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Original Research

Altered Neuromagnetic Activity in the Default Mode Network in Migraine and Its Subgroups (Episodic Migraine and Chronic Migraine)

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Abstract

Background: The differences in the resting state spectral power and functional connectivity of the default mode network between people with migraine without aura (MwoA) and its subgroups differentiated by frequency (episodic migraine (EM) and chronic migraine (CM)) and healthy controls (HC) were investigated using magnetoencephalography. **Methods**: In the resting state, the topological spatial structure of the brain in 33 MwoA patients and 22 HC was first studied using magnetoencephalography, followed by probing the neuroelectrical activity of 17 CM and 16 EM patients, to identify damage to their default mode network (DMN). The techniques used to investigate both spectral power and functional connectivity were minimum-paradigm estimation combined with Welch's technique and corrected amplitude envelope correlation. **Results**: The differences between MwoA and its subgroups (CM and EM) and HC based on spectral power were mainly in the delta, theta, and alpha bands, while the differences in functional connectivity were primarily in the delta, alpha, and beta bands. In the delta and theta bands, the spectral power of MwoA and its subgroups (CM and EM) was higher than in the HC group. The spectral power of MwoA and its subgroups (CM and EM) was lower in the alpha band. In terms of functional connectivity, the corrected amplitude envelope correlation of MwoA and its subgroups (CM and EM) was lower than the HC group in the bands with spectral differences. People with EM and CM differed in the spectral power in the left medial prefrontal cortex and the right lateral temporal cortex in the alpha band, where correlation analysis and logistic regression analysis showed that the intensity of the spectral power of the left medial prefrontal cortex was negatively correlated with headache frequency. **Conclusions**: The spectral power of the left medial prefrontal cortex in the alpha band may serve as a biomarker that is associated with the number of monthly headache attacks and may be a potential neuromodulatory target for controlling migraine chronicity.

Keywords: MwoA; CM; EM; DMN; magnetoencephalography

1. Introduction

Migraine is one of the most common health conditions in the world today. Recurrent attacks of migraines can affect daily life, especially when episodic migraine (EM) evolves into chronic migraine (CM). Migraine increases in pain and discomfort and often involves emotional and sensory problems, because migraine attacks are attributed to many neurophysiological changes in the cerebral cortex [1,2]. Primary CM is rare; most studies have shown that it usually evolves from episodic migraine with a progressive increase in the frequency of attacks and an annual progression rate of about 3% [3,4]. When EM turn into CM, the patient experiences greater physical and mental pain. This is because CM sufferers often suffer from comorbidities such as anxiety, depression, and some heart and lung diseases [5]. In addition, chronic migraineurs report reduced household productivity and inability to perform family activities and household chores at two to three times the rate of episodic migraineurs. In addition, the annual per capita cost of CM is approximately four times that of EM [6].

Due to the aforementioned dangers of migraine, especially CM, there has been a gradual increase in research on migraine. The commonly studied pain areas in the brain involved in migraine patients include the bilateral primary and secondary somatosensory cortices, insula, medial frontal cortex, anterior cingulate cortex, hippocampus, superior frontal gyrus, angular gyrus and lingual gyrus [7,8]. The default mode network (DMN) plays a vital role in migraine. The DMN-associated region consists of several cortical centers, including the inferior parietal cortex (IPC), medial frontal cortex (MFC), precuneus (PCU), posterior cingulate cortex (PCC), medial temporal cortex (MTC), and lateral temporal cortex (LTC) [9,10]. A functional magnetic resonance imaging (fMRI) study showed reduced functional connectivity (FC) within the DMN (e.g., precuneus, ventral medial prefrontal cortex (MPFC), angular gyrus) during spontaneous migraine without aura (MwoA) attacks [11]. Tessitore *et al*. [12] found reduced connectivity in prefrontal and temporal regions within the MwoA DMN. However, the characteristics of DMN changes in EM and CM have been less studied.

Migraine has been investigated using fMRI and electroencephalography (EEG), with inconsistent findings [11, 13,14]. Advanced neuroimaging techniques can help us better understand the cortical changes in migraine. Magnetoencephalography (MEG) has a very high temporal resolution compared with fMRI and a higher spatial resolution than EEG and is, therefore, more suitable for studying neuronal activity. The feasibility of MEG for migraine research has been confirmed by several scholars. Hsiao *et al*. [7] studied MwoA using MEG, revealing that reduced beta connectivity in the anterior cingulate region was associated with chronicing. Wu *et al*. [15] analyzed MEG in migraine and indicated that during the interictal period, patients could not process negative emotions normally.

Therefore, in our investigation, MEG was used to study the DMN of MwoA and its subgroups (CM and EM) in the interictal period to derive better neuroimaging markers of migraine and to understand the different electrophysiological characteristics of EM and CM, which may help to control the chronicity of migraine.

2. Materials and Methods

2.1 Subjects

Patients with EM and CM aged 18 to 60 years admitted to the headache clinic of the Department of Neurology, Brain Hospital of Nanjing Medical University (Nanjing, Jiangsu, China) were included for this study. The patients conformed to the International Classification of Headache Disorders, Third Edition, Migraine Diagnostic Guidelines [16]. The patients were classified according to the frequency of headaches. EM was classified as people having fewer than 15 headache days monthly. In contrast, CM was classified as having more than 15 days of headaches per month, lasting more than 3 months, and having migraine characteristics at least 8 days per month [17]. The selected patients were right-handed, and none received migraine prophylaxis. Patients with MwoA and no history of medication overuse were chosen for this study. Patients with psychiatric symptoms, or those taking medications that affect the central nervous system, were unable to undergo MEG examinations, and those who were uncooperative were excluded. The control group consisted of age-range-matched healthy individuals without headaches or a family history of headaches. This study was approved by the Institutional Review Board of Nanjing Brain Hospital (Batch number: 2016-KY023). Informed consent forms were signed by all participants.

2.2 Study Design

In this study, information on migraine was collected from the study population by trained neurology professionals, including the time of migraine onset, monthly headache attack frequency, headache duration, headache severity, and medication use of the patients. Scores for the Hamilton Anxiety Rating Scale (HAMA) and the Hamilton Depression Rating Scale (HAMD) were obtained for all included individuals. Visual Analog Scale (VAS) scoring was performed for CM and EM patients.

Patients with MwoA underwent resting state MEG recording during the interictal period, with the requirement of the subject being migraine attack-free 48 hours before and 24 hours after MEG data collection. If this was not the case, a new MEG examination was required.

2.3 MEG Recording

Data acquisition was performed using a whole scalp CTF 275-channel MEG system (VSM MedTech Systems, Inc., Coquitlam, BC, Canada) in a magnetically shielded room in the MEG room of Nanjing Brain Hospital. Before data collection, each subject was checked thoroughly to ensure no metal objects were on their body. We placed a coil at the base of the nose and in front of both ears as an anatomical marker for accurate integration with the cranial magnetic resonance imaging (MRI). First, the 3-minute empty chamber recording was performed, followed by MEG data recording. This would facilitate better capturing of the sensor and background noise and be used to determine the noise covariance for source analysis. The sampling frequency of MEG data was 6000 Hz, and each group of MEG data acquisition time was 120 s. A total of six groups were used for data acquisition, and at the same time, data collection underwent noise reduction. Subjects were required to remain supine, relaxed, awake, and with their eyes closed during MEG data collection. The subject's head movement distance was not to exceed 5 mm before and after data collection, which would lead to the rejection of the collected data. If the patient fell asleep, the data was rejected, requiring data re-collection.

2.4 MRI Recording

All patients enrolled were subjected to a 3.0 T head MRI scan (Siemens, Munich, Germany). Three-dimensional T1-weighted anatomical images were acquired using a fast gradient echo sequence (repetition time/echo time (TR/TE) = 1900/2.48 ms). The parameters were as follows: field of view, 250 $\times$ 250 mm; flip angle, 9°; voxel size, 0.48 $\times$ 0.48 $\times$ 1 mm^3; and matrix dimensions, 512 $\times$ 512. Three localization coils placed during MEG data acquisition were used to match with the cranial MRI in order to determine the anatomical location of the MRI presentation.

2.5 Data Preprocessing

We performed the following operations to eliminate environmental artifacts and non-brain activity signals from the MEG data: (1) manual removal of artifacts due to head position shifts or noise interference; (2) filtering of signals at 50 Hz and its harmonics to eliminate power line contamination; and (3) to capture sensor and ambient noise, MEG recording started with a 3-minute empty chamber recording, leading to noise covariance calculation for of-

fline source analysis to adjust for the residual and stationary instrument, ambient, and sensor noise components. A cortical source analysis model was obtained using the FreeSurfer image (Version 7.11, Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA, USA) analysis package to reconstruct T1-weighted structural body images in the surface model automatically. The program performs reconstruction work of the scalp, brain white matter, and gray matter and performs stereoscopic image analysis of the cerebral surface to assess the borders of the white and gray matter. A successive period of 60 s was chosen for the study to avoid peak discharge interferences on the magnetoencephalographic signal. Six frequency bands were selected for MEG analysis in this study: delta (2–4 Hz), theta (5–7 Hz), alpha (8–12 Hz), beta (15–29 Hz), gamma 1 (30–59 Hz), and gamma 2 (60–90 Hz).

2.6 Analysis of MEG Data

Depth-weighted minimum parametric estimation was used for assessing source-level-based cortical activation in the MEG data. This method has proved relatively stable in previous studies [18]. A forward model for the minimum norm estimation (MNE) analysis was developed using the overlapping spheres method, describing each cortical vertex as a current dipole with approximately 15,000 vertices. Then, the distribution of the current sources was estimated using the following inverse operators: (1) the direction of current sources was restricted to be positive to the cortical surface; (2) a depth-weighting algorithm compensated for the inhomogeneous sensitivity of the current direction and depth; and (3) to minimize numerical instability, we used the regularization parameter $\lambda^2 = 0.33$, which reduces the sensitivity of the MNE to noise and obtains the spatially smoothed solution, the inverse of the signal-to-noise ratio of the MEG record. Brainstorm software (http://neuroimage.usc.edu/brainstorm) was used to analyze the depth-weighted MNE, downloaded freely using the GNU (https://www.gnu.org/gnu/about-gnu.en.html#fl) General Public License.

Twelve brain regions associated with DMN were selected, including the bilateral IPC, MPFC, MTC, PCU, PCC, and LTC. We used the spm_maff8 function, which is derived from SPM12's Brainstorm (The University of Southern California, Los Angeles, Los Angeles, CA, USA; The Hôpital de la Salpêtrière, Paris, France; Los Alamos National Laboratory, Los Alamos, NM, USA), to register each subject's T1 MRI to the Montreal Neurological Institute (MNI) coordinate system, computed the 4 × 4 affine transform automatically, and in the T1 template body defined regions of interest (ROIs) using the Desikan-Killiany cortical atlas. The spectral power of the sources was estimated by calculating the average current density at each vertex within the ROI. The power spectral density (PSD) on every ROI derived using the Welch technique (window duration of 5 s with 50% overlap). The PSD value is the ratio of spectral power of every ROI chosen to the total power of entire spectrum over every frequency bin: Relative PSD (f) = PSD (f)/i [total PSD (fi)], where fi refers to the single frequency from the absolute PSD. This procedure normalizes PSD values across subjects' brain regions [19].

Corrected amplitude envelope correlation (AEC-c) analysis was used to assess the choppy functional connectivity of the ROI. Several studies have shown that AEC-c analysis is highly stable and reproducible in FC network studies [20,21]. Based on the approach reported in previous studies, the signal pairs were orthogonalized before envelope calculation to remove pseudo-connections resulting from field diffusion and volume conduction effects [22]. The amplitude envelope is the absolute value of the Hilbert transform of a given cortex, which reflects the amplitude fluctuation with time and can be obtained from the bandpass-filtered cortex source activity for each frequency band [21]. If s(t) is a random time segment, the Hilbert transform is defined as:

$$S_H(t) = \frac{1}{\pi} \int_{-\infty}^{+\infty} \frac{s(\tau)}{(t-\tau)} d\tau$$

The Hilbert envelope was then split into equal time units, and the mean values of the envelopes within every time window were obtained. The FC metric was determined based on the Pearson correlation between the mean values and indicated by AEC-c values. The amplitude envelope of cortical oscillatory activity that correlates the two ROIs is measured as the AEC-c value. If the AEC-c values are high, the amplitude envelope synchronization fluctuations are strong. The AEC-c values were calculated and the 12 × 12 adjacency matrix was estimated.

2.7 Statistical Analysis

Independent samples *t*-tests, one-way analysis of variances, or chi-squared tests were used to compare between-group differences in demographic and clinical data. We used the U test to compare the spectral power and AEC-c values of ROIs in six frequency bands between the MwoA and HC groups. Comparisons between the spectral power and AEC-c values of each ROI in every frequency band in all three groups were performed using the Kruskal-Wallis test. Statistical significance was set at $*p < 0.05$ after Bonferroni correction.

As there were three groups of subjects and 12 ROIs at the spectral power level for CM, EM, and HC, the *p*-value was corrected 3 × 12 = 36 times. For MwoA and HC, there were two groups and 12 ROIs, and the *p*-value in the spectral power analysis was corrected 12 times. Twelve ROIs were investigated in matrix analysis at the FC level. Thus, the *p*-values in the FC analysis of the two groups were corrected 66 times, and 66 × 3 = 198 times for the three groups.

In addition, correlation analysis and logistic regression analysis was used to investigate the correlation between the clinical features and the spectral power or FC dif-

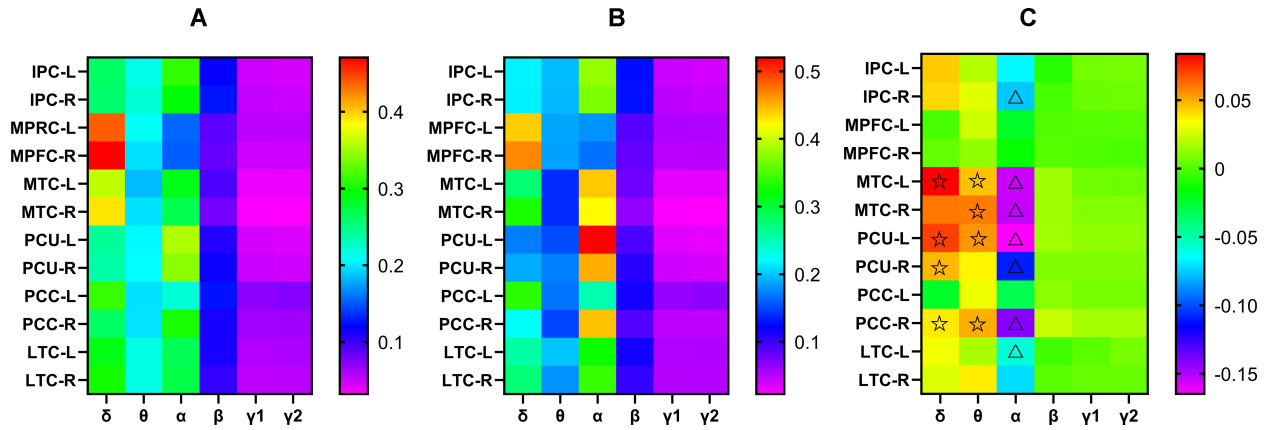

Fig. 1. Differences in the spectral power plots between the migraine without aura (MwoA) and HC groups. (A) Shows the spectral power plot of the MwoA group; (B) Shows the spectral power plot of the HC group; (C) Shows the spectral power plot with the differences between the MwoA and HC groups. In (C), ☆ denotes that the spectral power of the MwoA group is higher than that of the HC group; △ denotes that the spectral power of the MwoA group is lower than that of the HC group. IPC, inferior parietal cortex; MPFC, medial prefrontal cortex; MTC, medial temporal cortex; PCU, precuneus; PCC, posterior cingulate cortex; LTC, lateral temporal cortex; MwoA, migraine without aura; HC, healthy controls. $p < 0.05$ is statistically significant after Bonferroni correction for multiple comparisons.

Table 1. Patients' clinical data (mean ± SD).

Clinical characteristics	CM	EM	HC	*p*, CM vs EM	*p*, CM vs HC	*p*, EM vs HC
Sex	7 M/10 F	6 M/10 F	9 M/13 F	0.83	0.98	0.83
Age (y)	37.41 ± 7.366	38.25 ± 7.132	37.91 ± 7.03	0.74	0.83	0.88
Headache frequency (days/month)	18.29 ± 1.86	8.75 ± 3.38	/	<0.001*	/	/
Disease duration (y)	2.41 ± 1.228	2.25 ± 1.183	/	0.70	/	/
Painkiller frequency (days/month)	6.76 ± 1.678	3.13 ± 1.025	/	0.11	/	/
HAMA score	15.00 ± 2.18	13.81 ± 1.91	5.68 ± 1.40	0.11	<0.001*	<0.001*
HAMD score	10.29 ± 2.87	8.88 ± 2.22	4.68 ± 1.09	0.12	<0.001*	<0.001*
VAS score	6.35 ± 1.12	5.06 ± 1.12	/	0.002*	/	/

SD, standard deviation; CM, chronic migraine; EM, episodic migraine; HC, healthy controls; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; VAS, Visual Analogue Scale; M, male; F, female. *$p < 0.05$ is statistically significant.

ferences between EM and CM. Receiver operator characteristic (ROC) curve analysis was used to evaluate clinical diagnostic efficacy. All statistical analyses were performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Clinical Characteristics

After rigorous screening by headache specialists in the Department of Neurology at the Brain Hospital, 33 MwoA patients were included in this study, including 17 CM and 16 EM patients. An additional cohort of 22 HC participants was also included. There were no statistical differences between CM, EM, and HC regarding sex and age. Headache frequency, VAS score, and number of painkillers taken per month were higher in the CM group than in the EM group. HAMA scores and HAMD scores were higher in the CM and EM groups than in the HC group, while no significant differences were observed in anxiety and depression scores between the CM and EM groups. Detailed comparisons are shown in Table 1.

3.2 MwoA and HC Spectral Power and FC

Compared with HC, the spectral power of MwoA were different, mainly in the delta, theta, and alpha bands. In contrast, no significant differences were observed in the beta, gamma 1, and gamma 2 bands. The significant differences in FC were mainly in the theta, alpha, and beta bands, with no significant differences in the other bands.

In the MwoA group within the bilateral PCU (Left, L $p = 0.024$, Right, R p=0.024), PCC-R ($p = 0.048$), and MTC-L ($p = 0.012$), the spectral power of the delta band was significantly higher than that of the HC. In the theta band, significant differences were mainly concentrated in the bilateral cortices of the MTC (L $p = 0.024$, R $p = 0.0004$), PCU-L ($p = 0.036$), and PCC-R ($p = 0.012$), with higher spectral power in the MwoA group than in HC. In the alpha band, the spectral power was significantly lower within the bilateral MTC (L $p = 0.0006$, R $p = 0.0004$), PCU (L $p = 0.003$, R $p = 0.048$), IPC-R ($p = 0.036$), PCC-R ($p = 0.001$), and LTC-L ($p = 0.048$) in the MwoA group in comparison with HC (Fig. 1).

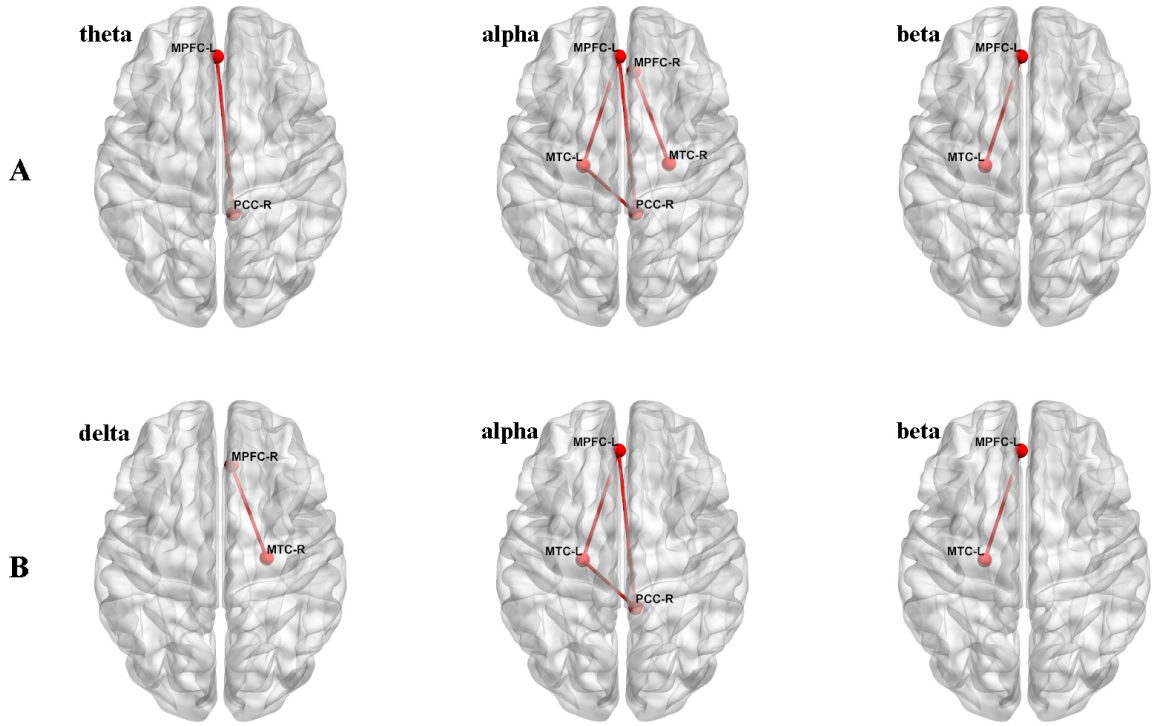

Fig. 2. Comparison of functional connections by group. (A) Shows functional connectivity plots of the MwoA with HC groups, showing the functional connectivity of two groups of regions of interest (ROIs) with significant differences in theta, alpha, and beta bands. (B) Shows the functional connectivity plots of the CM, EM, and HC groups, showing the functional connectivity of three groups of ROIs with significant differences in delta, alpha, and beta bands. PCC, posterior cingulate cortex; MPFC, ventral medial prefrontal cortex; MTC, medial temporal cortex.

For FC, the AEC-c values in the theta band in the MPFC-L and PCC-R (p = 0.019) were significantly lower in the MwoA group than in the HC group. The AEC-c values in the alpha band within the MPFC-L and MTC-L (p = 0.0003), MPFC-L and PCC-R (p = 0.032), MPFC-R and MTC-R (p = 0.006), and MTC-L and PCC-R (p = 0.028) were significantly lower in the MwoA group than in HC group. The AEC-c values within the beta band in the MPFC-L and MTC-L (p = 0.003) were significantly lower in the MwoA group compared with the HC group (Fig. 2).

3.3. Comparison of Spectral Power and FC between the CM, EM, and HC groups

The spectral power differences between the CM, EM, and HC groups were concentrated in the delta, theta, and alpha bands. The significant differences in FC were mainly in the delta, alpha, and beta bands, with no significant differences in other bands.

The spectral power in the theta band was significantly higher in the EM group within the MTC-R (p = 0.036) compared with the HC group (Fig. 3). The FC in the delta band was significantly lower in the EM group within the MPFC-R and MTC-R (p = 0.027) compared with the HC group. The FC in the beta band was significantly lower in the MPFC-L and MTC-L (p = 0.030) in the EM group compared with the HC group (Fig. 2).

The CM and HC groups differed in spectral power and FC in more cortical layers. The spectral power in the delta band within the IPC-R (p = 0.004), PCC-R (p = 0.004), and bilateral PCU (L p = 0.010, R p = 0.005) was significantly higher in the CM group than in the HC group. The spectral power in the theta band within the MTC-R (p = 0.014) and PCC-R (p = 0.010) was significantly higher in the CM group than in the HC group. The spectral power in the alpha band within the bilateral IPC (L p = 0.016, R p = 0.001), bilateral MTC (L p = 0.002, R p = 0.002), bilateral PCU (L p = 0.001, R p = 0.007), bilateral LTC (L p = 0.036, R p = 0.004), MPFC-L (p = 0.008), and PCC-R (p = 0.0005) was significantly lower in the CM group than in the HC group (Fig. 3). The ACE-c values in the alpha band within the MPFC-L and MTC-L (p = 0.0006), MPFC-L and PCC-R (p = 0.014), and MTC-L and PCC-R (p = 0.033) were significantly lower in the CM group than in the HC group (Fig. 2).

The spectral power in the alpha band within the MPFC-L (p = 0.002) and LTC-R (p = 0.036) cortex was significantly lower in the CM group than in the EM group (Fig. 3), while no significant differences were found in the FC between the two groups.

3.4 Clinical Correlation

The brain regions that differed in spectral power between the EM and CM groups were MPFC-L and LTC-R.

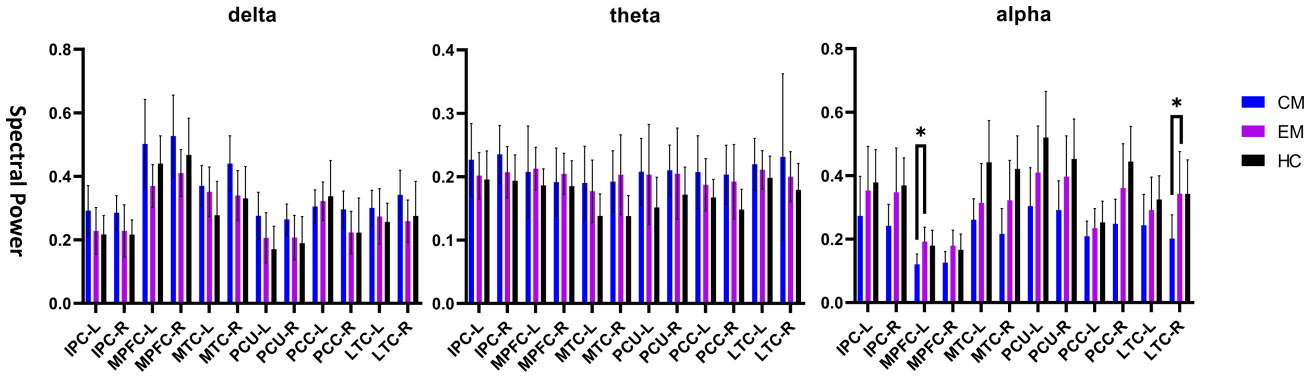

Fig. 3. Comparison of the spectral power of the CM, EM, and HC groups. Alpha spectral power with * indicates a significant difference between the spectral power of the EM and CM groups (the MPFC-L (p = 0.002) and LTC-R (p = 0.036)). *$p < 0.05$ after Bonferroni correction for multiple comparisons. The values corresponding to the bars in Fig. 3 are the mean ± SD.

Correlation analysis of the spectral power of MPFC-L and LTC-R with the number of days of headache in the EM and CM groups showed that the spectral power of MPFC-L in the alpha band was negatively correlated with the number of headache days per month (r = –0.90, $p < 0.001$) (Fig. 4). However, there was no correlation between LTC-R and the number of headache days ($p > 0.05$). Binary logistic regression analysis of the difference in MPFC-L spectral power between the CM and EM groups was statistically significant (odds ratio (OR) = 0.559, 95% confidence interval (CI) (0.378–0.828), p = 0.0004). The ROC curve of MPFC-L spectral power in the alpha band is shown in Fig. 5. The area under the curve, sensitivity, and specificity of the ROC are shown in Table 2.

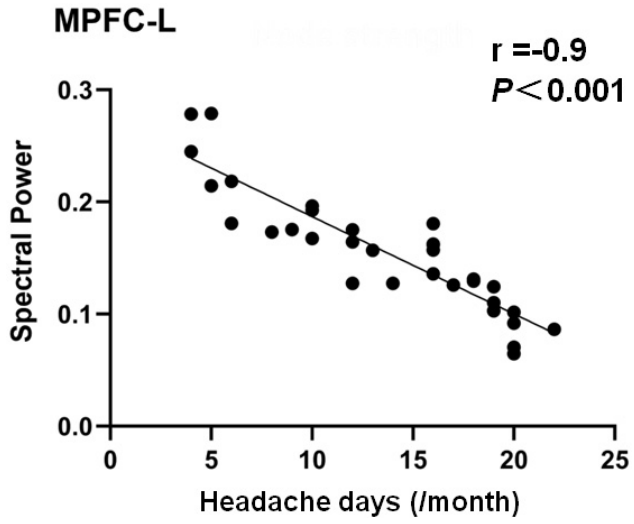

Fig. 4. Correlation between MPFC-L spectral power in the alpha band and number of headache days per month. MPFCL, left medial prefrontal cortex.

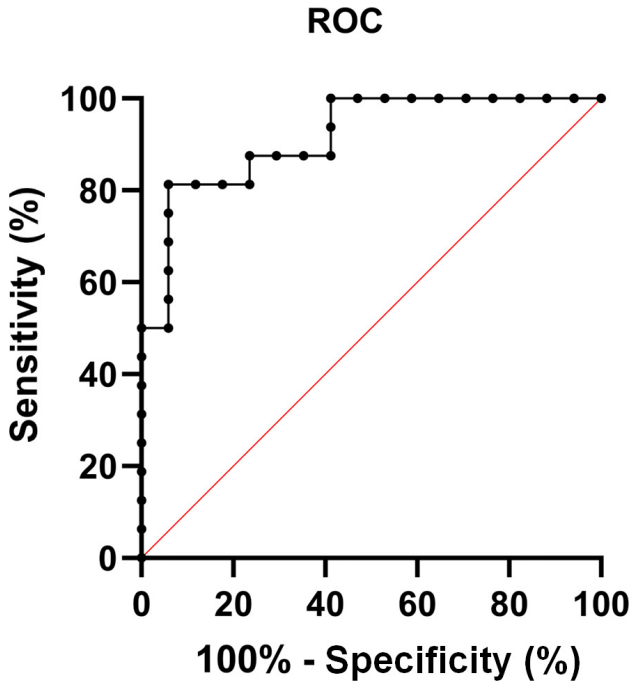

Fig. 5. ROC curve of the MPFC-L for differentiating episodic migraine from chronic migraine.

Table 2. Metrics for the ROC.

Indicator	AUC	Sensitivity	Specificity
Spectral power: alpha band MPFC-L	0.92	0.81	0.94

AUC, area under the curve; ROC, receiver operator characteristic.

4. Discussion

The spectral power and FC were compared between MwoA and its subgroups (CM and EM), with HC showing frequency-dependent changes in the DMN network topology. All MwoA patients had lower AEC-c values for FC than HC in the MPFC or PCC cortex. The difference in

spectral power between EM and CM in the MPFC-L and LTC-R, and MPFC-L was shown to be related to headache frequency by using correlation analysis and logistic analysis. Our results facilitate better migraine identification using neuroimaging markers and provide a basis for controlling the chronicity of EM.

This study showed that several cortical regions within the DMN differed significantly in spectral power and FC between the MwoA group and the HC group, which are necessary to regulate migraine. The MPFC attenuates pain perception through cognitive control mechanisms [23,24]. At the same time, the temporal cortex is involved in the emotional response to pain experience [25,26], and the PCC is involved in regulating cognitive processes [27]. The PCU in the DMN is involved in situational memory [10] and the PCU is vital for pain perception and pain processing in migraine [28]. The previous studies suggesting that migraine is a complex neurological disorder involving sensory, cognitive, and emotional processes are consistent with our findings [29–32]. Compared with HC, MwoA patients, especially with CM, had reduced FC strength in the DMN, as depicted in previous studies. Yu *et al*. [33] performed FC analysis of the DMN in 26 people with MwoA and similarly concluded that they have lower FC compared with HC. The same finding was reported by Faragó *et al*. [34]. An fMRI resonance study of 20 patients with MwoA showed decreased connectivity in the prefrontal and temporal regions of the DMN [24]. Thus, migraine alters the electrophysiological characteristics within the DMN network, causing a disturbance in intercortical FC within the DMN and a reduction in the ability of cortical interactions to modulate nociception. This is consistent with the general features revealed by studies investigating the effect of migraine on the DMN network [35].

Compared with HC, the frequency bands with significant differences in the MwoA group were in the delta, theta, alpha, and beta bands. In contrast, no significant differences were observed in the higher frequency ranges of the gamma 1 and gamma 2 bands, consistent with previous studies [7,36–39]. Our study found higher spectral power in the lower frequency ranges of delta and theta in people with CM compared with controls. An EEG study of chronic neurogenic pain noted that some pain-related cortical regions, such as the insula, anterior cingulate cortex (ACC), prefrontal and posterior parietal subcortices, as well as primary somatosensory cortex and secondary somatosensory cortex, were over-activated in the theta band [40]. Studies establishing a mouse model of CM to examine the activity of different cortical regions found enhanced activation in the MPFC, ACC, and the caudal part of the trigeminal spinal nucleus. This may be related to central sensitization of CM, with chronic migraineurs being more sensitive to the surrounding environment and stimuli [41]. The low spectral power of the migraine in the alpha band is considered to be a result of migraine induced neuronal dysfunction in the central neocortex, causing suppression of neuronal excitability in the alpha band. Interestingly, during the transition from low to high frequency bands, there was a change from high to low cortical excitability in the DMN of MwoA patients, which may be due to cortical dysfunction caused by recurrent headache attacks. However, whether this change is of general significance needs to be further verified by future MEG studies with large samples, multiple cortical regions, and refined headache frequency grouping.

The spectral power within the MPFC-L and LTC-R was lower in CM compared with EM. Correlation analysis and logistic regression analysis showed a correlation between MPFC-L and migraine frequency. Calculation of regional brain volumes by fMRI and comparison with clinical variables revealed that patients with CM exhibited smaller MPFC volumes compared with patients with EM, and correlation analysis showed a negative correlation between headache frequency and MPFC volume [42]. The relationship between the MPFC and migraine frequency is further confirmed by the structural aspects of the aforementioned studies. The MPFC has extensive connections with many cortical layers, as well as the thalamus, periaqueductal gray matter, hippocampus, amygdala, and basal nucleus. Thus, it plays a key role in cognitive and pain modulation processes [43]. Interestingly, in EM or CM, the MPFC may play a dual and opposite role: as part of the pain control loop, reducing the upward transmission of pain impulses in the upstream pathway, as well as to promote pain chronicity by affecting the striatum [30]. The lower MPFC excitability in CM compared with EM and HC may be the result of MPFC-induced chronicity of migraine pain followed by inhibition of other pain modulating cortices and the anti-pain impairing effect of MPFC itself. It has been shown that a decrease in MPFC spectral power within theta band leads to an increase in pain perception [44], and it is noteworthy that our study did not find a decrease in MPFC excitability within the theta band, but rather the spectral power within the alpha band was lower in CM in the MPFC compared with the other groups. This is interesting because theta and alpha are two adjacent frequency bands, so it is possible that MPFC spectral power reduction within the alpha band may also lead to an increase in pain perception. MPFC may also modulate the amplification effect of pain perception [45] and reduce the activity of the sympathetic nervous system that causes pain [46]. One study found increased concentrations of metabotropic glutamate receptor 5 (mGluR5) within the MPFC in animals with chronic neuropathic pain, and mGluR5 improved aversive behaviors including tactile hypersensitivity and depression-like activity [47], which is a biochemical basis for pain inhibition by the MPFC. PCC is an important component of the DMN and exhibits extensive FC in migraine patients, which is related to its extensive structural connectivity [48–50]. PCC is associated with cognitive function [10,27], and the reduced FC of PCC with MPFC and MTC in the migraine group may be related to impaired cognitive function in migraine patients.

5. Limitations

The sample size in this study was small, patients were strictly enrolled in this study, and all patients were not receiving migraine prophylaxis. Therefore, the sample size should be increased to validate the current results in the future. According to a literature review [51], the migraine frequency of EM can be more finely divided into high frequency and low frequency. The difference between low frequency EM and CM may represent a gradual trend across a spectrum, which is something that needs to be evaluated in future studies, as it may yield more accurate results. Our study compared the differences between EM and CM using spectral power and FC, which does not provide a comprehensive analysis of the differences between EM and CM. Analyses such as graph theory can provide a more comprehensive comparison of these groups. The disadvantage of cross-sectional studies is that causality cannot be discerned, and it is difficult to clarify whether the electrophysiological changes in migraine are its cause or effect; therefore, longitudinal studies should be conducted to show whether the reduced spectral power of MPFC and LTC is the cause or effect of CM.

6. Conclusions

The results of this study illustrate a significant difference in the spectral power in the alpha band within the MPFC-L between CM and EM. Furthermore, a negative correlation between the spectral power intensity of MPFC-L and headache frequency was found. This suggests that the spectral power intensity of MPFC-L may serve as a biomarker related to the number of monthly headache attacks, which indicates that it may be a potential neuromodulatory target for controlling migraine chronicity.

Abbreviations

FC, functional connectivity; DMN, default mode network; MwoA, migraine without aura; EM, episodic migraine; CM, chronic migraine; HC, healthy controls; MEG, magnetoencephalography; fMRI, functional magnetic resonance imaging; EEG, electroencephalography; MNE, minimum norm estimation; AEC-c, corrected amplitude envelope correlation; MPFC, medial prefrontal cortex; LTC, lateral temporal cortex; IPC, inferior parietal cortex; MTC, medial temporal cortex; PCU, precuneus; PCC, posterior cingulate cortex; ROI, region of interest; PSD, power spectral density; SD, standard deviation; ROC, receiver operator characteristic; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; VAS, Visual Analog Scale; MNI, Montreal Neurological Institute.

Availability of Data and Materials

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author Contributions

XZ, XW and YW designed the research study. XZ and FX performed the research. XW, DW, QC and FS provided help and advice on acquiring and analyzing the raw data. XZ, FX and YL analyzed the data. XW revised the manuscript. XZ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Ethics approval was provided by the Affiliated Brain Hospital of Nanjing Medical University's Human Research Ethics Committee (2016-KY023). Participants provided written consent.

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Conflict of Interest

The authors declare no conflict of interest.

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