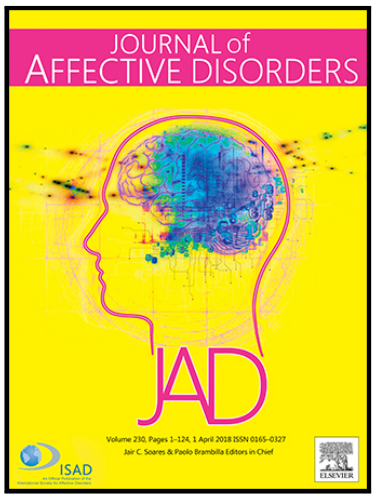

CACNB2 rs11013860 polymorphism correlates of prefrontal cortex thickness in bipolar patients with first-episode mania

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Highlights:

- All thickness measurements of prefrontal cortex were significantly reduced in patients with first-episode mania compared with healthy controls.

- A significant interaction between the presence of CACNB2 rs11013860 risk A allele and diagnosis (patients vs healthy controls) on right superior frontal cortical thickness was detected.

- Patients carrying rs11013860 risk A-allele had thinner superior frontal thickness compared to patients carrying rs11013860 CC-allele.

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Abstract

Background: The β2 subunit of the voltage-gated L-type calcium channel gene(*CACNB2*) rs11013860 polymorphism is a putative genetic susceptibility marker for bipolar disorder (BD). However, the neural effects of *CACNB2* rs11013860 in BD are largely unknown. Methods: Forty-six bipolar patients with first-episode mania and eighty-three healthy controls (HC) were genotyped for *CACNB2* rs11013860 and were scanned with a 3.0 Tesla structural magnetic resonance imaging system to measure cortical thickness of prefrontal cortex (PFC) components (superior frontal cortex, orbitofrontal cortex, middle and inferior frontal gyri). Results: Cortical thickness was thinner in patients on all PFC measurements compared to HC ($p < 0.050$). Moreover, we found a significant interaction between *CACNB2* genotype and diagnosis for the right superior frontal cortical thickness ($F = 8.190$, $p = 0.040$). Bonferroni corrected post-hoc tests revealed that, in *CACNB2* A-allele carriers, patients displayed thinner superior frontal thickness compared to HC ($p < 0.001$). In patients, *CACNB2* A-allele carriers also exhibited reduced superior frontal thickness compared to *CACNB2* CC-allele carriers ($p = 0.016$). Limitations: Lithium treatment may influence our results, and the sample size in our study is relatively small. Conclusions: Our results suggest that the *CACNB2* rs11013860 might impact PFC thickness in patients with first-episode mania. These findings provide evidence to support *CACNB2* rs11013860 involvement in the emotion-processing neural circuitry abnormality in the early stage of BD, which will ultimately contribute to revealing the link between the variation in calcium channel genes and the neuropathological mechanism of BD.

Key words: bipolar disorder; first episode; *CACNB2*; rs11013860; prefrontal cortex; imaging

Introduction

The heritability of BD was up to 85% based on previous research (McGuffin et al., 2003). Though the genetic foundations of BD are not yet clear, various studies have highlighted that aberrant variants in genes coding for calcium channel were the important genetic susceptibility markers for BD (2011; Ferreira et al., 2008; Muhleisen et al., 2014; Sklar et al., 2008; Stahl et al., 2019; Starnawska et al., 2016). For instance, rs1006737 and rs4765913 in *CACNA1C* showed a significant association with BD in several large genome-wide association studies (2011; Ferreira et al., 2008; Muhleisen et al., 2014; Sklar et al., 2008). Suggestive associations in other genes coding calcium channels have also been identified (2011; Nurnberger et al., 2014a). Specifically, rs11013860 (NC_000010.11:g.18365098A>C) in *CACNB2*, located on the intronic region of *CACNB2*,has been reported as associated with BD more than once (Jan et al., 2014; Lee et al., 2011).

Emerging evidence has revealed that neuroimaging acts as an intermediate phenotype that could link the genetic effect to symptoms of mental diseases (Hashimoto et al., 2015; Rasetti and Weinberger, 2011). Thus, a growing number of researchers tried to study the relationships between BD genetic risk variations and neuroimaging abnormalities, aimed at uncovering the pathophysiological role of risk variations in BD (Hashimoto et al., 2015; Pereira et al., 2017b). Interestingly, among BD patients, the positive findings about the impact of coding calcium channel genes on the brain seem more consistent in the prefrontal cortex (PFC). Under the same experimental paradigm, two studies found a hyperactivation on the ventrolateral PFC in BD patients with *CACNA1C* risk allele A (Dima et al., 2013; Jogia et al., 2011). BD patients also revealed differed expression of the *CACNA1C* gene in the PFC compared to HC (Nurnberger et al., 2014b). Another study demonstrated that BD patients with the *CACNB2* rs11013860 AA/CA genotype exhibited decreased resting-state functional connectivity between the PFC subregion and the hippocampus compared to patients carrying the CC-allele (Liu et al., 2019). The PFC is a key component of emotion-processing neural circuitry, which plays a pivotal role in mood modulation (Drevets, 2000; Phillips et al., 2003; Zink et al., 2010). Abnormalities of this area were linked to those suffering from BD (Almeida et al., 2009; Ghosh et al., 2017; Herold et al., 2017; Kafantaris et al., 2009; Konopaske et al., 2014). Even among the BD patients who were not receiving lithium treatment, BD patients showed significantly thinner cortical thickness in the bilateral PFC than HC (Folandross et al., 2011).

So far, no studies have investigated the influence of the *CACNB2* rs11013860 on PFC morphology in BD. *CACNB2* encodes the β2 subunit of the voltage-gated L-type calcium channel (Cavβ2), which may modulate the L-type calcium channel activity (Buraei and Yang, 2013). This modulation may lead to a change in synaptic function, which may play a vital role underlying the neuropathogenesis of BD (Föcking et al., 2016; Kim et al., 2010).

Manic episodes have been reported to be associated with morphological changes in PFC (Abe et al., 2015). However, none of the genetic-neuroimaging studies involving genes coding calcium channel were carried out with the patients with first-episode mania, as well as most of the other genetic-neuroimaging studies (Cao et al., 2016a; Pereira et al., 2017a;

Zeni et al., 2016). So the findings from previous genetic-neuroimaging studies cannot eliminate the effect of the multiple manic episodes on brain morphology.

In this study, we use structural brain MRI to investigate the influence of the *CACNB2* rs11013860 on the morphological structure of the PFC, such as the PFC thickness, in BD patients with first-episode mania and HC. We hypothesized that the *CACNB2* rs11013860 could affect PFC thickness in BD patients with first-episode mania, and the thinner PFC thickness would be observed in the BD patients carrying risk allele A.

Materials and methods

Study participants

We received the approval of our study from the Institutional Review Boards at Guangzhou HuiAi Hospital (Affiliated Brain Hospital of Guangzhou Medical University) and written informed consent was provided to each participant in advance. BD Patients who were presenting their first manic episode were recruited through two centers, the outpatient mood disorders clinic and the inpatient department, in the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou HuiAi Hospital), China. HC were recruited by advertisement in local wall newspapers. All potential participants were evaluated by the Structured Clinical Interview for DSM-IV (SCID) to confirm the first-episode mania in BD patient group and the absence of any lifetime or current Axis I psychiatric diagnosis in the HC group. Exclusion criteria for both groups included severe neurological or distinct somatic illnesses currently, a history of trauma with loss of consciousness caused by brain injury, any MRI contraindications, or left-handedness. Healthy volunteers were excluded if they had past or current psychiatric diseases (including substance abuse), used any psychiatric medication currently, or had a familial history of psychiatric illnesses. BD patients who had any other axis I psychiatric conditions were also excluded. Additionally, we obtained information including gender, age, years of education, Body Mass Index (BMI), clinical subtypes, age of onset, Hamilton Rating Scale for Depression (HAM-D), Young Mania Rating Scale (YMRS), duration of illness and medication use from BD patients. We enrolled 153 BD patients and 83 HC during 2012-2017, and then selected a total of 46 first-episode mania patients and 83 HC for the current study.

Genotyping

DNA samples were extracted from blood cells with the phenol-chloroform method, the MassARRAY Assay (Sequenom, USA) was carried out to genotype for CACNB2 rs11013860. Sequenom TYPER version 4.0 software was used to get the genotyping results of rs11013860. The minor allele of rs11013860 is A allele. As A allele of rs11013860 in *CACNB2* confers risk of developing BD, participants were divided into two groups by genotype: A-allele carriers (participants with AA or AC genotype) and CC carriers (participants with CC genotype).

MRI acquisition and Image processing

MRI scans were performed within three days of clinical assessment. Structural MRI data

were acquired on a 3.0 Tesla MRI system (Achieva X-series, Philips Medical Systems, Best, Netherlands) in the department of radiology at Guangzhou HuiAi Hospital (Affiliated Brain Hospital of Guangzhou Medical University). High-resolution T1-weighted images were collected with a sagittal T1-weighted 3D turbo field echo (T1W 3D TFE) sequence (field of view 256×256mm^2; repetition time 8.2 ms; echo time 3.8 ms; view matrix 256×256; slice thickness 1 mm).

The FreeSurfer software v. 6.0 was used to performed a series of procedures including intensity normalization, motion correction, automatic segmentation and automated topology corrections of cortical regions, subcortical grey and white matter volumetric structures, white matter/cerebrospinal fluid (CSF) boundary and triangular tessellation of the grey and white matter interface, as documented previously (Desikan et al., 2006; Fischl, 2012; Fischl and Dale, 2000). For each participant, per hemisphere, we extracted PFC thickness measures as following: medial and lateral orbitofrontal cortex, rostral and caudal middle frontal cortex, superior frontal cortex, pars triangularis, pars orbitalis and pars opercularis (Lavagnino et al., 2016). Inferior frontal gyrus thickness was derived by averaging the cortical thickness value for pars triangularis, pars opercularis and pars orbitalis. Orbitofrontal cortex thickness was obtained by averaging medial and lateral orbitofrontal cortex thickness value. Using this approach, we merged rostral and caudal middle-frontal thickness values to derive middle-frontal gyrus thickness.

Statistical analyses

Statistical analyses were conducted using IBM SPSS statistics (Version 22.0). Demographic and clinical differences between groups were calculated with Analysis of Variance (ANOVA) and chi-square. A general linear model (GLM) was performed with bilateral cortical thickness measurements of PFC regions (superior frontal cortex, orbitofrontal cortex, middle and inferior frontal gyri) as dependent variables, and diagnosis (BD vs HC) and genotype (A-allele carriers vs CC-allele carriers) as two between-subjects factors. Age and gender included as covariates. The threshold of statistical significance was set at $P < 0.05$ and Bonferroni correction was applied to all post-hoc multiple comparison results.

Results

Demographic characteristics

Study participants included 46 BD patients with first-episode mania and 83 HC subjects. For demographic characteristics, as displayed in Table 1, there were no significant differences in gender or age between BD and HC groups. BD patients had significantly fewer years of education than HC ($p < 0.05$). Distributions of *CACNB2* genotypes conformed Hardy-Weinberg predictions for both BD patients and HC (both $p > 0.05$). There were no significant differences in *CACNB2* allele and genotype distributions between BD patients and HC ($\chi^2 = 0.170$, df = 1, $p = 0.680$ and $\chi^2 = 0.800$, df = 2, $p = 0.670$, respectively). The minor allele of rs11013860 is A allele, with a frequency of 0.42 in patients group and

0.40 in HC group.

PFC thickness

The BD group results revealed smaller cortex thickness vs. HC on all PFC thickness measurements ($p < 0.050$) (see mean and SD values in Table 2). There was a significant interaction between diagnosis and *CACNB2* genotype for right superior frontal thickness ($F = 8.190$, 0.040) (Fig.1) (Table 3). Post-hoc tests revealed that within A carriers, BD patients displayed reduced superior frontal thickness compared to HC ($p < 0.001$). Within BD patients, *CACNB2* A-allele carriers showed reduced superior frontal thickness compared to *CACNB2* CC-allele carriers ($p = 0.016$).

Discussion

This is the first report of an association between the *CACNB2* rs11013860 and PFC thickness in BD patients with first-episode mania. We report two main findings: (1) BD patients displayed thinner cortex thickness on all measurements of PFC compared to HC. (2) A significant interaction between *CACNB2* genotype and diagnosis was observed for right superior frontal thickness. In A-allele carriers, BD patients displayed lower superior frontal thickness compared to HC. Within BD patients, *CACNB2* A-allele carriers superior frontal thickness was reduced in comparison to *CACNB2* CC-allele carriers.

These observations of PFC thickness abnormalities in patients with BD are strongly in line with findings from previous studies (Abe et al., 2015; Folandross et al., 2011). Disease-related grey matter loss in PFC regions has been observed frequently in BD. For example, significantly smaller cortical thickness was observed for left and right PFC in BD type I (BD-I) patients compared to HC (Folandross et al., 2011). A longitudinal study that followed patients with BD-I for 6 years also reported significantly decreased dorsolateral PFC volume in the mania group, but no difference in the no-mania group (Abe et al., 2015) and other abnormalities of this area have been detected in BD (Almeida et al., 2009; Ghosh et al., 2017; Herold et al., 2017; Kafantaris et al., 2009; Konopaske et al., 2014). Besides, patients with other mental disorders like schizophrenia also exhibited reduced PFC cortical thicknesses (Asmal et al., 2018). Taken together, these results suggest PFC brain thickness abnormalities may be a neuroimaging biomarker of mental disorders.

It is also worth mentioning that the minor allele (allele A) frequency of rs11013860 in patients group (0.42) is higher than in HC group (0.40). But the group difference of minor allele frequency of rs11013860 did not reach the statistically significant difference. And the AA allele, AC allele, CC allele frequencies of rs11013860 in our study (0.24, 0.37, 0.39 in patients vs. 0.18, 0.43, 0.39 in HC) is different than the results from another study with the same ethnic samples (Lee et al., 2011). This inconsistent result may due to our relatively small sample size.

In our study, a significant interaction between rs11013860 genotypes and diagnoses was observed on right superior frontal thickness. Decreased superior frontal thickness was observed within A-allele carriers with BD compared to HC. In BD patients, A-allele carriers

also showed reduced superior frontal thickness compared to CC-allele carriers. Previous brain morphology research in BD has not focused on rs11013860 and our study is the first to report the impact of the *CACNB2* rs11013860 risk allele A on PFC thickness. In this context recent work indicates that BD patients expressing the A-allele of rs11013860 displayed impaired prefrontal-hippocampal cortical connectivity compared to BD patients with the CC-allele (Liu et al., 2019). That finding, together with the present results, suggests that the *CACNB2* rs11013860 risk allele A might have an impact on both PFC structure and function related to expression of BD. Though the sample in our study are not the first episode patients, they are thought to be in the early stage of BD (Kauer-Sant'Anna et al., 2009). Thus our results with first-episode mania patients indicate the possibility that *CACNB2* rs11013860 may affect PFC structure in the early stages of BD.

The mechanism by which the *CACNB2* rs11013860 A-allele may influence brain morphology in BD remains to be elucidated. Based on current knowledge we offer the following possible explanation. *CACNB2* encodes the β2 subunit of the voltage-gated L-type calcium channel, belonging to the Cavβ-subunits family, which is capable of impacting L-type calcium channel activity (Cens et al., 1996; Jangsangthong et al., 2010). Even a small alteration within the structure of the Cavβ-subunit could modify L-type calcium channel function, which plays a key role in neural plasticity by controlling the influx of calcium into neurons and calcium-dependent processes (Clapham, 2007). As *CACNB2* could express within brain (Volsen et al., 1997), and particularly within the PFC (Arion et al., 2007), the risk allele A of rs11013860 in *CACNB2* may be associated with disruption of L-type calcium channel function, which may in turn lead to abnormal neural plasticity, and may result in morphological changes in the PFC ultimately. This proposal fits with our current results, suggests that rs11013860 in *CACNB2* may impact PFC development in the early stages of the BD. BD patients with risk allele A showed significantly thinner PFC thickness compared to BD patients with CC-allele A, as well as HC with risk allele A.

Our study has several limitations worth noting. First, cycles of depression may influence the structure and function of hippocampus (Sheline, 2011), but previous studies found that reduction on brain volumetric measurements, such as hippocampus, were more consistent in BD-I patients than patients with other BD subtypes and MDD(Cao et al., 2017; Cao et al., 2016b; Hibar et al., 2016). And it remains unclear whether depressive episodes are associated with changes of PFC in BD. In addition, we found no differences in episodes of depression across rs11013860 genotypes in our patient group, so, in view of our allele-specific interaction, it seems unlikely that our results can be explained in relation to prior experience of depressive episodes. Second, cortical thickness in BD patients has been associated with exposure to lithium treatment (Hibar et al., 2018). As we found no significant differences in the number of the subjects who used lithium between rs11013860 genotypes in the BD group, our findings are not likely attributable to effects of lithium. Third, BD patients in our study showed a lower level of education compared to HC, however our results were still significant after adjusting the education, which suggested that our results were not affected by the education. Fourth, due to the relatively small sample size in our study, and the novelty of the current findings, these results should be replicated in additional larger samples of BD patients with first-episode mania and

compared to HC.

In summary, this is the first study to investigate the impact of *CACNB2* rs11013860 on the prefrontal anatomy in subjects with first-episode mania and HC. Our results suggested that, possibly through disruption of L-type calcium channel function, the *CACNB2* rs11013860 may play an important role in the morphologic changes of PFC thickness in patients with first-episode mania. These findings provide evidence to support *CACNB2* rs11013860 involving in the morphologic changes in emotion-processing neural circuitry in the early stage of BD, which will ultimately contribute to revealing the link between the variation in calcium channel genes and the neuropathological mechanism of BD.

Declaration of Competing Interest

None

Role of funding sources

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Author Statement

Author contributions: Bo Cao designed the analysis scheme, processed the image data and supervised the paper writing. Jair C. Soares, Xinmin Li, Andrew J Greenshaw, Jeff Sawalha, Yang Liu, Muhammad Yousefnezhad, Xiangyang Zhang critically edited the paper. Liping Cao, Tao Li, Jiuwei Tan, Xiaofei Zhang, Wenjin Zou, Xiaofang Cheng, Wenhao Deng, Yizhi Zhang, Liqian Cui, Chuihong Liu, Jiaqi Sun, Xiongchao Cheng, Qiuxia Wu, Suyi Li, Siming Mai, Xiaofeng Lan, Yingmei Chen, Yinglian Cai, Chaodun Zheng,

Daomeng Cheng, Bin Zhang, Chanjuan Yang, Xuan Li, Yamin Zhang, Liansheng Zhao, Biyu Ye collected the data. Jianshan Chen performed the analysis and wrote the paper.

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Table 1. Demographic and clinical features of study participants (Mean ± standard deviation (SD))

	HC (n = 83)	BD patents (n = 46)	Statistic (p)
Sex (male/female)	45/38	24/22	0.855
Age (years)	24.5 ± 4.7	24.3 ± 6.6	0.035 (0.852)
Rs11013860			
Genotype (AA/AC/CC)	15/36/32	11/17/18	0.642
AA	15	11	0.494
AC	36	17	0.576
CC	32	18	1
Allele frequency (A/C)	0.40/0.60	0.42/0.58	0.693
HAM-D		3.4±3.9	NA
YMRS		3.1±5.8	NA
Education (years)	15.1 ± 1.8	11.9 ± 3.6	46.486 (< 0.001)
BMI	20.7 ± 2.9	22.0 ± 3.3	3.637 (0.060)

Table 2. Comparisons of the thickness measurements (mm) on PFC subregions by diagnostic groupings (Mean ± SD).

Measurements	BD	HC	F	df	p value
left superior frontal thickness	2.78 ± 0.16	2.92 ± 0.13	28.644	1	< 0.001
right superior frontal thickness	2.80 ± 0.17	2.93 ± 0.13	21.896	1	< 0.001
left middle frontal thickness	2.44 ± 0.13	2.55 ± 0.11	24.756	1	< 0.001
right middle frontal thickness	2.43 ± 0.14	2.55 ± 0.11	23.200	1	< 0.001
left inferior frontal thickness	2.60 ± 0.16	2.73 ± 0.11	25.677	1	< 0.001
right inferior frontal thickness	2.60 ± 0.17	2.72 ± 0.11	29.016	1	< 0.001
left orbitofrontal thickness	2.59 ± 0.14	2.66 ± 0.09	10.216	1	0.016
right orbitofrontal thickness	2.59 ± 0.14	2.66 ± 0.10	8.634	1	0.032
Age of onset	NA	21.2 ± 6.6			NA
Psychotic symptom (n)		23			
Depressive episode		1.1 ± 1.2			
Duration of depression (month)		27.8 ± 39.5			
Medication use (n)					
Lithium		20			
Anticonvulsants		28			
Antidepressants		4			
Antipsychotics		36			
Anxiolytics		16			

Table 3. Comparisons of the thickness measurements (mm) on PFC subregions by genotype under different diagnostic groupings (Mean ± SD).

Measurements	HC		BD		F	df	p value
	A-allele carriers	CC carriers	A-allele carriers	CC carriers			
left superior frontal thickness	2.93 ± 0.14	2.91 ± 0.11	2.74 ± 0.14	2.83 ± 0.17	4.72	1	0.253
right superior frontal thickness	2.95 ± 0.14	2.92± 0.12	2.76 ± 0.14	2.86 ± 0.19	8.19	1	0.04
left middle frontal thickness	2.54 ± 0.12	2.55 ± 0.09	2.41 ± 0.12	2.47 ± 0.15	2.17	1	1.144
right middle frontal thickness	2.56 ± 0.12	2.54 ± 0.09	2.41 ± 0.13	2.47 ± 0.16	4.05	1	0.371

left inferior frontal thickness	2.73 ± 0.11	2.72 ± 0.11	2.58 ± 0.15	2.64 ± 0.18	3.62	1	0.474
right inferior frontal thickness	2.72 ± 0.12	2.73 ± 0.11	2.58 ± 0.17	2.62 ± 0.17	1.47	1	1.823
left orbitofrontal thickness	2.66 ± 0.09	2.65 ± 0.08	2.59 ± 0.14	2.60 ± 0.14	1.07	1	2.417
right orbitofrontal thickness	2.66 ± 0.09	2.66 ± 0.11	2.57 ± 0.11	2.61 ± 0.17	1.76	1	1.498

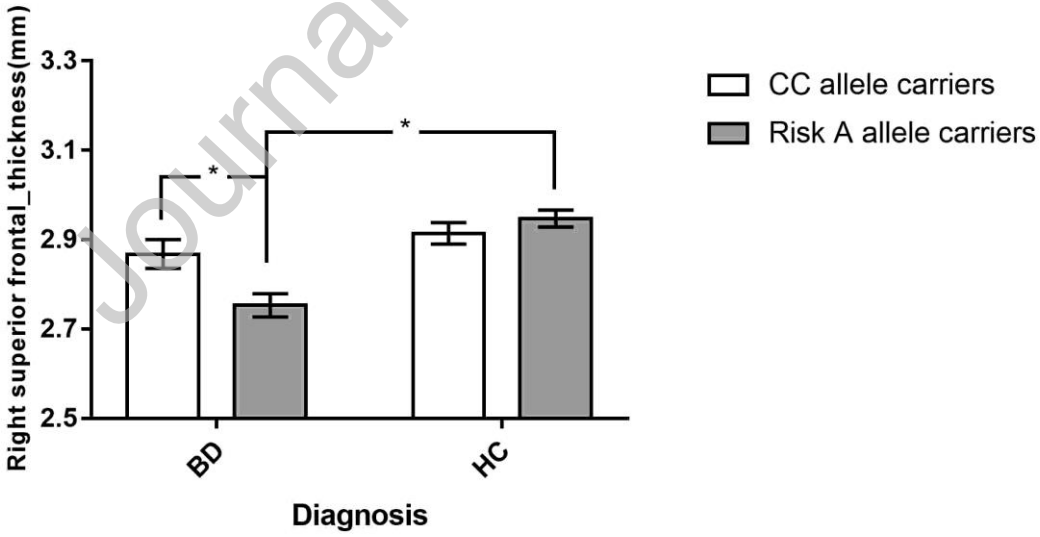

Fig1. A significant interaction between diagnosis and CACNB2 genotype on the right superior frontal thickness. Data are expressed as mean index value ± standard error of the mean; * $p < 0.05$.