Abnormalities of Thalamic Functional Connectivity in Patients with Migraine: A Resting-State fMRI Study

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ABSTRACT

Introduction: Migraine is a common headache disorder. Many studies have used magnetic resonance imaging (MRI) to explore the possible pathogenesis of migraine, but they have not reached consistent conclusions and lack rigorous multiple comparison correction. Thus, this study investigates the mechanisms of migraine development from the perspective of altered functional connectivity (FC) in brain regions by using data-driven and regions of interest (ROI)-based approaches.

Methods: Resting-state functional MRI data were collected from 30 patients with migraine and 40 healthy controls (HCs) matched for age, gender, and years of education. For the data-driven method, we used a voxel-mirrored homotopic connectivity (VMHC) approach to compare the FC between the patients and HCs. For the ROI-based method, significant differences in VMHC maps between the patients and HCs were defined as ROI. The seed-based approach further revealed significant differences in FC between the seeds and the other brain regions. Furthermore, the correlations between abnormal FC and clinical characteristics of patients were investigated. A rigorous multiple comparison correction was used with false discovery rate and permutation test (5000 times).

Results: In comparison with the controls group, patients showed enhanced VMHC in the bilateral thalamus. We also observed enhanced FC between the left thalamus and the left superior frontal gyrus, and increased FC between the right thalamus and the left middle frontal gyrus (Brodmann area 45 and Brodmann area 8) in patients. Further analysis showed that the FC values in the left superior frontal gyrus and left middle frontal gyrus were negatively corrected with visual analogue scale scores or attack times for headaches.

Conclusions: Patients with migraine showed altered VMHC in the bilateral thalamus, and abnormal FC of bilateral thalamus and other brain regions. The abnormalities in thalamic FC are a likely mechanism for the development of migraine.

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Key Summary Points

Why carry out this study?

Migraine is considered to be one of the most serious chronic dysfunctional disorders worldwide, with a high prevalence and significant loss and damage to personal health and socio-economic well-being.

The etiology of migraine is still unclear, effective treatments are lacking, and further research into its pathogenesis is urgently needed. At present, structural MRI of patients with migraine has not revealed any problems and functional MRI (fMRI) is expected to reveal biomarkers.

What was learned from this study?

This study used fMRI techniques to investigate the functional connectivity differences in the brain between patients with migraine and healthy controls. Compared with healthy controls, the patients exhibited abnormal voxel-mirrored homotopic connectivity and functional connectivity in the bilateral thalamus. This may be related to the fact that the thalamus is an important sensory relay hub.

These results provide solid evidence for the pathogenesis of migraine. In the future, studies with larger samples will be needed to further validate these findings.

INTRODUCTION

Migraine is a common primary headache disorder characterized by recurrent pulsating moderate to severe pain attacks [1]. It can be accompanied by nausea and/or vomiting, photophobia, or phonophobia [2]. According to the latest study, migraine affects approximately 1.25 billion people worldwide [3]. The prevalence of migraine in China is 9.3% [4]. There are apparent gender differences in the incidence of migraine. It disproportionately affects women three times more than men [5]. Migraine, one of the five most chronic severe dysfunctional diseases listed by the World Health Organization (WHO), causes disability and affects the quality of life [6]. Like low back pain, old age and other hearing loss, iron deficiency anemia, and depression, migraine places a substantial socio-economic burden on society in addition to the physical and mental health toll they take on individuals [7–11]. The pathogenesis of migraine is still unclear, and there is no targeted treatment at present. Therefore, it is crucial to explore the mechanism of migraine.

Resting-state functional magnetic resonance imaging (rs-fMRI) has been used to explore the neurophysiological mechanisms of migraine [12–15]. Some previous studies have shown that rs-fMRI can be an effective method for studying the pathogenesis of migraine [16, 17]. Altered functional connectivity (FC) has been identified in several existing studies [12, 13, 18, 19]. Li et al. found reduced resting-state FC between the periaqueductal gray and rostral anterior cingulate cortex/medial prefrontal cortex in patients with migraine compared to healthy subjects [18]. Zhang et al. revealed that the brain regions with increased FC in the left lateral geniculate nucleus of patients with migraine compared to healthy controls (HCs) were mainly located in the left cerebellar and right lingual gyri [20]. It can be seen that the results obtained from the different tests vary relatively widely. Also, these studies suffered from a lack of rigorous correction or correction of false positives [21, 22].

The FC between the bilateral hemispheres is essential, and disruption of this connectivity may be an early change in neurological pathology [23]. Alterations in interhemispheric FC have been found in some clinical trials on neurological disorders and animal studies, both in humans and in animals [24–28]. Voxel-mirrored homotopic connectivity (VMHC) measures the resting-state FC between each voxel in one hemisphere and its mirror counterpart in the other hemisphere [29]. A systematic VMHC analysis provides a possible way to observe FC between the resting states of the cerebral hemispheres [30]. The different intensities of VMHC in other symmetrical regions may represent various features of interhemispheric information for bilateral sensory integration and motor coordination [31]. Previous study showed decreased VMHC of the anterior cingulate cortex (ACC) in patients with migraine without aura relative to the controls [32]. Our study is conducted to further investigate the pattern of contralateral connections in the brains of patients with migraine in order to clarify the potential pathogenesis of migraine.

In the present study, we collected rs-fMRI data from patients with migraine and healthy controls. We hypothesized that patients with migraine would have abnormal VMHC values compared to healthy controls. VMHC was performed to assess only the voxel-mirrored regions of both hemispheres. Further seed-based rs-fMRI analysis was performed to map the FC pattern between the seed region and the whole brain regions to investigate the impaired FC between the two hemispheres. We also assessed whether the clinical features of migraine were associated with altered FC in patients with migraine.

METHODS

Recruitment

The study was approved by the Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (DZMEC-KY-2020-38). Thirty right-handed patients with migraine without aura and 40

right-handed healthy subjects were recruited from the outpatient department of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine between August 2020 and June 2021. The healthy controls had no significant differences in age, gender, or education level from the patients with migraine.

The inclusion criteria for patients with migraine were (i) age from 18 to 65 years; (ii) the patients satisfy the definition of migraine according to the International Classification of Headache Disorders, 3rd edition, beta version; (iii) no use of prophylactic treatments during the last month (including beta-blockers, calcium channel blocker, antiepileptic, antidepressant, 5-HT blocker, etc.); (iv) no use of any injectable prophylactic treatment; (v) age of the first onset less than or equal to 50 years; (vi) duration of migraine more than or equal to 1 year; (vii) at least two to no more than eight headache attacks every 4 weeks during the last 3 months. The duration of migraine is defined as how long the patient has suffered from migraine. Exclusion criteria were (i) the number of times analgesics taken for headache attacks is more than 10 per month; (ii) has taken antiepileptic or antidepressant in the last month before the study; (iii) has taken prophylactic treatments in the last month before the study; (iv) drug or alcohol abuse; (v) any other psychiatric, neurological, endocrine, cardio-cerebrovascular diseases, and other major system diseases; (vi) headache as a symptom of other diseases (e.g., hypertension, traumatic brain injury, intracranial organic disease); (vii) pregnancy or breastfeeding; (viii) any different types of headaches. All patients were asked to record in a headache diary the number of headaches, headache severity, and duration of each headache in the last month.

The inclusion criteria for HCs were (i) age from 18 to 65 years; (ii) no experience of migraine; (iii) no mental or other major systemic diseases; (iv) no MRI contraindications. The criteria for exclusion include (i) headache caused by organic disease; (ii) neurological disease, immunodeficiency, bleeding disorders, or allergy; (iii) has taken prophylactic treatments in the last 3 months before the study; (iv) drug or alcohol abuse; (v) underwent other medical

examinations; (vi) pregnancy or breastfeeding; (vii) MRI contraindications.

In the present study, we obtained brain imaging data from all participants. No participants were excluded because of incomplete MRI data or other data. All participants were asked to complete a questionnaire that included demographic data, Self-rating Anxiety Scale (SAS), and Self-rating Depression Scale (SDS). In addition, patients with migraine were asked to complete duration of illness, visual analogue scale (VAS), and Migraine-Specific Quality of Life Questionnaire (MSQ, including Emotion function, Preventive, and Restrictive) [33].

MRI Data Acquisition

MRI scans were performed using a Siemens 3.0-Tesla scanner (Skyra, Siemens, Erlangen, Germany) in the Department of Radiology for Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University. Ear plugs and sponge pads were used to minimize noise exposure and head movements. During resting-state fMRI scans, subjects were asked to observe a centrally placed gaze cross (+) with their eyes open and to avoid systematic thinking as much as possible. A high-resolution t1-weighted magnetization intensity preparation of a fast gradient echo sequence was obtained and covered the entire brain [192 sagittal slices, repetition time (TR) = 2530 ms, echo time (TE) = 2.98 ms, field of view (FOV) = 240 × 240 mm, flip angle = 7°, acquisition matrix = 256 × 256, 290 scans]. Rs-fMRI data were acquired using a single-shot gradient echo-planar imaging sequence [32 axial slices, TR = 2000 ms, TE = 30 ms, FOV = 224 × 224 mm, flip angle = 90°, matrix = 256 × 256, slices thickness = 3.5 mm, voxel size 3.5 × 3.5 × 3.5 mm^3].

Data Preprocessing

The functional images were preprocessed with Statistical Parametric Mapping software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) and Resting-State fMRI toolbox (DPARSF) [34]. To reduce the effect of unstable magnetization, the first ten volumes from each participant were discarded. The remaining volumes were then slice-time corrected, rearranged, and spatially normalized. Subjects whose head movements exceeded 3 mm in any direction were excluded. The images were spatially normalized into the Montreal Neurological Institute (MNI) space with a resampled voxel size of 3 × 3 × 3 mm^3. After that, the data were linearly trended and band-pass filtered (0.01–0.08 Hz) to reduce the effects of low-frequency drift and high-frequency noise. The 6-mm full-width at half-maximum Gaussian kernel was used to smooth the functional images.

VMHC Analysis

Homotopic resting-state FC was calculated as the resting-state FC between any pair of symmetrical voxels between hemispheres. More specifically, in symmetrical brain space, Pearson's correlation coefficients were calculated for the homotopic resting-state FC between each voxel's residual time series and its symmetrical interhemispheric counterpart. Then, to obtain the normalized z-map data, Fisher's r to z transformation was performed on the calculated correlation coefficients. The resulting values constituted the VMHC and were used in the subsequent group-level analysis.

Seed-Based FC

The seed-based FC was performed using a time-dependent process. Brain regions that showed significant differences in VMHC maps between the patients with migraine and the HCs were regions of interest (ROI). For each seed, we created whole-brain FC diagrams and tested the differences between groups of these diagrams. All seed-based FC analyses were performed using functional data sets that had been preprocessed and registered in the MNI standard space. The seeds and all symmetrical hemispheric voxels were performed using correlation analyses. To improve the normality, the correlation coefficients were switched to z values with Fisher's r to z transformation.

Statistical Analysis

Demographic and clinical data were analyzed using SPSS statistical analysis software (version 20.0, IBM Corporation, Armonk, NY, USA). The gender distribution differences between patients with migraine and HCs were tested with the Pearson chi-square test. The independent t test was used to compare the distribution of continuous variables (age, education level). All measurement data were summarized using mean and standard deviation. $P < 0.05$ was considered statistically significant, and all hypothesis tests were two-tailed.

The independent t test was used to analyze VMHC comparison between groups adjusting for gender, age, and education level. The resulting P values were corrected for multiple comparisons by using permutation test (5000 times) and false discovery rate (FDR). Additionally, the VMHC value of the brain regions showed the abnormal connections between hemispheres that were extracted as ROI. For seed-based correlation analysis, the permutation test (5000 times) was performed to detect significant differences between the migraine and HCs adjusting for age, gender, and education level with the independent t test and FDR corrected. Pearson's correlation analysis was used to detect the relationships between abnormal VMHC values or seed-based FC values and clinical characteristics in patients with migraine, including VAS, SAS, and SDS.

RESULTS

Demographic and Clinical Characteristics

As shown in Table 1, 30 patients with migraine (mean age 36.17 ± 13.28 years, 24 women) and 40 healthy controls (mean age 36.88 ± 14.97 years, 25 women) were enrolled in the study. A total of 49 (70%) of subjects were women. There were no significant differences in age, gender, and education level between the two groups ($P > 0.05$). SAS and SDS were significantly different between patients and HCs ($P < 0.05$).

## VMHC Differences Between Groups

Compared with the HCs group, the patient group showed enhanced VMHC values in the

Table 1 Demographic and clinical characteristics of patients with migraine and healthy controls

Parameter	Patients with migraine ($N = 30$)	Healthy controls ($N = 40$)	P value
Age (years)	36.17 ± 13.28	36.88 ± 14.97	0.839
Gender (male/female)	6/24 (20/80%)	15/25 (37.5/62.5%)	0.114
Education (years)	16.57 ± 2.73	15.93 ± 3.31	0.393
Duration (months)	85.23 ± 54.78	NA	NA
VAS	7.03 ± 0.98	NA	NA
SAS	43.73 ± 7.40	35.03 ± 7.034	< 0.001
SDS	43.20 ± 9.22	36.75 ± 7.96	0.001
MSQE	75.56 ± 15.52	NA	NA
MSQP	70.23 ± 14.68	NA	NA
MSQR	60.09 ± 10.50	NA	NA

VAS visual analogue scale, *SAS* Self-rating Anxiety Scale, *SDS* Self-rating Depression Scale, *MSQE* Migraine-Specific Quality of Life Questionnaire-Emotion function, *MSQP* Migraine-Specific Quality of Life Questionnaire-Preventive, *MSQR* Migraine-Specific Quality of Life Questionnaire-Restrictive, *NA* no applicable
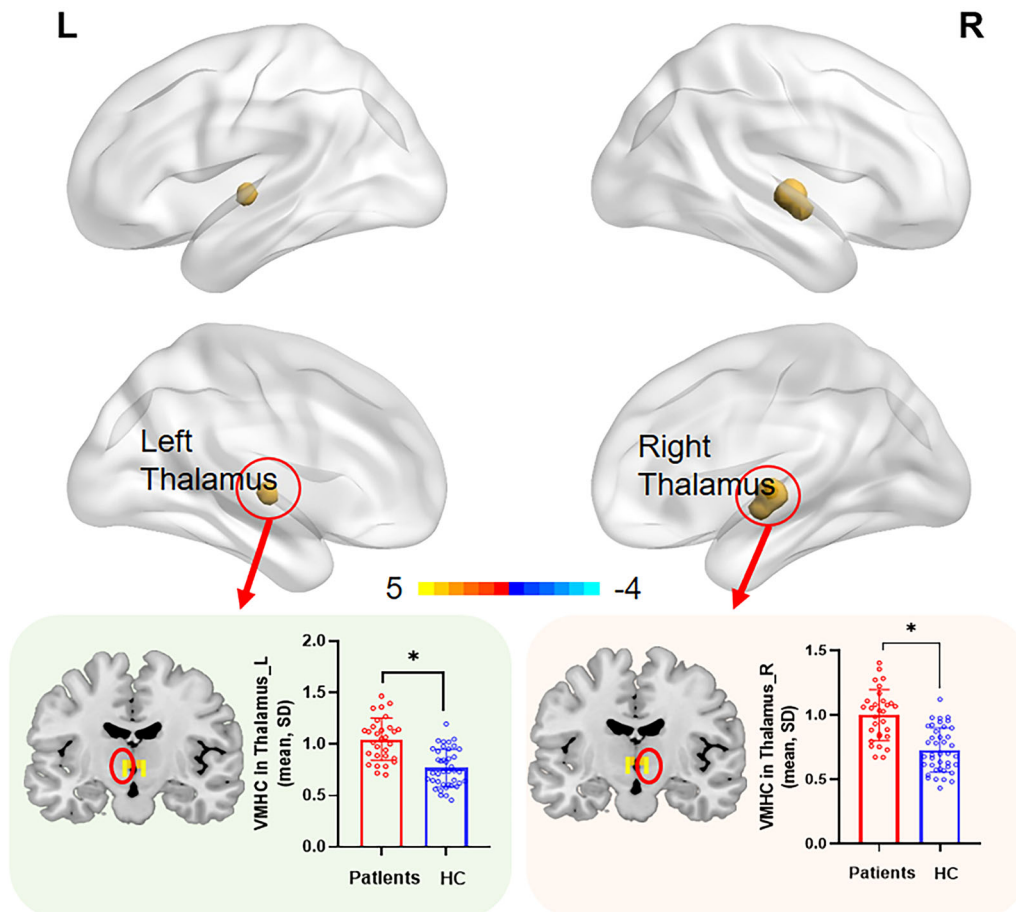
Fig. 1 Brain regions with VMHC alterations in patients with migraine. Compared with healthy controls, patients with migraine show significantly increased VHMC in bilateral thalamus. Results from two-tailed, $P < 0.05$, corrected by false discovery rate, permutation test 5000 times. *VMHC* voxel-mirrored homotopic connectivity, *HC* healthy controls, *L* left, *R* right, red points = patients with migraine, blue points = healthy controls

bilateral thalamus (FDR corrected $p < 0.05$, Fig. 1, Table 2). There were no regions that exhibited decreased VMHC values in the patient group relative to the HCs group.

As the bilateral thalamus showed remarkable VMHC differences between the patient group and the HCs group, it was used as a biological differentiator between the two groups (Fig. 2).

Seed-Based Functional Connectivity Between Groups

As mentioned earlier, the bilateral thalamus possessed higher VMHC values in the patient group compared to the HCs group. The seed-

Table 2 Brain regions showing VMHC differences between patients with migraine and healthy controls

Brain regions	Side	MNI coordinates			Intensity	Cluster size
		x	y	z		
Patients > HCs						
Thalamus	R	6	− 12	0	4.9271	153
Thalamus	L	− 6	− 12	0	4.9271	135

VMHC voxel-mirrored homotopic connectivity, *HCs* healthy controls, *MNI* Montreal Neurological Institute, *L* left, *R* right
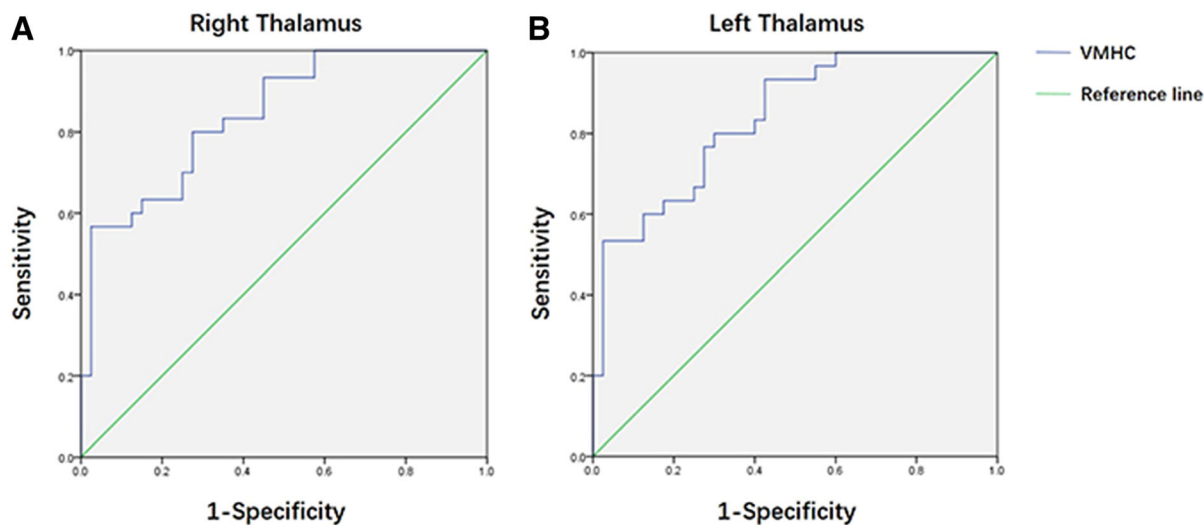
Fig. 2 ROC curves for the VMHC of bilateral thalamus in patients with migraine versus healthy controls. **a** AUC of right thalamus for patients vs. HCs was 0.84 ± 0.05. **b** AUC of left thalamus for patients vs. HCs was 0.84 ± 0.05. *ROC* receiver-operating characteristic, *VMHC* voxel-mirrored homotopic connectivity, *AUC* area under the receiver-operating characteristic curve

based FC analysis of the left thalamic seed sites revealed enhanced FC between the left thalamus and the left superior frontal gyrus (SFG) and right thalamus (FDR corrected $p < 0.05$, Fig. 3a, Table 3). When the right thalamus is used as a seed point correlation analysis, FC between the right thalamus and the bilateral middle frontal gyrus (MFG), which includes the left Brodmann area 8 and 45, is enhanced (FDR corrected $p < 0.05$, Fig. 3b, Table 3). No regions exhibited decreased FC in the patients with the HCs group.

Relationships Between FC and Clinical Characteristics

As displayed in Fig. 4a, the FC values between the left thalamus and left SFG were negatively correlated with VAS ($P = 0.011$, $r = -0.458$). In Fig. 4b, FC between the left thalamus and left SFG was negatively correlated with attack times for headaches ($P = 0.034$, $r = -0.388$). Furthermore, the FC values between the right thalamus and the left MFG (Brodmann area 45) were negatively corrected with VAS ($P = 0.012$, $r = -0.455$) in Fig. 4c. Also, in Fig. 4d, FC between the right thalamus and the left MFG

(Brodmann area 8) was negatively correlated with attack times for headaches ($P = 0.023$, $r = -0.415$). There was no significant correlation between the FC values and other clinical characteristics including SAS, SDS, Migraine-Specific Quality of Life Questionnaire-Emotion function (MSQE), Migraine-Specific Quality of Life Questionnaire-Preventive (MSQP), Migraine-Specific Quality of Life Questionnaire-Restrictive (MSQR), and the number of painkillers taken.

DISCUSSION

To date, there are no specific biomarkers for migraine. The diagnosis of migraine is largely dependent on medical history and clinical symptoms. Computer tomography and conventional MRI often fail to detect any abnormalities in patients with migraine. Resting-state fMRI is considered to be a more sensitive technique for neuropsychological assessment [16, 20]. To improve our understanding of the pathogenesis of migraine, this study used resting-state fMRI methods. We found bilateral FC alterations in the thalamus of patients with migraine in the resting state. The increased FC
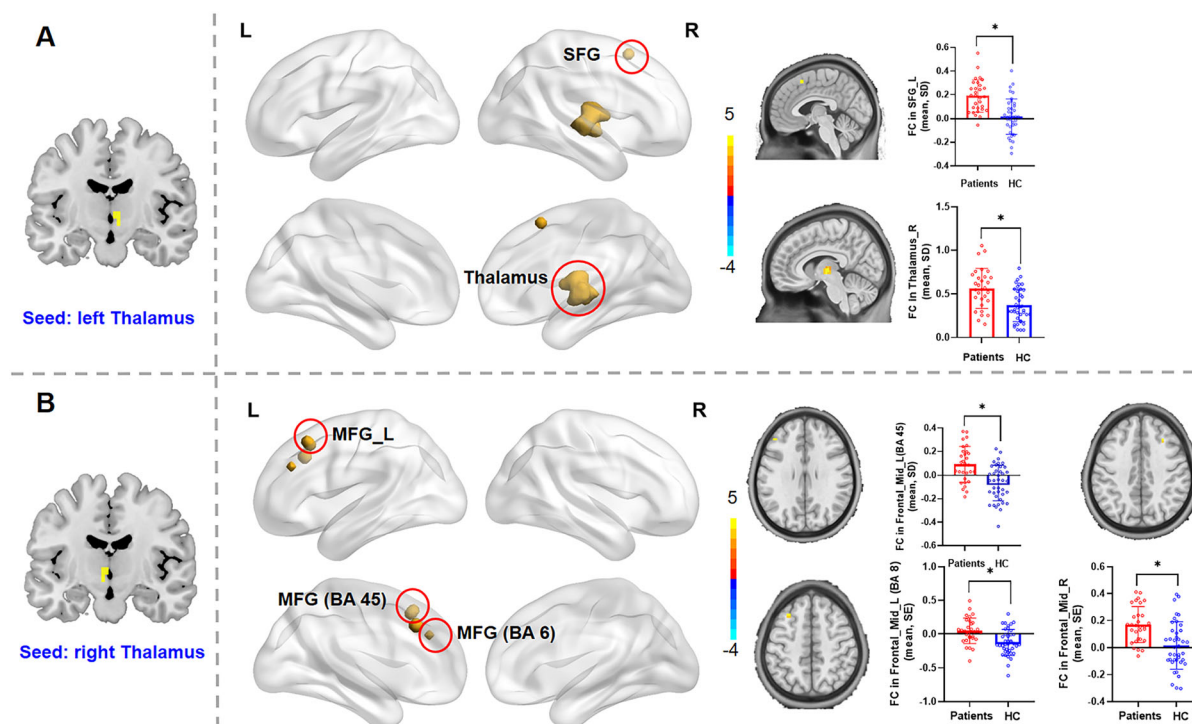
Fig. 3 Brain regions with FC alterations in patients with migraine. **a** Relative to the healthy controls, patients with migraine show increased FC between the left thalamus and superior frontal gyrus, right thalamus. **b** Patients with migraine show increased FC between the right thalamus and the left middle frontal gyrus, including the Brodmann area 45 and 8. Notes: Results from two-tailed, $P < 0.05$, corrected by false discovery rate, permutation test 5000 times. *FC* functional connectivity, *SFG* super frontal gyrus, *SFG_L* left super frontal gyrus, *Thalamus_R* right thalamus, *MFG* middle frontal gyrus, *MFG_L* left middle frontal gyrus, *BA 45* Brodmann area 45, *BA 8* Brodmann area 8, *L* left, *R* right, red points = patients with migraine, blue points = healthy controls

was also found between the left thalamus and the left SFG, and right thalamus. In the right thalamus, increased FC was found with the bilateral MFG, including the left Brodmann area 45 and 8. These results revealed that the patients with migraine exhibit anomalous functional coordination between both right and left hemispheres. Further analysis showed that the FC values between the left thalamus and the left SFG were negatively corrected with VAS scores or attack times for headaches; FC between the right thalamus and the MFG were negatively corrected with VAS scores or attack times for headaches.

The thalamus is considered to be an important hub for the transmission of sensory information, transmitting received stimuli such as touch, pain, vision, and hearing to the cerebral cortex [35]. Pain is a multidimensional complex of sensations, including sensory discrimination, cognitive and emotional components. The thalamus, a critical cortical structure in the pain-related network, plays a key role in the development of pain. The thalamus is involved in the processing, perception, and modulation of pain [36]. A previous study found that pain-induced neurotransmitter transmission of endogenous opioid-activated peptides was responsible for altered thalamic blood flow and the production of nociception [37]. The blood flow and functional and structural changes of the thalamus in migraine have been reported in previous studies [38–41]. A study using arterial spin labeling methods to measure cerebral blood flow found significant relative hypoperfusion in the median region of the thalamus and significant relative hyperperfusion in the frontal cortex bilaterally during the attack

Table 3 Brain regions showing seed-based resting-state FC differences between patients with migraine and healthy controls

Brain regions	Side	MNI coordinates			Intensity	Cluster size
		x	y	z		
Right thalamus, patients with migraine > HCs						
Middle frontal gyrus	R	30	27	39	4.1051	36
Middle frontal gyrus/Brodmann area 8	L	− 30	24	48	4.047	54
Middle frontal gyrus/Brodmann area 45	L	− 45	36	30	4.294	18
Left thalamus, patients with migraine > HCs						
Thalamus	R	6	− 12	0	4.9699	999
Superior frontal gyrus	L	− 3	18	57	5.0319	81

FC functional connectivity, *HCs* healthy controls, *MNI* Montreal Neurological Institute, *L* left, *R* right

phase in patients with migraine [41]. In a large multicentre study using an advanced 3-Tesla scanner, a comparison with healthy controls revealed that patients with migraine had smaller volumes of thalamic subnuclei (including the central nuclear complex, anterior nucleus, and dorsolateral nucleus) [38]. Evidence from fMRI studies have shown altered thalamic functional connectivity in patients with migraine [15, 16]. A study observed the dynamic functional connectivity of thalamo-cortical networks, and found that patients with migraine spent more time in a state of strong internetwork connectivity and less time in a state of sparse connectivity compared to healthy controls [42]. Another study found that people with migraine exhibited a reduction in the thalamic-pain pathway while showing an enhancement in the thalamic-visual pathway [16]. The current findings suggest significantly increased in VMHC values and enhanced FC between the bilateral thalamus, indicating a reduction in functional pain pathways in the thalamus, which may be associated with disruptions in projection, pain processing, perception, and regulation due to recurrent pain episodes. Our findings of changed function in the thalamus support previous studies. This result is valuable to further our understanding of the clinical manifestation and pathogenesis of migraine.

The SFG, located in the superior lateral frontal lobe, is a brain region responsible for emotion regulation. It is a higher center involved in the convergence and processing integration of injurious information transmitted by the internal and external nociceptive systems and has a specific role in weakening nociception [43]. Previous studies have shown that signals from the cognitive and emotional components of pain, uploaded via the medial conduction system, project via the thalamus to the prefrontal lobes and that motivated emotional responses to pain and cognitive evaluations are performed by brain regions including the prefrontal lobes [44, 45]. A study using fMRI techniques showed decreased cerebral blood flow in the right super temporal gyrus and middle frontal gyrus in patients with tinnitus and migraine [46]. Patients with migraine treated with acupuncture were found to have altered FC between the SFG and other brain regions [13]. We observed that FC between the left thalamus and the left SFG was enhanced. This provides a basis for the possible involvement of the SFG in the production of migraine.

The MFG is an important centre associated with attention. Previous research has shown that this area plays a key role in the reorientation of attention, working memory, speech, and language comprehension [47]. A study on vestibular migraine found increased FC between the left thalamus and the right MFG [16].
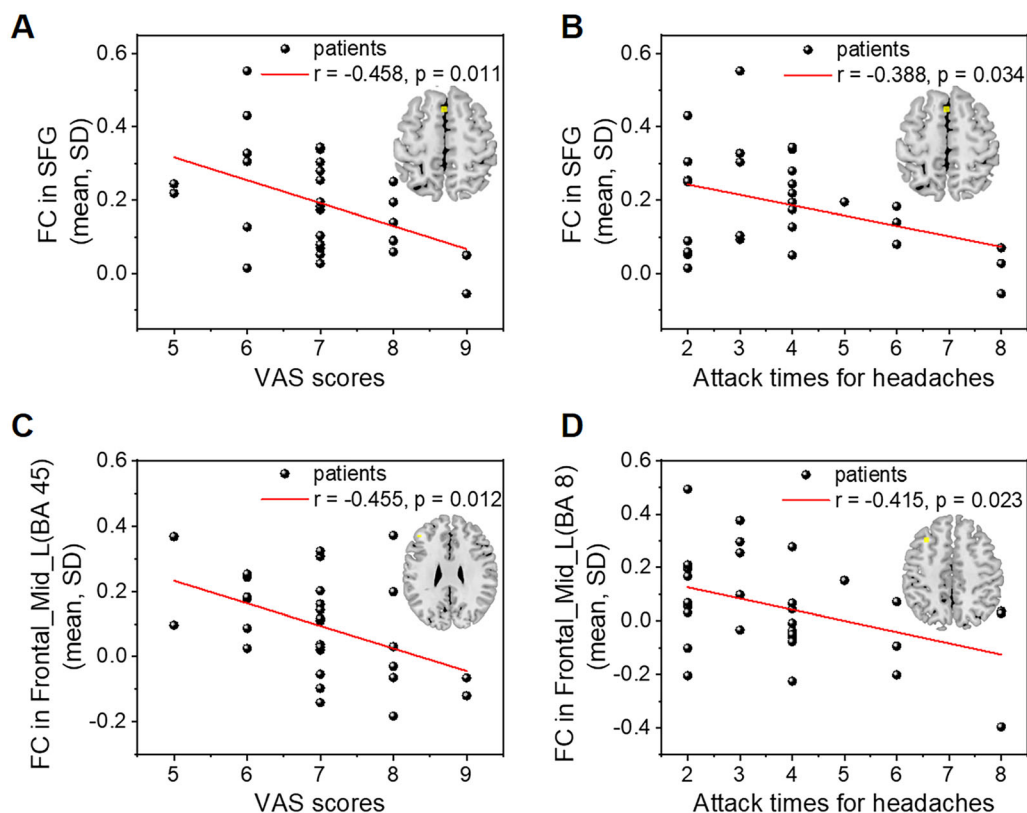
Fig. 4 Correlation between VAS scores, attack times for headaches, and FC of the left SFG and the left MFG. **a** FC between the left thalamus and the left SFG was negatively corrected with VAS scores. **b** FC between the left thalamus and the left SFG was negatively corrected with attack times for headaches. **c** FC between the right thalamus and the left MFG (BA 45) was negatively corrected with VAS scores. **d** FC between the right thalamus and the left MFG (BA 8) was negatively corrected with attack times for headaches. Notes: Results from two-tailed, $P < 0.05$, Pearson correlation coefficient; *FC* functional connectivity, *SFG* super frontal gyrus, *Frontal_Mid_L* left middle frontal gyrus, *BA 45* Brodmann area 45, *BA 8* Brodmann area 8, *VAS* visual analogue scale

However, another study on migraine without aura has found reduced FC between the thalamus and the right MFG [35]. We found decreased FC between the right thalamus and the left MFG, which is consistent with previous findings.

Compared with healthy controls, we found negative corrections in the FC values between the left thalamus and the left SFG with VAS scores or attack times for headaches, and FC between the right thalamus and the left MFG was negatively corrected with VAS scores or attack times for headaches in patients with migraine. However, this correlation is positive between patients. This may be because we do not further classify migraine sufferers, or

because we do not analyze the degree of pain and the duration of the illness. Detailed subgroup analyses will be needed in the future to complement our results.

Some previous studies have considered the brainstem, hypothalamus, somatosensory cortex, or visual cortex as key regions in migraine [12, 39, 40]. Our study did not find alterations in VMHC or FC in these regions. The inconsistent result may be due to that the difference in method. In some previous studies, the analytical methods were based on a priori hypotheses, and the key brain regions in pain were defined as the ROI. Different observation metrics between this study and previous studies may contribute to this inconsistent result, and in the

future we will also consider using the same observation metrics to verify our results. Besides, some of the previous studies suffered from a lack of rigorous correction, and we used a more rigorous false discovery rate corrected and permutation test (5000 times).

As with all the studies, the current research needs to be considered with several potential limitations. First, our study is cross-sectional research, and the causal relationship between the brain changes and migraine is still unclear. Second, the sample size in our study is small, but we have performed a rigorous calibration and future studies with larger samples could further validate our results. Third, we did not record the time from the scan to the previous attack in patients with migraine. Some studies requested a scan 48 or 72 h after a migraine attack [35, 48]. In future, in order to further improve our study, we will more strictly limit the time in which patients receive scans. Fourth, we adopted the whole thalamus as the seeds in the current study; however, different subregions of the thalamus may have particular functions. Therefore, further research is needed to understand better the correlation between other regions of the thalamus and the pathogenesis of migraine.

CONCLUSION

Overall, although our findings need to be validated using larger sample size, the present results reveal that abnormalities in thalamic functional connectivity are a likely mechanism for the development of migraine. Resting-state fMRI may be an essential diagnostic modality for differentiating migraine from other types of headaches. Scientific explanations of the underlying mechanisms of migraine need increasing attention.

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with the Declaration of Helsinki. All researchers protected the health and rights of each participant. Before the study, each participant received informed consent.

Data Availability. The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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