Effect of acupuncture at Zulinqi (GB41) on the amplitude of low frequency fluctuations in migraine without aura patients: a resting-state functional magnetic resonance imaging study

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Abstract: To study the modulatory effects of acupuncture on the amplitude of low frequency fluctuations (ALFF) in migraine without aura (MWoA) patients. 16 MWoA patients and 16 healthy controls were recruited to undergo resting-state fMRI scanning before and after needling at GB41. Voxel-based analysis to characterize the difference of amplitude of low frequency fluctuations was employed. Before needling, compared with healthy controls, the MWoA patients showed decreased ALFF values in the left calcarine, cuneus, parietal gyrus, and increased ALFF values in the right hippocampus, parahippocampal gyrus, insula, middle temporal gyrus and superior temporal gyrus. After acupuncture at GB41, decreased ALFF values in the bilateral precuneus, right middle frontal gyrus and right inferior parietal lobule, and increased ALFF values in the right precentral and postcentral gyri were observed in MWoA patients. Compared with healthy controls, the MWoA patients after needling showed mainly decreased ALFF values in the left precuneus, calcarine, cuneus, parietal gyrus, and increased ALFF values in the right precentral, postcentral gyri, hippocampus, middle temporal gyrus and superior temporal gyrus. Our findings provided further insight into possible mechanisms of the modulatory effects of acupuncture, which could be interpreted in terms of pain processing.

Keywords: Acupuncture, functional magnetic resonance imaging (fMRI), amplitude of low frequency fluctuations (ALFF), migraine without aura (MWoA) patients

Introduction

Migraine is a chronic neurological disorder with episodic attacks. The morbidity of migraine patients is about 12% in Western countries [1, 2]. The migraine has been ranked as the first disabling diseases among neurological disease by the Global Burden of Disease (GBD 2010) [3]. It has brought a large burden with personality, family and society [4]. Therefore, it is vital to explore effective intervention measures to treat migraine.

Acupuncture, as a main part of Traditional Chinese medicine, has gained popularity in China from ancient times. In recent years, it has become increasingly popular among patients and physicians across the world. In the United States, as many as 3.1 million Americans received acupuncture treatment per year [5]. Acupuncture could induce pain relief and prophylaxis of migraine, which had been confirmed by abundant randomized, controlled clinical trials [6-10]. Acupuncture is beneficial for migraine in the reduction of attack days and pain intensity of attacks. A recent review indicated that acupuncture is an effective, safe, long lasting, and cost-effective therapy for migraine [11]. However, the underlying neural mechanisms of acupuncture therapy for migraine are still not well interpreted.

Noninvasive Functional magnetic resonance imaging (fMRI) has been widely applied to measure intrinsic fluctuations, especially resting-state fMRI (rs-fMRI) which has attracted important attention in studies of various neurological diseases. As a main method of rs-fMRI, amplitude of low frequency fluctuations (ALFF) which is used to measure the total power of a given
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Table 1. The demographic and clinical information of MWoA patients and healthy controls

<table>
<thead>
<tr>
<th>Items</th>
<th>Healthy controls (N = 16)</th>
<th>MWoA patients (N = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>3/13</td>
<td>3/13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.1 ± 4.8</td>
<td>28.3 ± 6.0</td>
</tr>
<tr>
<td>Migraine history (months)</td>
<td>/</td>
<td>57.3 ± 42.3</td>
</tr>
<tr>
<td>Educational level (years)</td>
<td>14.6 ± 5.6</td>
<td>15.1 ± 4.3</td>
</tr>
<tr>
<td>Frequency of migraine attacks (times/month)</td>
<td>/</td>
<td>4.1 ± 1.7</td>
</tr>
<tr>
<td>Duration of migraine attacks (days/month)</td>
<td>/</td>
<td>5.9 ± 3.1</td>
</tr>
<tr>
<td>VAS scores</td>
<td>/</td>
<td>5.4 ± 1.6</td>
</tr>
</tbody>
</table>

Note: *results from two-sample non-parametric test of the comparison between MWoA patients and healthy controls, z = -0.344, P = 0.731 (for age), z = -0.306, P = 0.759 (for educational level). VAS: Visual analogue scale.

Table 2. Comparison of ALFF between healthy controls and MWoA patients before acupuncture treatment

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Voxels of cluster</th>
<th>Brain region</th>
<th>Peak MNI coordinates (X Y Z)</th>
<th>t-value</th>
<th>Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>357</td>
<td>Temporal_Mid_R</td>
<td>39 -21 -18</td>
<td>5.5003</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hippocampus_R</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Temporal_Sup_R</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>ParaHippocampal_R</td>
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<tr>
<td>Cluster 2</td>
<td>131</td>
<td>Rolandic_Oper_R</td>
<td>39 -12 24</td>
<td>4.0941</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insula _R</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cluster 3</td>
<td>97</td>
<td>Temporal_Inf_L</td>
<td>-66 -18 -12</td>
<td>3.7864</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temporal_Mid_L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster 4</td>
<td>97</td>
<td>Calcarine_L</td>
<td>-18 -54 6</td>
<td>3.3768</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cuneus_L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster 5</td>
<td>94</td>
<td>Parietal_Sup_L</td>
<td>-30 -57 48</td>
<td>3.867</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parietal_Inf_L</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Results from two-sample t-test between healthy controls and MWoA patients before acupuncture (P < 0.05, corrected by Monte Carlo Simulations, iterated 1000 times, cluster size > 70 voxels). R: Right; L: Left; Mid: Middle.

Time period, has been proved to be a useful parameter to reflect the intensity of regional spontaneous neural activity [12]. Hence, the ALFF has been used in studies of various brain diseases [12-16]. Previous studies had demonstrated that migraine without aura (MWoA) patients had the abnormalities in functional connectivity (FC) within the default mode network (DMN) [17], salience network (SN) [18], periaqueductal gray networks [19], and the right front oparietal networks (RFPN) [20]. Unfortunately, there are few studies focusing on the regional spontaneous neural activity of MWoA patients compared with healthy controls and MWoA patients after acupuncture treatment. Yu et al. and Zhao et al. applied the regional homogeneity method to investigate regional homogeneity abnormalities in migraine patients [21, 22]. Thus we hypothesized that the intensity of regional spontaneous neural activity of MWoA patients would be altered compared with healthy controls.

Our previous studies supported that acupuncture could increase the FC of the frontal and temporal lobe [23], RFPN in MWoA patients [24]. A review also showed that acupuncture could lead to a stronger interplay between DMN in MWoA patients [25]. Accordingly, we also hypothesized that acupuncture could modulate the intensity of regional spontaneous neural activity and the modulated brain regions could be associated with pain processing, which would give more interpretation of the effect of acupuncture. To test our hypotheses, we collected the resting-state fMRI data of 16 MWoA patients before and after acupuncture therapy and 16 matched healthy controls. Based on traditional Chinese acupuncture theory and practice, acupoints on Gallbladder Meridian are the classical targets for migraine treatment. Hence, the acupoint Zulinqi (GB41), a frequently used acupoint belonging to the Gallbladder Meridian, was chosen to investigate the effect of acupuncture for MWoA patients.

Material and methods

Subjects

A total of 16 MWoA patients (13 females), were recruited from Dongzhimen Hospital Affiliated...
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to Beijing University of Chinese Medicine. All 16 patients were diagnosed as MWoA according to the classification criteria of the International Headache Society and met the criteria below: Right-handed; From 18 to 60 years old; At least 2 migraine attacks every month in the past 3 months; With a more than one-year history of migraine; With no history of prophylactic or therapeutic medicine in the past 3 months; With no history of drug or alcohol abuse; With no history of long-term use of analgesics; With no history of dysmenorrhea or other chronic pain; Without any MRI contraindications. The exclusion criteria were as follows: Other types of migraine; With history of other neurological disease; With history of chronic medical diseases; The first attack occurred after 50 years old. Another 16 right-handed normal subjects (13 females) matched in age and education levels were recruited to serve as healthy controls. All 16 healthy subjects underwent normal neurological test and had no history of migraine or other neurological disease or any MRI contraindications. The clinical and

Figure 1. Differences in ALFF between MWoA patients and healthy controls. The warm color represents a higher ALFF value.
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Demographic information of patients and controls was showed in Table 1.

The Ethical committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine approved the research. All procedures were conducted in accordance with the Declaration of Helsinki and the data was analyzed anonymously.

Experimental paradigm

In the current research, we employed then on-repeated event-related-fMRI (NRER-fMRI) design to investigate the prolonged effects after needling, which was used in our previous study [26]. Following the design paradigm of our previous study, we employed 1-minute needle manipulation before 1-minute resting epoch and followed by 8-minute resting scan (without acupuncture manipulation). Acupuncture was performed at Zulinqi (GB41, located in the depression between the fourth and fifth metatarsal bones on the dorsum of the foot). Acupuncture was performed by inserting a sterile, single-use silver needle (25 mm in length and 0.30 mm in diameter) vertically into GB41 to a depth of 2-3 cm, and the stimulation included rotating the needle clockwise and counterclockwise at 1 Hz with even reinforcing and reducing manipulation for 60 s. All acupuncture procedures were performed by one licensed and skilled acupuncturist. Another 8-minute resting scan was performed before the acupuncture procedure as the baseline.

De-qi is believed to be crucial to the therapeutic effectiveness of acupuncture [27]. After each fMRI scanning, subjects were asked to fill questionnaires to record their experience of De-qi. Since the sharp pain was thought to be an inadvertent noxious stimulation, we would rule out the subjects if they reported the sharp pain. Among all the subjects, none reported the sharp pain.

Data acquisition and processing

A 3.0T MRI scanner (Siemens, Sonata, Germany) was used to acquire fMRI images. During the scanning, foam cushions were used to reduce head translation movement and rotation. The fMRI data was collected using an echo-planar imaging sequence with the scan parameters as follows: Repetition time = 2000 ms, echo time = 30 ms, field of view = 225 mm × 225 mm, matrix = 64 × 64, thickness = 3.5 mm flip angle = 90°). All subjects were required to keep their eyes closed and to remain conscious.

The structural and functional images were pre-processed by using Data Processing Assistant for Resting-State fMRI (DPARSF, http://www.restfmri.net) and SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first 10 time points of the functional images were discarded to ensure subjects adapted the scanning circumstance. Then, slicing time, spatial realignment, normalization into the Montreal Neurological Institute (MNI) space, and smoothing were performed. Finally, we removed the linear trends. Two patients and one healthy control were ruled out, for exhibiting head motion > 1.5° rotation maximum translation and/or 1.5 mm during the course of scans.

ALFF analysis

The ALFF was performed using REST software (http://restfmri.net) [12]. First, the time series were transformed into a frequency domain with a fast Fourier transform and the power spectrum was then obtained. The power spectrum, crossing 0.01-0.08 Hz at each voxel, was square-rooted and averaged, and the result was taken as the ALFF. The ALFF value, which implied the sum of amplitudes within the low-frequency range (0.01-0.08 Hz), was extracted from voxels in whole brain [28]. The ALFF maps

<p>| Table 3. Comparison of ALFF in MWoA patients after and before acupuncture treatment |</p>
<table>
<thead>
<tr>
<th>Cluster</th>
<th>Voxels of cluster</th>
<th>Brain region</th>
<th>Peak MNI coordinates</th>
<th>t-value</th>
<th>Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>74</td>
<td>Precuneus_R</td>
<td>15 -51 24</td>
<td>-4.418</td>
<td>66</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>185</td>
<td>Precuneus_L</td>
<td>0 -57 42</td>
<td>-4.9094</td>
<td>98</td>
</tr>
<tr>
<td>Cluster 3</td>
<td>111</td>
<td>Frontal_Mid_R</td>
<td>39 15 60</td>
<td>-5.1039</td>
<td>96</td>
</tr>
<tr>
<td>Cluster 4</td>
<td>96</td>
<td>Angular_R</td>
<td>42 -54 36</td>
<td>-5.3583</td>
<td>36</td>
</tr>
<tr>
<td>Cluster 5</td>
<td>149</td>
<td>Precentral_R</td>
<td>27 -30 57</td>
<td>5.4424</td>
<td>64</td>
</tr>
<tr>
<td>Note: Results from paired t-test (P &lt; 0.05, corrected by Monte Carlo Simulations, iterated 1000 times, cluster size &gt; 70 voxels). R: Right; L: Left; Mid: Middle; Inf: Inferior.</td>
<td></td>
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</tbody>
</table>
were divided by mean ALFF value of the whole brain to ensure the data to coincide with normal distribution.

Data analyses

For the group-level analyses, the mean ALFF values were conducted by two-sample t-test between MWoA patients and healthy controls before needling. The paired t-test was applied in MWoA patients before and after needling. The two-sample t-test was also applied between healthy controls and MWoA patients after needling. Differences between any two groups were considered significant if $P < 0.05$, corrected by Monte Carlo Simulations, iterated 1000 times, and cluster size $> 70$ voxels in the AAL (Anatomical Automatic Labeling) brain mask without cerebellum. The reported statistics were normalized to MNI space based on AAL and mapped by REST software.

Results

Before acupuncture treatment, compared with the controls, the MWoA patients showed significantly decreased ALFF values in the left calcarine, cuneus, superior parietal gyrus, inferior parietal but supramarginal and angular gyri. Besides, increased ALFF values in the right hippocampus, superior temporal gyrus, parahippocampal gyrus, rolandic operculum and insular lobe, bilateral middle temporal gyrus and left inferior temporal gyrus were observed (shown in Table 2). Specific cluster locations are shown in Figure 1.

After acupuncture treatment, the MWoA patients showed decreased ALFF values in the bilateral precuneus, right inferior parietal lobe and middle frontal gyrus. The right precentral and postcentral gyri of ALFF values
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Increased (shown in Table 3). Specific cluster locations are shown in Figure 2.

Compared with healthy controls, the MWoA patients after needling showed mainly decreased ALFF values in the left precuneus, calcarine, cuneus, superior parietal gyrus, inferior parietal but supramarginal and angular gyri, and increased ALFF values in the right precentral, postcentral gyri, hippocampus, middle temporal gyrus and superior temporal gyrus (shown in Table 4). Specific cluster locations are shown in Figure 3.

Discussion

In this study, we found differences in ALFF between MWoA patients and healthy controls, which suggested abnormalities in pain processing. Furthermore, the results, that the participants showed deactivation of important components in DMN and increased regional activity in right precentral and postcentral gyri, may provide possible interpretations for the central neural mechanisms of acupuncture for pain modulation.

Differences in ALFF between MWoA patients and healthy controls

In this study, we observed significant differences in ALFF between MWoA patients and HC.

Table 4. Comparison of ALFF between after acupuncture treatment for MWoA patients and healthy controls

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Voxels of cluster</th>
<th>Brain region</th>
<th>Peak MNI coordinates</th>
<th>t-value</th>
<th>Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>Y</td>
<td>Z</td>
</tr>
<tr>
<td>Cluster 1</td>
<td>170</td>
<td>Temporal_Inf_L</td>
<td>-27</td>
<td>-42</td>
<td>-30</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>621</td>
<td>Temporal_Mid_R</td>
<td>39</td>
<td>-24</td>
<td>-18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temporal_Sup_R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rolandic_Oper_R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hippocampus_R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster 3</td>
<td>378</td>
<td>Precentral_R</td>
<td>0</td>
<td>-24</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postcentral_R</td>
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<tr>
<td>Cluster 4</td>
<td>300</td>
<td>Precuneus_R</td>
<td>9</td>
<td>-69</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Precuneus_L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcarine_L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cuneus_L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster 5</td>
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<td>Frontal_Sup_Medial_L</td>
<td>-3</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>Cluster 6</td>
<td>101</td>
<td>Parietal_Sup_L</td>
<td>-27</td>
<td>-60</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parietal_Inf_L</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Results from paired t-test (P < 0.05, corrected by Monte Carlo Simulations, iterated 1000 times, cluster size > 70 voxels). R: Right; L: Left; Mid: Middle; Sup: Superior; Inf: Inferior.

Brain regions with lower ALFF mainly located in occipital lobe, superior parietal lobule and inferior parietal lobule within the main regions of the DMN. Xue et al. also applied the same way to explore differences in ALFF between MWoA patients and HC, and found increased ALFF values in the right thalamus as well as decreased ALFF values in the bilateral prefrontal cortex (PFC) [29]. Obviously, our results matched those observed in this study. As we know, the DMN is considered to be related with adaptive behavior, cognitive, emotional and attention processing [30]. Important components of DMN are involved in the “medial pain system”, which are considered to respond to pain stimulus [31]. The disruption of the DMN caused by pain will affect the individual’s ability to properly regulate internal experiences. A prior study had showed decreased FC within DMN for MWoA patients [17]. The occipital lobe is closely associated with visual sense and motion perception. Numerous studies had revealed abnormalities of function in the occipital lobe during attacks of migraine with aura, based on the cortical spreading depression [32]. An fMRI study also found that the occipital cortex showed structural deficits in MWoA patients [33].

We also found that MWoA patients showed increased ALFF values in the right hippocampus (Hip) and parahippocampal gyrus (PHG). The PHG is the main part of the cortico-basal ganglia-thalamic-cortical loop, which is known to be critical in pain processing [34]. The Hip is involved in memory consolidation and very often found in investigating pain anxiety [35], which is also known to have an inhibitory effect on the hypothalamic-pituitary-adrenal axis [36]. Maleki et al. studied the hippocampal structure and function in migraine, and found the voxels of Hip negatively correlated with the number of migraine attacks. Meanwhile the functional neuroimaging study demonstrated that the Hip dysfunction occurs with increasing frequency of migraine attacks [37]. Furthermore, the insu
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la, which had been proved to play a vital role in pain processing [18, 38], was also observed with increased ALFF. Previous functional neuroimaging studies had also found insula hyperactivations in migraine patients [39, 40]. It seems possible that these results are due to the impairment in pain processing.

Taken together, our findings improved the understanding of intrinsic functional architecture of baseline brain activity in MwoA.

Differences in ALFF between before and after acupuncture treatment for MWoA patients

In the present study, we found decreased ALFF values in the bilateral precuneus, right inferior parietal lobule and middle frontal gyrus after needling. The precuneus and inferior parietal lobule are included in the main distribution of DMN. The results were consistent with previous studies that DMN activity was diminished during needling [37, 41]. Previous studies had con-
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confirmed that acupuncture treatment could help to establish psychophysical pain homeostasis by enhancing the FC of the DMN in MWoA patients [23, 25]. Consequently, the intensity of regional spontaneous neural activity belonging to DMN would probably be stronger after needling, if attention to the stimulus solely accounted for the neural response. However, our study applied a temporary acupuncture treatment rather than a long-term treatment, which might lead to the decreased ALFF values. As it had been revealed, the DMN is activated during the resting state. Conversely, the DMN is inhibited during the task state [30]. Furthermore, a previous study showed the genuine acupuncture led to the decreased DMN deactivation in comparison with the sham acupuncture, which indicated that attentional processes could not fully explain the DMN deactivation evoked by acupuncture [41]. Thus, we speculated that the DMN deactivation elicited by acupuncture probably reflected the central neural mechanism of acupuncture analgesia.

Right middle frontal gyrus (MFG) locates in the prefrontal cortex (PFC). The PFC, which also belongs to the DMN, is considered to be critical to process the painful stimuli [42]. A previous study revealed that the PFC was a hub of the descending pain modulatory system [43]. Moreover, several studies revealed that the abnormalities in MFG were correlated with the pain intensity of migraine attacks [20, 22]. Hence, the decreased ALFF value in the MFG after needling may reflect the neural mechanism of acupuncture for pain modulation.

In this study, we also found increased ALFF values in the right precentral gyrus and postcentral gyrus after needling. The postcentral gyrus, referred as the primary somatosensory cortex (S1), is the main part of the pain matrix and accepts pain signals directly [44]. A precious study had found its cortex got thicken in migraine patients [45]. The precentral gyrus, called primary sensorimotor cortex (M1), is thought to be an abnormal hub related to pain processing [46]. The results of this study showed increased regional activity in both S1 and M1, which suggested that the S1 was closely associated with the M1 in pain processing. Taken together, our result might provide further evidence that the two brain regions were associated with pain modulation. Meanwhile, we also speculated that the increased activity reflected the neural mechanism of acupuncture for pain modulation.

Differences in ALFF between after acupuncture treatment for MWoA patients and healthy controls

Compared with healthy controls, the MWoA patients after needling showed not only most of the same changes of ALFF values in the comparison of MWoA patients and healthy controls before needling, but also part of the same changes with the comparison in MWoA Patients after and before needling. It could be easily understood that the changes of ALFF values could not be entirely reserved by the temporary acupuncture treatment. In hence, compared with healthy controls, the MWoA patients after needling showed some unchanged ALFF values in comparison of the MWoA patients and healthy controls before needling.

The increased ALFF values in the right precentral gyrus and postcentral gyrus are included in the main distribution of RFPN. The RFPN is recognized as an important brain network that corresponds to perception, somesthesis, and pain [47]. Our previous study had confirmed that the decreased FC in the RFPN could be reversed by acupuncture treatment [24]. Accordingly, we speculate that the increased ALFF values are possibly related with the recovery of MWoA.

Limitations of this study

This study might have some limitations. First, as a preliminary study, the sample size was small. This could be the reason that there was no finding in some regions related to pain processing, such as the thalamus which was thought to be the hub for pain processing [29]. Second, it would be better to set up a sham acupuncture group for proving specificity of acupuncture effect. In the future, these findings need to be further confirmed by enlarging sample size, including a placebogroup for the acupuncture.

Conclusions

In the current study, we demonstrated that widespread ALFF abnormalities in MWoA patients, and that needling GB41 could change the amplitude of the intrinsic cortical activity of the brain. Taken together, this study provided
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further insights into the complex scenario of migraine mechanisms, and indicated that mechanisms of the effect of acupuncture could be interpreted in terms of pain processing.

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Disclosure of conflict of interest

None.

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