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Research article

A study on alterations in functional activity in migraineurs during the interictal period

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ABSTRACT

Migraine is a recurrent disease in which the cumulative effect of repeated pain attacks over a long period of time causes changes in brain function. Although there are some studies focusing on the interictal period of migraine, the reproducibility of these results is poor. Therefore, we intend to use a data-driven functional connectivity (FC) approach to probe the alterations in cerebral functional activity during the interictal period, as well as underlying no-task mechanisms of inducing headache attack in migraine patients. In the current research, 24 episodic migraine patients and 23 healthy controls (HCs) were recruited. By analyzing the magnitude of regional homogeneity (ReHo) and low-frequency fractional fluctuation (fALFF), We identified alterations in spontaneous brain activity in migraineurs, including the bilateral middle frontal gyrus, left postcentral, and right lingual gyrus. Thereafter such abnormalities were selected as seeds (ROIs) for FC analysis to further explore the underlying changes between ROIs and the whole brain areas. Compared with HCs, FC between the right middle frontal gyrus with the left precuneus cortex, and bilateral thalamus were enhanced in migraineurs. In addition, increased FC has been showed between the left postcentral gyrus with the bilateral thalamus. Furthermore, negative correlation existed between fALFF values of the left middle frontal gyrus and the pain intensity of migraine attacks ($r = -0.4578$, $p = 0.0245$). In summary, abnormal FC between the bilateral thalamus and right middle frontal gyrus, or the left retrocentral gyrus may occur between attacks in migraineurs, which may be the basis for sensory integration and pain regulation dysfunction. Thus, this could become a promising biomarker for the early diagnosis and evaluation of migraine in the interictal period, and provide a novel view for further investigation of the pathogenesis and etiology of recurrent migraine.

1. Introduction

Migraine, a common chronic neurological syndrome, can be divided into episodic migraine and chronic migraine based on the frequency of attacks. The majority of migraineurs are clinically asymptomatic in the interictal period and the time course varies from interictal to episodic [1]. However, many migraineurs in the interictal period are not treated with prophylactic medication, leading to the abuse of acute analgesics and the chronicity of the headache [2]. The transformation or chronicity of episodic migraine is not only

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an increase in the frequency of headaches, but also in severe cases the development of a persistent migraine state with very frequent disabling headaches and accompanying symptoms, causing acute medication shortages, wasted high levels of healthcare and declining quality of life [3, 4]. Surveys report that approximately 2.5% of episodic migraines develops into chronic migraine every year [4], but the chronic mechanism of episodic migraine is still unclear. Thus, identifying characteristic brain regions of migraine in the interictal period may distinguish disease states from healthy states, and provide a new perspective into the chronic mechanisms of episodic migraine.

Conventional imaging examinations of the migraine cycle were unremarkable, including cranial CT imaging, cranial magnetic resonance imaging (MRI) and cranial MRI enhanced scans, but the perspective has been changed by the rapid progress of functional MRI (fMRI) recently. Resting-state fMRI is an advanced tool developed in recent years, which could be used to locate lesions, probe neural networks, and identify brain-behavior relationships [5]. Repeated migraine attacks may lead to abnormal regional brain activity and network connectivity in brain areas involved in pain processing, including increased cortical excitability and impaired function of pain modulatory systems [6]. Therefore, alterations in brain function should be measurable at any stage of migraine [7]. The basic forms of functional organization of the brain include functional differentiation and functional integration. Regional homogeneity (ReHo) and frequency fluctuation fractional amplitude (ALFF) analysis are the common indicators of functional segregation, while functional connectivity analysis (FC) is commonly used functional integrational measures. Based on this, numerous fMRI studies on migraine have demonstrated abnormal local activities in various brain regions, mainly notably the frontal lobe, insula, thalamus, anterior cingulate cortex, precuneus and posterior cingulate gyrus [8, 9, 10]. Unfortunately, these studies did not perform FC analysis of the abnormal brain regions. There were also studies exploring interictal FC changes in migraine, with one study finding FC abnormalities in the right middle frontal gyrus and dorsal anterior cingulate gyrus in migraineurs [11]. Another research indicated normal FC in these two brain regions, but the connectivity between the temporal and frontal lobes was reduced [12]. It can be seen that the choice of different seed points (ROIs) leads to widely varying results and a lack of rigorous correction for false positives.

ALFF detects the strength of neural spontaneous activity at the level of a single voxel, while ReHo describes the local synchronization of a particular voxel with its neighbors [13]. Low-frequency fluctuation fractional amplitude (fALFF) is a modified measure on the original ALFF approach to dispose of the disturbance of nonspecific noise components and heighten the effectiveness [14]. ReHo reflects the functional state of the whole brain in terms of temporal similarity and does not specifically reflect the activity state of each brain region in the resting state, whereas the ALFF method quantifies blood oxygen dependent signal strength for each voxel and directly reflects neuronal activity intensity in each voxel in the whole brain, so the two can complement each other [15]. Resting-state FC analysis can reveal correlations of activity in discrete brain regions in the resting state [16] and has been widely used to detect abnormality in functional integration in a variety of neurological diseases, playing an important role in further understanding these illness, such as Alzheimer's disease [17], schizophrenia [18], and depression [19, 20]. Seed point-based analysis is regarded as the most generally accepted means in resting-state FC analysis, in which the average time series of a region of interest is related to the time series of the entire brain voxels based on seed points selected by the researcher, including hypothesis-driven FC and data-driven FC. Hypothesis-driven FC draws on subjective prior knowledge to accurately select ROIs in advance, whereas data-driven FC is based on activation maps obtained from other methods of brain function computation as ROIs. In addition, data-driven FC analysis balances out the subjective differences in ROI selection, allowing for greater objectivity in the results [21].

Therefore, this study used fALFF- and ReHo-based analyses to select ROIs for FC analysis from the perspective of functional separation combined with functional integration, with a more rigorous calibration approach, to gain a more comprehensive understanding of functional brain changes in migraine. The aim is to obtain new biomarkers identifying the interictal period, and explore possible mechanisms of task-free headache attacks, which may provide probable direction for carrying out follow-up diagnostic and therapeutic investigation.

2. Materials and methods

This study has received approval documents from the Institutional Ethics Review committee of the Second Affiliated Hospital of Nanchang University, China, and was conducted in strict accordance with the ethical standards of the Declaration of Helsinki. Age-, and gender-matched migraineurs and healthy controls (HCs) in this trail were recruited from December 2020 to January 2022 in the hospital Neurology Clinic and Physical Examination Center, respectively and required to signed an informed consent. According to migraine diagnostic criteria of the International Headache Society Classification (ICHD-3-beta) [22], migraineurs were diagnosed by two neurological specialists. The inclusion criteria of all migraineurs were: as follow: 1) The age range is 18–55 years old, 2) right-handed, 3) a migraine course at least six months, and 4) migraine attacks less than 15 days per month. Moreover, the exclusion criteria of all migraineurs were: as follow: 1) an abnormal neurological examination, 2) pregnant or lactating woman, claustrophobia and other common contraindications for having MRI examination, 3) chronic pain disorders other than migraine, 4) nicotine, alcohol, or other substance abuse, and 5) brain magnetic resonance examination finding any lesions with asymmetric brain anatomy. Meanwhile, all HCs were right-handed, and with no past or family history of headache.

2.1. Data processing and analysis

2.1.1. Clinical evaluation

Before the MRI scans, all participants completed neuropsychological evaluationusing a self-rating anxiety (SAS) and depression (SDS) scale, and visual analogue scale (VAS) of migraine attack severity on a scale of 0–10. Interviews were conducted and detailed clinical information was recorded, including the general demographic information, disease course, headache attack information

(attack form, attack frequency), past medical history, family history, and medication use.

2.2. MRI data acquisition

All migraineurs underwent MRI scans during the interictal period of migraine, that is, at least 48 h before and after the scan without a migraine attack. All participants were asked not to drink coffee, alcoholic beverages or take any headache related medication for at least 48 h before the MRI scan. And, all MRI data were collected at the Imaging Center of the Second Affiliated Hospital of Nanchang University, using a GE Discovery MR750 3.0 T system (General Electric, Milwaukee, WI, USA) equipped with an eight-channel, phased-array head coil. During scanning, all participants have used foam padding to avoid involuntary head motions, and all were asked for keeping their eyes closed, remaining awake and lying motionless with no thinking about anything. A resting-state echoplanar imaging scan over 8 mins with the parameters was collected: repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, slice thickness = 4 mm, slices = 39, data matrix = 64 × 64, FOV = 24 mm × 24 mm. Then, the 3-mins structural scan with with the parameters was obtained for anatomical reference: TR = 8.5 ms, TE = 3.3 ms, slice thickness = 1.4 mm, matrix = 256 × 256.

2.3. MRI data preprocessing

All MRI data were preprocessed using the statistical parametric mapping software package (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and the Resting-State fMRI Data Processing Assistant (DPARSF 5.1, http://rfmri.org/DPARSF) on MATLAB2013b (MathWorks, Natick, MA, USA) [23]. First, we converted all DICOM files to NIFTI images, and discarded the first 10 volumes about each individual. Then, we performed slice timing and head motion correction on the rest of volumes to get rid of the data with mean head motion translation >2 mm and/or rotation >2°. We eliminated the skull strips and concentrated the T1 images to the mean EPI image, which was then de-linear drift and low frequency filtering from 0.01 to 0.08 Hz. All irrelevant signals such as white matter and cerebrospinal fluid, 6-direction head movement parameters, and whole-brain signals were removed by regression. Moreover, we spatially normalized to Montreal Neurological Institute (MNI) standard space using "Dartel +new segment" [24] and resembled to a voxel size of $3 \times 3 \times 3$ mm^3, and spatial smoothing with a 4-mm full width at half maximum (FWHM) Gaussian kernel to decrease spatial noise.

2.4. Static fALFF analysis

ALFF studies local brain neural activity by analyzing regional spontaneous fluctuations in BOLD signals over a specific frequency range (0.01–0.08 Hz) [25]. fALFF analysis was conducted on DPABI and SPM, and refers to the ratio of fluctuations in the BOLD signal in the low-frequency range to the entire frequency [26]. First, a single ALFF map is computed by transforming the time series of each voxel into the frequency domain by performing a fast Fourier transform (FFT), without temporal bandpass filtering. Then, individual fALFF maps were generated by dividing the total amplitude of the low frequency range from 0.01 to 0.08 Hz by that of the full frequency range from 0 to 0.25 Hz. To reduce individual heterogeneity between subjects, the fALFF values were transformed to z-fALFF values using Fisher's z transformation, then spatially smoothed using a 4 mm full-width anisotropic Gaussian kernel at half-maximum, and the smoothed Z-fALFF values were served as the final metric for the statistical analysis.

2.5. Static ReHo analysis

The individual ReHo value was acquired on DPABI software and SPM by computing Kendall's coefficient of consistency (KCC) value to the time series of the 26 nearest neighbors corresponding to each voxel [27]. ReHo is based on a data-driven approach that requires no prior knowledge and thus has good test-retest reliability [15]. A mask was created by removing nonbrain tissues providing statistics for the next step. The individual ReHo maps were normalized by their respective mean KCC in the mask, divided by the globally average ReHo value for standardization. Then, the ReHo values were transformed to z-ReHo values by Fisher's z transformation to eliminate individual heterogeneity. All z-ReHo values were smoothed with a Gaussian kernel of 4 mm FWHM, and utilized as the statistical indicators.

2.6. fALFF and ReHo-based FC analysis

The significantly different regions in brain activity by fALFF and ReHo analysis were created as ROIs to probe the integration of the whole brain functional network. After preprocessing the MRI data, the data was filtered with a bandpass filter from 0.01 to 0.08 Hz, and then spatially smoothed using a 4 mm FWHM Gaussian kernel. A linear correlation between the average timeseries in signal ROI and the rest of the brain voxels were calculated for each participant to carry out a voxel wise FC analysis. Finally, the correlation coefficients (r) were normalized to Z scores with the Fisher r-to-z transformation to create subject specific maps using the following formula:

$$z = 0.5\log[1 + r/1 - r]$$

The Z score FC maps of each ROI were for statistical analysis.

2.7. Statistical analysis

Demographic and clinical characteristic data were analyzed by the IBM Statistical Package based on the Social Sciences 23.0 software (IBM SPSS Inc, Chicago, IL). Continuous variables were tested by the homogeneity of variance test and normality test, and correspondingly expressed as the median, or mean ± standard deviation (SD). The Mann–Whitney U test and student's t-test were used to compare continuous variables between two groups. The enumeration data were expressed as the relative number constituent ratio (%) or rate (%), and compared by the $\chi 2$ test or Fisher's exact test. The significance level was set at $p < 0.05$.

Then, group comparisons were performed for fALFF and ReHo using two sample t-tests with covariances of sex, age, educational degree and framewise displacement (FD) values. For the FC analysis, a one-sample t test was conducted on each Z-maps for within-group comparisons (within the grey matter mask), and a mask was created to provide statistics for the next step. Two-sample t-tests were conducted to compute the significantly distinct Z-FC values using the previous mask in the two groups, and with age, gender, educational level as covariates. With Gaussian random field (GRF) theory, multiple comparison correction was performed and the significance voxel level and cluster value were respectively set at $P < 0.001$, $P < 0.05$. Next, pearson correlation analyses was performed by regressing for age, gender and education level.

3. Results

3.1. Subject demographics

Twenty-eight migraineurs and thirty-one HCs completed all the study procedures. After excluding migraine attacks within 48 h of completing the MRI scan and excessive motion, 24 migraineurs and 23 HCs were finally involved in the analyses (Table 1). In this study, there was no significant difference in age, gender or mean FD values between these two groups.

P values resulted from chi square analyses (sex) or independent samples t tests (all others). HCs, healthy controls. Y, Year. M, Median. p25, Lower quartile. p75, Higher quartile. MFD, mean framewise displacement. P, P value. NA, not applicable.

3.2. Alterations in local functional brain activity in fALFF and ReHo

Compared with the HCs, fALFF levels in the left middle frontal gyrus were significantly increased in migraineurs (Figure 1a, Table 2). ReHo values in the right middle frontal gyrus were enhanced, while the values in the right lingual gyrus, and left postcentral gyrus were decreased (Figure 1b, Table 2).

3.3. FC analysis result

The bilateral middle frontal gyrus, the right lingual gyrus, and the left postcentral gyrus were used as ROIs to perform FC analysis (Table 3, Figure 2). Relative to HCs, migraineurs showed increased FC of the right middle frontal gyrus (seed 1) with the bilateral thalamus, and the precuneus cortex (Figure 2a). Meanwhile, migraineurs showed increased FC of the left postcentral gyrus (seed 2) with the bilateral thalamus (Figure 2b).

FC, functional connectivity. MFG, middle frontal gyrus. POCG, postcentral gyrus. MNI, Montreal Neurological Institute. R, right. L, left.

3.4. Correlation analysis

fALFF in the left middle frontal gyrus had a negative correlation with VAS ($r = -0.4578$ $p = 0.0245$) (Figure 3). No significant correlation with the clinical variables or the other abnormal brain regions was found in migraineurs.

4. Discussion

Pain is regarded as a multidimensional complex of sensations caused by the effects of injury, damage or irritation to human tissues, with both sensory discrimination, and cognitive and emotional components [28, 29]. The prefrontal cortex, a key brain region associated with cognition, emotion, pain and behavior management, is relatively "sensitive" to painful stimuli and can be indirectly

Table 1
Demographics and clinical characteristics.

Parameter	Migraineurs	HCs	Z/T	p
N	24	23		
Age (Y, M/p25, p75)	31.00/25.00, 49.00	27.00/24.00, 37.00	-0.725	0.469
Sex (male/female)	7/17	6/17	0.056	0.813
MFD (M/p25, p75)	0.04/0.04, 0.06	0.04/0.03, 0.05	-0.426	0.670
Disease duration (M/p25, p75)	6.50/3.00, 10.00	NA	NA	NA
Attack frequency (times/month)	6.71 ± 2.54	NA	NA	NA
Pain severity (M/p25, p75)	6.00/3.00, 7.50	NA	NA	NA

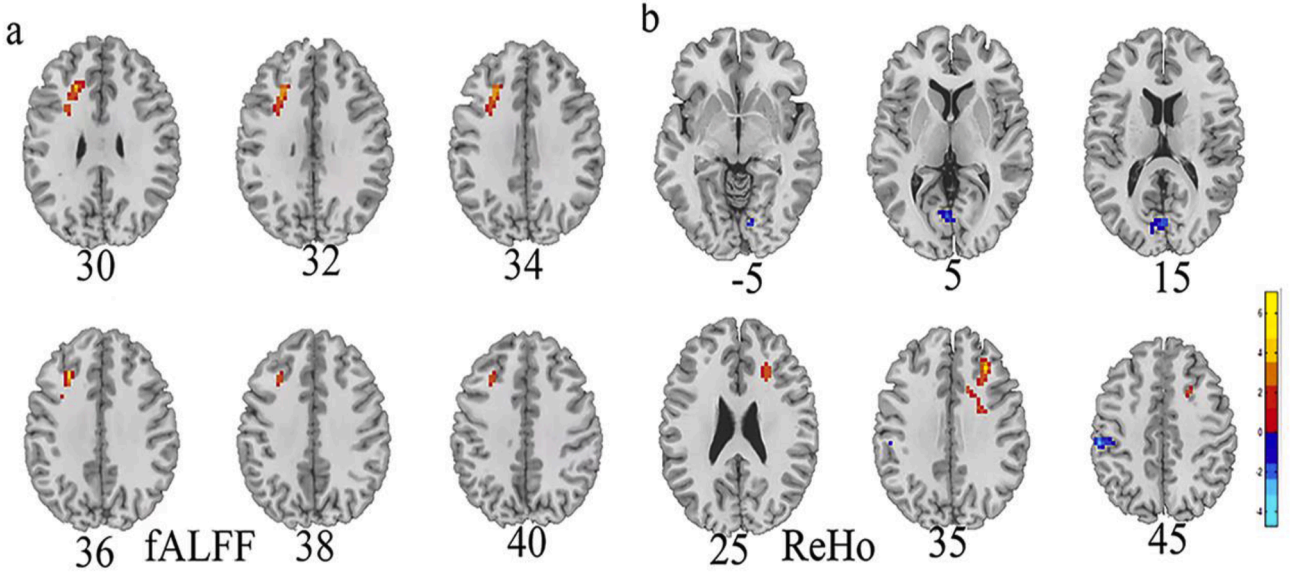

Figure 1. Brain regions showing differences in fALFF (a) and ReHo (b) values in migraineurs and HCs, respectively. Regions where the fALFF or ReHo values have enhanced are shown in red, while the values have reduced are shown in blue (GRF corrected, voxel value $P < 0.001$, cluster value $P < 0.05$). The color bar indicates the T value. fALFF, fractional amplitude of low-frequency fluctuation.

Table 2
Alterations in local functional brain activity in migraineurs compared with HCs.

Areas	Side	Total voxels	MNI coordinates of peak point			Peak intensity
			x	y	z	
fALFF						
Middle Frontal Gyrus	L	37	-27	27	36	4.5490
ReHo						
Middle Frontal Gyrus	R	43	27	30	30	7.0976
Lingual Gyrus	R	20	3	-78	18	-3.7415
Postcentral Gyrus	L	98	-39	-27	60	-4.7090

MNI, Montreal Neurological Institute. R, right. L, left.

Table 3
Brain areas with different FC in migraineurs compared with HCs.

Areas	Side	Total voxels	MNI coordinates of peak point			Peak intensity
			x	y	z	
Seed 1: right middle frontal gyrus (MFG.R)						
Thalamus	L	112	-3	-15	6	4.7359
	R	112	3	-15	6	4.7359
precuneus cortex	L	23	0	-63	0	4.6489
Seed 2: left central posterior gyrus (POCG.L)						
Thalamus	L	93	-2	-15	4	4.2476
	R	93	2	-15	4	4.2476

involved in pain regulation through the brainstem, affecting the downstream pain transmission pathway [30]. At the same time, studies have shown reduced grey matter volume in the bilateral inferior frontal gyrus and left middle frontal gyrus in migraine patients, with structural changes further highlighting the significance of the frontal cortex in migraine attacks [31]. The present study found increased fALFF values in the left middle frontal gyrus and ReHo values in the right middle frontal gyrus in migraineurs, suggesting that the region of functional activation of the middle frontal gyrus may be involved in regulating endogenous pain processes and may be a biomarker for differentiating migraineurs from healthy individuals. Szabo et al. [32] also demonstrated that the right middle frontal gyrus is involved in cognitive/attentional and emotional processes in migraine (during the interictal period). As part of the dorsolateral prefrontal cortex (DLPFC), this region also shows higher pain-related activity in migraineurs [33]. In addition, fALFF values in the left middle frontal gyrus has a negative correlation with headache pain intensity, and fALFF values in this region could be used as an index to predict pain intensity or assess therapeutic effects. Of note, the local brain functional activities of the same brain region in the left and right cerebral hemispheres were not identical, and the different emphases on the pathological mechanism of the bilateral cerebral hemispheres involved in migraine need further exploration. The findings of previous investigation have indicated that the cognitive and emotional components of pain stimulus signals were transmitted though the medial conduction system and project to the prefrontal lobes via the thalamus, thereby eliciting pain responses [34]. The thalamus is a key center in the process of transmission and integration of sensory information, transmitting painful stimuli between numerous cortical areas [35]. Meanwhile, this region is a key subcortical structure in the pain-related network, and is involved in pain processing and modulation processes [36]. Several studies including structural and functional imaging have showed enhanced thalamic neurons activation during migraine attacks and produced globally aberrant FC in the thalamocortical limb of the trigeminal pathway, supporting the presence of pain processing dysfunction in migraine [35, 37, 38]. An fMRI research demonstrated that migraineurs may be hypersensitive to aversive or negative emotional stimuli as a result of increased activation of neurons in their nociceptive and emotional processing structures, including the thalamus, following visual aversive or negative emotional stimulation [39]. The higher thalamic activation can potentially amplify the severity of migraine attack and risk of pain chronification [39]. In this finding, there was no differences in fALFF and ReHo of the thalamus in migraineurs during the interictal period, not in line with previous results about thalamic alterations, which may account for the diverse neuroimaging processing methods and needs further exploration. In addition, transcutaneous vagus nerve stimulation (taVNS) has been shown to relieve headaches in migraineurs, increase connectivity between the thalamic subregion and anterior cingulate cortex/medial prefrontal cortex, and modulate thalamocortical circuits [29]. Another resting-state fMRI study found that migraine patients had altered bilateral thalamic voxel-mirror homotopy connectivity, and increased FC in the thalamus and middle frontal gyrus, supporting that aberrant thalamic functional connectivity may be the pathogenesis of migraine [40]. However, consistent with the above investigations, the present study demonstrated higher FC between the bilateral thalamus and the right middle frontal gyrus in migraine patients, and we speculate that the thalamo-thalamic functional pain pathway activity in migraineurs is enhanced to continuously transmit pain perception information, causing recurring migraine attacks.

The primary somatosensory cortex is a higher-order sensory receptive area located in the retrocentral gyrus, that receives sensory afferents projected by the thalamocortical cortex, and is responsible for somatosensory information processing [41]. Two structural studies found a thickening somatosensory cortex in migraineurs during the interictal period, thought to be related to the fact that migraine may be mediated by increased noxious stimulus input within the trigemino-thalamo-cortical pathway [41]. Another

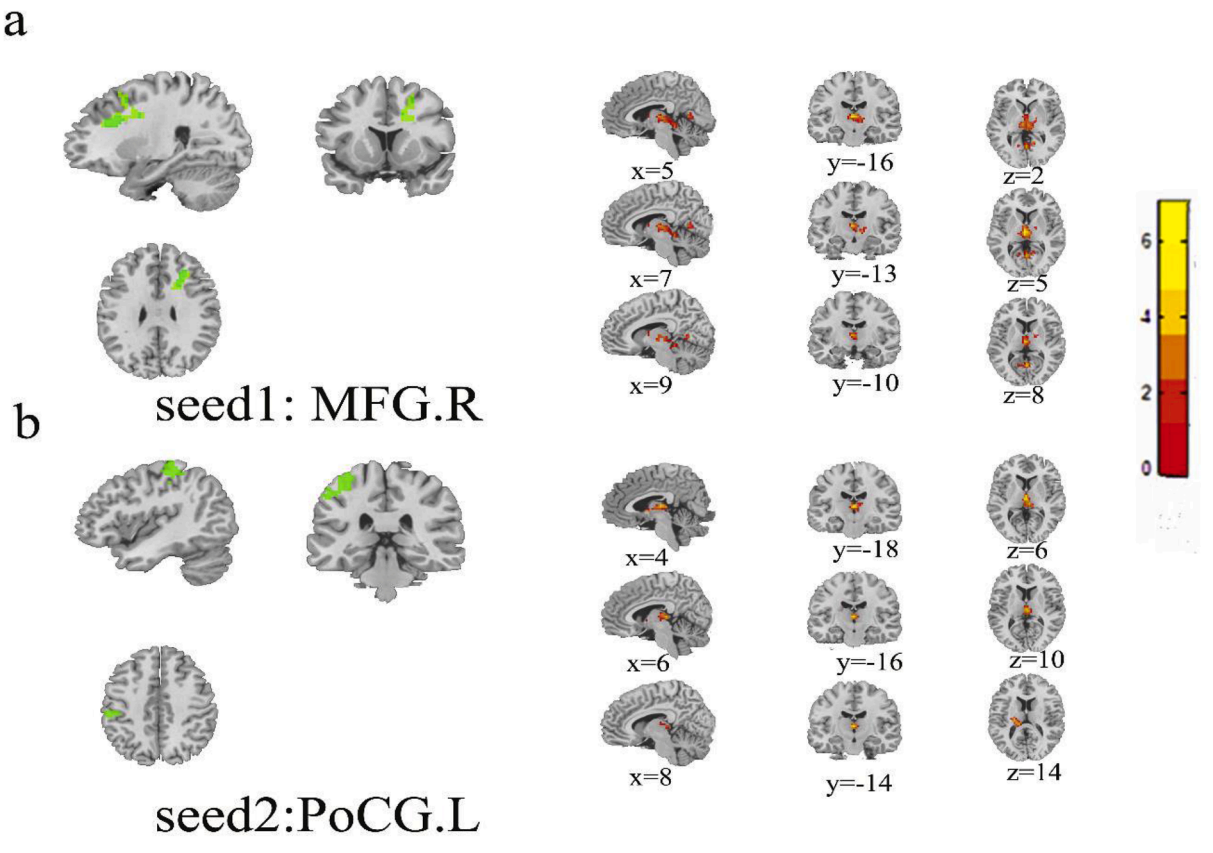

Figure 2. Group differences in FC analysis among migraineurs and HCs groups. Green represents ROIs for functional connectivity analysis. Red and blue respectively show increased and decreased FC, and the color bar indicate the t value (GRF corrected, voxel value $P < 0.001$, cluster value $P < 0.05$). (a) Differential brain regions for whole-brain FC using Seed1 (MFG.R) as a seed point. (b) Differential brain regions for whole-brain FC using Seed2 (POCG.L) as a seed point. MFG, middle frontal gyrus. POCG, postcentral gyrus. R, right. L, left.

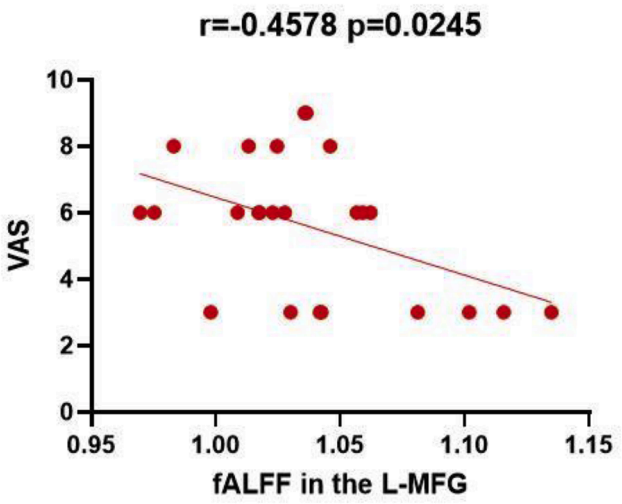

Figure 3. Correlation analysis between VAS (pain severity) and average increased fALFF value in migraineurs. VAS, pain visual analogue scale. MFG, middle frontal gyrus. L, left.

magnetoencephalography study with paired electrical stimulation of the left index finger showed altered somatosensory gating in migraineurs and an association with chronicity of migraine [32]. Studies have revealed increased FC between the retrocentral gyrus and thalamus, which may lead to central pain hypersensitivity by altering sensory responses to general inputs [44]. In the present trail, we identified decreased ReHo values in the left retrocentral gyrus, suggesting that the synchronous activity of this brain region and surrounding brain regions was weakened. At the same time, the FC between this brain region and the bilateral thalamus was increased, while the FC in this circuit was negative in healthy people, which may be related to the central sensitization caused by the dysfunction of the descending regulation system [45].

The precuneus is a part in the default mode network, a group of brain regions that are more active at rest than during a task, and related to the function of pain discrimination, cognition, and perception [31]. In addition, the area is involved in the process of information transmission, multimodal integration, visuospatial representation and pain sensitivity expression [46, 47]. A study found that during interictal migraine, abnormal dynamic functional network connections between the precuneus and visual cortex were associated with headache frequency [48]. One fMRI study indicated increased FC between the lingual gyrus and visual default network in migraineurs during the interictal period [49], further validating the presence of abnormal cortical excitability in migraine. In this study, the FC between the right middle frontal gyrus and left precuneus was increased in migraineurs, suggesting default network dysfunction in migraine during the interictal period. Aberrant FC may lead to multisensory integration abnormalities, which may induce hypersensitivity to external stimuli such as vision, hearing, somatosensory, and smell, affecting the course of pain regulation and processing [50]. One study found enhanced FC between the right precuneus and left retrocentral gyrus during migraine attacks and was inversely associated with headache intensity [51]. However, we focused on the interictal period of migraine and found a significant ReHo decline in the left retrocentral gyrus, while there was no abnormal FC between the precuneus and the retrocentral gyrus, suggesting that restoration of FC between the primary somatosensory cortex and the default network could positively regulate the migraine attack process. These studies suggest that migraine is a progressive disorder in which the patient's brain is plastic in its development and maintenance.

Despite some trustworthy findings were obtained in our work, there were still some limitations. First, the sample size of this research was small, and future research with larger samples is needed. Second, this trail was a cross-sectional study, and longitudinal follow-up covering all migraine phases and pre- and posttreatment data may be required to further validate our results in the future.

5. Conclusion

In summary, abnormal FC between the bilateral thalamus and right middle frontal gyrus, or left retrocentral gyrus may occur between attacks in migraineurs, which may be the basis for sensory integration and pain regulation dysfunction. Thus, these results may become promising biomarkers for early diagnosis and evaluation of migraine in the interictal period, and provide a novel view for further investigation of the pathogenesis and etiology of recurrent migraine.

Declarations

Author contribution statement

Lanxiang Wu, Xuan Wang: Performed the experiments; Wrote the paper.
Wei Wu: Conceived and designed the experiments.

Qian Liu: Contributed reagents, materials, analysis tools or data.
Lijun Chai and Sheng Tian: Analyzed and interpreted the data.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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