gyrus in HCs demonstrates a significant decrease when compared with non-risk allele carriers (the CC group); however, the association disappeared in BD patients. Moreover, compared to HCs, BD patients showed elevated GMV in these regions in the AA group. "Synaptic pruning", which refers to the targeted elimination of functional synapses in early stages of neurodevelopment with the goal of fine-tuning mature circuits and forming an adaptable brain, is one possible theory that could explain the phenomena. The aberration of synaptic pruning has been described to be the foundation for certain mental disorders, such as autism [48]. In this scenario, CACNB2 variants might be related to deficient synaptic pruning, resulting in superabundant synapses and exhibiting increased GMV on neuroimaging.

We didn't find any significant interaction between the genotype of CACNB2 rs11013860 and diagnosis either in ReHo or DC. Nonetheless, Liu et al. documented a D×G interaction between BD and HC groups within the hippocampus - right pars triangularis neural circuit, wherein rs-FC was shown to be lower in BD patients who carried the A allele than in those who simply carried the C allele [14]. The discrepancy between the results could be attributed to various indicators of concern, namely the difference between the regional rs-FC of the hippocampal-cortical area and the values of ReHo and DC throughout the brain. Additionally, the validity of the patients' emotional states as mentioned in the studies may also have an impact on the findings. Taken together, the neurobiological processes underlying both the structural and functional abnormalities associated with BD still remain to be clarified.

There are several limitations worth noting in our study. First, we didn't perform a stratified analysis based on BD subtypes (BD-I and BD-II). The two subtypes exhibit some different clinical characteristics [49] which partly due to unique genetic features [50], and previous study also found genetic convergence and divergence between BD-I and BD-II [51]. Second, despite controlling for age, sex, years of education and TIV as covariates, the current

study did not include some confounding factors that could affect brains of BD patients, such as the depression cycle [52], pharmacological treatments [53] and comorbid medical conditions (like substance use disorders, cardiovascular diseases or obesity) [54, 55]. Specifically, distinct cerebral blood flow levels relating to BMI were identified in the reward circuit of BD, which may relate to underlying differences in cerebral metabolism as well as function [56], and according to a prior study, substance users exhibited abnormalities in the bilateral anterior cingulate cortex/medial prefrontal cortex in terms of both function and anatomy [57]. Third, we only covered one of subunits of Ca_v, while interactions were detected between different subunits [8]. Therefore, future research including a wider range of subunits will be necessary. Fourth, despite the sample size of current study is sufficient for persuasiveness in neuroimaging studies, it is relatively modest in the context of genetic researches. However, the combination of neuroimaging and genetics would somehow supply the deficiency.

In summary, this is the first study to look into how CACNB2 rs11013860 polymorphism affects both whole-brain structure and function in BD patients. According to our findings, CACNB2 rs11013860 may play an important role in the morphological changes of grey matter in BD, possibly by disrupting the function of L-type calcium channels. These results indicate the involvement of CACNB2 rs11013860 in the morphological changes in the brain circuitry responsible for processing emotions in BD, and they also provide insight on potential connections between calcium channel gene variation and the neuropathological mechanisms underlying BD.

Abbreviations

BD	Bipolar disorder
HC	Healthy control
GMV	Grey matter volume
ReHo	Regional homogeneity
DC	Degree centrality
Ca_v	Voltage-gated calcium channel
GWA	Genome-wide association
CACNB2	Calcium channel, voltage-dependent, β-2 subunit
PFC	Prefrontal cortex
VBM	Voxel-based morphometry
Rs-fMRI	Resting-state functional magnetic resonance imaging
DSM-IV	the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders
SCID	Structured Clinical Interview for DSM-IV
HDRS	Hamilton Depression Rating Scale
YMRS	Young Mania Rating Scale
PANSS	Negative Syndrome Scale
GM	Gray matter
WM	White matter
MNI	Montreal Neurological Institute
DPARSF	Data Processing Assistant for Rs-fMRI
FD	Framewise displacement
CSF	Cerebrospinal fluid
TIV	Total intracranial volume
FDR	False discovery rate
ROI	Region-of-interest
BMI	Body mass index
WMV	White matter volume
FC	Functional connectivity
STG	Superior temporal gyrus
OFC	Orbitofrontal cortex
ACC	Anterior cingulate cortex
dPFC	Dorsolateral prefrontal cortex
dALFF	Dynamic amplitude of low-frequency fluctuation
LTCC	Voltage-gated L-type calcium channel
D×G	Diagnosis-by-genotype

Supplementary Information

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Supplementary Material 1

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Author contributions

XFC wrote the main manuscript text and QY prepared figures and tables. XFC, QY, YMZ, MMZ, HY, PYN and XJL collected and analyzed the data. LML and TL made the contribution to the conception and revised the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Human ethics and consent to participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the Ethics Committee of Sichuan University West China Hospital (Reference No. 2021(943)), which is in line with the Helsinki Declaration of 1975, as revised in 2013. Informed consent is signed by all study participants.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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