HEADACHE & FACIAL PAIN SECTION

Original Research Article

Functional Alterations of Pain Processing Pathway in Migraine Patients with Cutaneous Alloodynia

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Abstract

Objective. Cutaneous allodynia (CA) is a characteristic of central sensitization, predicting migraine progression, and poor response to therapy. The present study aimed to find out the cerebral functional alterations related to the establishment of central sensitization in migraineurs using functional magnetic resonance imaging (fMRI).

Design. The experiment was performed in 15 migraineurs with Cutaneous allodynia (MWCA) and 19 patients without Cutaneous allodynia (MWoCA) in the interictal phase, and 20 matched healthy controls. Blood oxygen level dependent-fMRI was applied in all subjects when they were given transcutaneous electrical nerve stimulation at the left medial forearm, achieving a predetermined level of pain sensation (i.e., visual analogue scale [VAS] = 40). Contrast images were then produced to determine whether this disorders present functional changes in the brain during pain processing.

Results. Demographic and headache characteristics were balanced between groups. The contrast images of both migraine groups comparing to healthy controls exhibited weaker activation of various brain regions (e.g., cerebellum and insulae), which might be relevant to the pathophysiological procedure of migraine. The direct comparison between the two migraine groups revealed that activation in the dorsal pons and contralateral (right) inferior parietal lobule of MWCA subjects were significantly lower than it in MWoCA ones.

Conclusions. The interictal dysfunction of pain processing pathway may be responsible for (at least relevant to) central sensitization in migraine patients, via abnormal modulations of nociceptive transmission.

Key Words. Migraine; Alloodynia; Central Sensitization; Magnetic Resonance Imaging; Function

Introduction

Migraine is one of the most common primary headache disorders worldwide, affecting people of any age with the peak onset between 20 and 24 years old in women and 15 and 19 years in men [1,2]. The mechanism of migraine has not been clearly explained despite the wide concern for its significant socioeconomic impact.

Central sensitization, defined as an amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity [3], is a latest hypothesis regarding the pathophysiological mechanism of
migraine. Yet it seems to be a supplementary theory rather than an alternative to existing hypotheses [4]. Cutaneous allodynia (CA, a painful response to an innocuous stimulation) is a characteristic manifestation of central sensitization. It has been reported in more than 60% of patients with migraine during their headache attacks [5–9]. Recent studies also suggested CA was a risk factor for migraine progression [8,10] and a predictor of poor response to triptan therapy [11,12]. It indicated that central sensitization might play an important role in the development and aggravation of migraine. In spite of abundant relevant studies, the detailed mechanism of central sensitization in migraine has not been thoroughly explored.

Neuroimaging is a direct and reliable method to investigate CNS of living subjects, but it has been rarely used in the research of central sensitization, much less in migraine. The main reason might be that central sensitization is considered to be a reversible change in the excitability of neurons during headache attacks [3], rendering the timing of image taking difficult. However, CA has also been observed in the interictal phase of migraine, in a small proportion of patients though [8,13]. Furthermore, results of studies based on large population have proved the association between CA and headache frequency and disability [14]. Therefore, it is possible that there would be some persistent structural and functional changes of the central nociceptive pathway responsible for the susceptibility of central sensitization, in spite of the short duration of CA. Based on this hypothesis, Schwedt and colleagues have recently found that migraineurs with CA, comparing with nonalldynic ones, have atypical functional connectivity among pain processing regions, using resting-state functional magnetic resonance imaging (fMRI) [15]. The current study was designed to further explore the brain areas related to the establishment and/or maintenance of sensitization and allodynia in migraineurs during pain processing using active-state blood oxygen level dependent (BOLD) fMRI. The possible mechanism of their roles on migraine was also discussed.

Methods

Participants

Migraine patients without aura were recruited, as well as age- and sex-matched healthy controls, after their written informed consent. The study protocol was approved by the Local Ethics Committee of West China Hospital, Sichuan University.

Diagnosis of migraine without aura was assigned according to the criteria from the Second Edition of the International Classification of Headache Disorders (ICHD-II) [16]. Right-handed subjects aged 18 to 45 years old of both genders were eligible. They had to be weaned off analgesic drugs 1 week or longer, not in years old of both genders were eligible. They had to be weaned off analgesic drugs 1 week or longer, not in years old of both genders were eligible. They had to be weaned off analgesic drugs 1 week or longer, not in years old of both genders were eligible. They had to be weaned off analgesic drugs 1 week or longer, not in years old of both genders were eligible. They had to be weaned off analgesic drugs 1 week or longer, not in years old of both genders were eligible. They had to be weaned off analgesic drugs 1 week or longer, not in years old of both genders were eligible. 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electrical stimulation therapeutic instrument (HJ6805-1, Chengdu), which was connected to two cylindrical stainless-steel electrodes placed on the subject’s skins of the left medial forearm. CA is reported to be unrelated to the predominant side of pain [8], so the absence of side-to-side differences in exhibition of CA allowed us to give TENS stimulation at the same side of all subjects. Stimulation was applied at 50 Hz, and the levels of pain were evaluated when the output intensity of the stimulator was slowly continuously adjusted. All subjects rated the pain sensation using the visual analogue scale (VAS; 0, no pain; 100, intolerable pain), and the output intensity of stimulus with which subjects reported a VAS score as 40 (moderate pain) was recorded for each individual.

All participants were scanned immediately after the stimuli adaptation and pain sensation assessment. Any subjects could withdraw from the experiment anytime before or during the MRI scanning. After MRI scanning, all participants were asked to recall the actual severity of pain during their scanning; those ones with pain sensation more than 10 points (VAS) different from 40 (<30 or >50 points) were also excluded from analyses.

**Design of the fMRI Experiment**

All MRI experiments were performed on a 3.0 Tesla scanner (Trio Tim, Siemens, Erlangen, Germany) with a 16-channel birdcage head coil, and tightly padded clamps were used to minimize head motion. A routine T1 weighted imaging was first obtained, and then the fMRIs were obtained by using an echo-planar imaging sequence with the following protocols: voxel size 3.75 × 3.75 × 5 mm³, TR 2,000 ms, TE 30 ms, FOV 240 × 240 mm², matrix 64 × 64, and slice thickness 5 mm with no gap.

During fMRI scanning, the same skin area of the left medial forearm was stimulated and the intensity was adjusted to achieve the predetermined level of pain sensation (i.e., VAS = 40). We did not assess the intensity of pain experienced during MRI scanning again, to avoid the impact of visual and motion (or language) tasks on BOLD-fMRI results. Imaging data were collected immediately after the stimuli test outside the MRI room, so the experiment environment, stimulation mode, as well as the sensation state of each subject should remain unchanged. Furthermore, we asked all participants to rate the actual pain immediately after the scanning and excluded those subjects with obviously different sensations. Every TENS persisted for 4 seconds and the same intensity of stimulus was repeated for five times with inter-stimulus intervals of 26 seconds, when subjects were asked to relax and keep motionless, thus allowing high effective sampling of the BOLD signal after stimulation.

**Data Analysis**

The two sample t-test and Pearson χ² test were performed using SPSS (version 17.0) to compare the demographic and clinical data among groups. Between-group difference was considered significant if the statistical analysis resulted in a P value less than 0.05.

The fMRI data analyses were performed with the Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The first five images in rest state were discarded to account for subjects’ adaptation and spin saturation effects. The pre-processing procedure included slice timing, motion-correction, realigning individual scans, normalizing to Montreal Neurological Institute (MNI), and smoothing images. Then, we performed statistical analysis using the general linear model with hemodynamic response function. Afterwards, groups were compared using t-test to demonstrate the BOLD signal differences between groups in a whole-brain analysis. The HAM and HAMA scores of each subject were integrated into the analyses as a control variable, to rule out the impacts from emotional factors on brain activation. Contrast results were rebuilt on the subjects’ T1 weighted image, showing significantly different activation during TENS stimulation (cluster size > 10; voxel-wise intensity threshold P < 0.001).

**Results**

**Clinical Data**

A total of 58 subjects (37 migraine patients without aura and 21 healthy controls) were enrolled, but data of four participants were not included in the analyses because they experienced another attack of headache within 48 hours after MRI scanning (one from each migraine group), or reported an obviously different pain intensity during MRI scanning from the prior tests (VAS < 30 or > 50; 1 from MWCA group; and 1 from control group, respectively). Of the remaining 54 participants, 15 migraineurs were classified as MWCA patients and 19 as MWoCA, according to their ASC scores. The range of ASC scores of migraineurs was three to eight in the present study. It means all enrolled MWCA subjects were with mild (3–5 scores) or moderate (6–8 scores) allodynia [9]. The mean ASC score of participants in MWCA group was 5.07 ± 1.62, significantly higher than it of MWoCAs (0.58 ± 0.84, P = 0.001; Figure 1). The subject population comprised 40 females (74.07%) and 14 males with an average age of 27.54 ± 6.67 years and a mean education level of 15.30 ± 1.92 years. Demographic and psychiatric characteristics of all subjects are given in Table 1. No significant difference was found for gender, age, education, body mass index (BMI), or MoCA scores among the three groups. The 24-HAMD (MWCA vs control, P = 0.001, t = 4.424; MWoCA vs control, P = 0.043, t = 2.179) and 14-HAMA scores (MWCA vs control, P < 0.001, t = 5.186; MWoCA vs control, P = 0.013, t = 2.750) of both migraine groups were significantly higher than those of the control group, wherever there was no significant difference in either the depression or anxiety assessment results comparing the two migraine groups (P value was
0.087 and 0.102, respectively), although both scores seemed a little higher in MWCA subjects compared with MWoCA ones (Table 1).

Table 2 shows the headache features of two groups of migraineurs, respectively. It indicates that there were no significant differences between MWCA and MWoCA patients in course of disease, frequency of attack, length of one attack without treatment, percentages of subjects with classical characteristics of migraine (i.e., unilateral location, pulsating quality, and aggravated by daily activities) or common accompanying symptoms (i.e., nausea, vomiting, photophobia, and phonophobia) \((P > 0.05)\). Those migraineurs with CA tended to get a higher average intensity of headache pain evaluated by VAS comparing to MWoCA patients \((64.33 \pm 17.26 \text{ vs } 54.74 \pm 11.24)\), but the difference did not achieve to a statistical significance neither \((P = 0.059)\). The impacts of migraine on living ability and daily life assessed by MIDAS and HIT-6 were also balance between the two migraine groups \((P > 0.05; \text{Table 2})\). The mean electric current intensity for the defined set of pain sensation \((\text{VAS} = 40)\) was \(2.16 \pm 0.72 \text{ mA}\) for the MWCA group, \(2.01 \pm 0.69 \text{ mA}\) for the MWoCA, and \(2.28 \pm 0.83\) for controls, respectively. None statistically significant difference was found between groups \((\text{MWCA vs MWoCA}, P = 0.664; \text{MWCA vs controls}, P = 0.760; \text{MWoCA vs controls}, P = 0.523)\).

**fMRI Results**

The contrast between stimulation and rest state of the three groups all revealed increased activation in several similar cerebral areas related to pain perception, including ipsilateral (left) pons, contralateral (right) postcentral gyrus cortex and thalamus, bilateral temporal lobes, insulae, cingulate gyri, and posterior cerebella lobes (Figure 2).

The general comparison between migraneurs and controls demonstrated that several areas in cerebral regions such as bilateral parahippocampal gyrus, cerebellum, thalamus, midbrain, and insula had less BOLD signals in the migraine group (Figure 3A). And then we contrasted the images of MWCA and MWoCA group with controls, respectively, finding that both migraine groups showed similar regions with significantly weaker BOLD signals comparing to controls, including bilateral cerebellum and left insulae. However, there were also some differences in less-activated regions between the two migraine groups: the contrasting images of MWCA patients and controls showed significantly weaker signal in left pons, bilateral parahippocampal gyri, and right superior temporal gyrus, whereas MWoCA images demonstrated weaker activation in left medial frontal gyrus and thalamus, comparing to controls (Figure 3B,C; Table 3).

**Table 1** Demographic and psychiatric characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>MWCA Patients ((n = 15))</th>
<th>MWOCA Patients ((n = 19))</th>
<th>Control ((n = 20))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>3/12</td>
<td>5/14</td>
<td>6/14</td>
</tr>
<tr>
<td>Age (mean ± SD, y)</td>
<td>28.13 ± 8.03</td>
<td>26.47 ± 7.06</td>
<td>28.10 ± 5.93</td>
</tr>
<tr>
<td>Education (mean ± SD, y)</td>
<td>16.27 ± 2.60</td>
<td>15.68 ± 3.59</td>
<td>16.90 ± 2.40</td>
</tr>
<tr>
<td>BMI (mean ± SD, kg/m²)</td>
<td>19.92 ± 1.65</td>
<td>20.97 ± 2.28</td>
<td>20.97 ± 2.90</td>
</tr>
<tr>
<td>24-HAMD (mean ± SD)</td>
<td>9.20 ± 5.97*</td>
<td>5.68 ± 5.60*</td>
<td>2.70 ± 2.43</td>
</tr>
<tr>
<td>14-HAMA (mean ± SD)</td>
<td>6.47 ± 3.87*</td>
<td>4.16 ± 4.05*</td>
<td>1.45 ± 1.70</td>
</tr>
<tr>
<td>MoCA (mean ± SD)</td>
<td>27.47 ± 1.85</td>
<td>27.53 ± 1.47</td>
<td>28.35 ± 1.31</td>
</tr>
</tbody>
</table>

MWCA = migraine with cutaneous allodynia; MWOCA = migraine without cutaneous allodynia; SD = standard deviation; y = year; BMI = body mass index; HAMD = Hamilton Depression Scale; HAMA = Hamilton Anxiety Scale; MoCA = Montreal Cognitive Assessment.

* \(P < 0.05\), comparing to the control group; No significant difference was found between the two migraine groups.
To determine the cerebral regions with functional changes directly involving in the induction of CA, also the brain areas probably relevant to central sensitization, we further contrasted the images of MWCA group with MWoCA group. The results suggested that the BOLD signals in the dorsal pons and contralateral (right) inferior parietal lobule of MWCA patients were significantly lower than those in MWoCA subjects (Figure 4) with TENS stimulation.

**Discussion**

The present study aimed to explore cerebral functional alterations related to central sensitization in patients with migraine and CA, comparing to migraineurs without CA and healthy controls. We recorded BOLD signal data of all participants during moderate noxious stimulation applied on the forearm. Our findings may explain the possible central mechanisms of migraine to some extent.

**Imaging Findings**

We found activation of several brain regions belonging to the pain matrix [13,24] during painful stimulation delivered to the left medial forearms of all three groups of participants (Figure 2). The first key finding was that the contrast images of both migraine groups comparing to healthy controls exhibited less activation of various brain regions (e.g., cerebellum and insulae; Table 3). These cerebral abnormalities might be relevant to the pathophysiological procedure of migraine. They may not directly lead to CA, but such patients’ susceptibility to headaches with or without inducing factors suggests the existence of generalized sensitization in both kinds of migraineurs without aura.

**Table 2**  Headache features of migrainuers

<table>
<thead>
<tr>
<th></th>
<th>MWCA Patients</th>
<th>MWoCA Patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease course (mean ± SD, y)</td>
<td>10.03 ± 7.88</td>
<td>9.42 ± 6.31</td>
<td>0.803</td>
</tr>
<tr>
<td>Frequency (mean ± SD, attacks/m)</td>
<td>3.90 ± 3.08</td>
<td>3.66 ± 3.91</td>
<td>0.494</td>
</tr>
<tr>
<td>Attack duration (mean ± SD, h)</td>
<td>12.17 ± 11.04</td>
<td>12.28 ± 18.01</td>
<td>0.240</td>
</tr>
<tr>
<td>Unilateral location (n (%))</td>
<td>12 (80.0)</td>
<td>11 (57.9)</td>
<td>0.165</td>
</tr>
<tr>
<td>Pulsating quality (n (%))</td>
<td>12 (80.0)</td>
<td>15 (78.9)</td>
<td>0.940</td>
</tr>
<tr>
<td>Aggravated by daily activities (n (%))</td>
<td>10 (66.7)</td>
<td>9 (47.4)</td>
<td>0.260</td>
</tr>
<tr>
<td>Mean intensity of headache (VAS, mean ± SD)</td>
<td>64.33 ± 17.26</td>
<td>54.74 ± 11.24</td>
<td>0.059</td>
</tr>
</tbody>
</table>

Accompanying symptoms:
- Nausea and/or vomiting (n (%)): 10 (66.7) vs. 10 (52.6), P = 0.409
- Photophobia (n (%)): 9 (60.0) vs. 12 (63.2), P = 0.851
- Phonophobia (n (%)): 10 (66.7) vs. 11 (57.9), P = 0.601
- MIDAS (mean ± SD): 15.47 ± 12.36 vs. 17.79 ± 19.69, P = 0.693
- HIT-6 (mean ± SD): 60.53 ± 5.30 vs. 61.63 ± 5.10, P = 0.544

MWCA = migraine with cutaneous allodynia; MWoCA = migraine without cutaneous allodynia; SD = standard deviation; y = year; VAS = visual analogue scale, score range 0–100; MIDAS = Migraine Disability Assessment; HIT = Headache Impact Test.

To determine the cerebral regions with functional changes directly involving in the induction of CA, also the brain areas probably relevant to central sensitization, we further contrasted the images of MWCA group with MWoCA group. The results suggested that the BOLD signals in the dorsal pons and contralateral (right) inferior parietal lobule of MWCA patients were significantly lower than those in MWoCA subjects (Figure 4) with TENS stimulation.

**Figure 2** Cerebral regions activated with TENS stimulation (A. MWCA group, B. MWoCA group, C. control group) (MWCA: migraine with cutaneous alldynia; MWoCA: migraine without cutaneous alldynia, P < 0.001). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Our major concerns were alterations of pain processing pathway relevant to central sensitization. We grouped migraineurs without aura in the present study using manifestations of CA as the clinical markers, and the contrast fMRI results showed two significantly differently activated cerebral regions—the dorsal pons and the right (contralateral) inferior parietal lobule. These differences can first verify our hypothesis that there are functional changes, even in interictal phase of headache, in CNS of migraineurs with CA responsible for (at least relevant to) central sensitization. Second, as both the two cerebral regions take part in pain perception processing, as discovered by previous researches [25,26], their weaker activation in MWCA patients can reasonably interpret the phenomenon of CA.

The abnormality in brainstem of migraine patients we observed is in keeping with other studies. Previous experiments reported changes in several regions of brainstem in migraine patients, including periaqueductal gray (PAG), locus ceruleus (LC), red nuclei, and substantia nigra [27–29]. A recent systematic review

Table 3  Cerebral regions of significant BOLD signal differences between migraine patients and controls

<table>
<thead>
<tr>
<th>Cerebral Regions</th>
<th>Peak Voxel MNI Coordinates</th>
<th>Cluster Size</th>
<th>T value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MWCA &lt; CON</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left cerebellum</td>
<td>–6</td>
<td>–66</td>
<td>–15</td>
</tr>
<tr>
<td>Right cerebellum</td>
<td>9</td>
<td>–66</td>
<td>–15</td>
</tr>
<tr>
<td>Left insula</td>
<td>–30</td>
<td>–18</td>
<td>–6</td>
</tr>
<tr>
<td>Left pons</td>
<td>–21</td>
<td>–33</td>
<td>–33</td>
</tr>
<tr>
<td>Left parahippocampal gyrus</td>
<td>–18</td>
<td>–15</td>
<td>–18</td>
</tr>
<tr>
<td>Right parahippocampal gyrus</td>
<td>24</td>
<td>–3</td>
<td>–15</td>
</tr>
<tr>
<td>Right superior temporal gyrus</td>
<td>42</td>
<td>–57</td>
<td>18</td>
</tr>
<tr>
<td>MWoCA &lt; CON</td>
<td></td>
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</tr>
<tr>
<td>Left cerebellum</td>
<td>–9</td>
<td>–39</td>
<td>–27</td>
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<tr>
<td>Right cerebellum</td>
<td>18</td>
<td>–60</td>
<td>–24</td>
</tr>
<tr>
<td>Left insula</td>
<td>–18</td>
<td>–18</td>
<td>–6</td>
</tr>
<tr>
<td>Left medial frontal gyrus</td>
<td>–9</td>
<td>45</td>
<td>24</td>
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<tr>
<td>Left thalamus</td>
<td>–21</td>
<td>–27</td>
<td>6</td>
</tr>
<tr>
<td>MWCA &lt; MWoCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right inferior parietal lobule</td>
<td>57</td>
<td>–33</td>
<td>42</td>
</tr>
<tr>
<td>Right dorsal pons</td>
<td>3</td>
<td>–33</td>
<td>–30</td>
</tr>
</tbody>
</table>

All $P < 0.001$; MNI = Montreal Neurological Institute; MWCA = migraine with cutaneous allodynia; MWoCA = migraine without cutaneous allodynia; Con = controls; MWCA < CON = regions with weaker fMRI signal in MWCA group comparing to controls; MWoCA < CON = regions with weaker fMRI signal in MWoCA group comparing to controls.
suggested that migraineurs have more structural changes in several gray matter and white matter regions, and a special increased density was only found by voxel-based morphometry (VBM) in the PAG and the dorsolateral pons in patients with migraine with aura [30]. They all indicated that these parts might contribute to the onset of this kind of headache. Using resting-state fMRI, Schwedt recently found that migraineurs with severe allodynia had stronger PAG and nucleus cuneiformis connectivity to regions that participate in pain processing and modulation, and speculated that such dysfunction was specific to allodynia and sensitization [15]. However, the precise regions contributing to central sensitization and their real-time function remain unclear. Gray matters located in brainstem (e.g., LC in superior part of dorsal pons and PAG in midbrain) are essential elements of endogenous analgesic system, which was considered to be a descending inhibitory network altering the incoming flow of painful signals, thus, decreasing the intensity of pain [25]. The significantly weaker activation in dorsal pons of MWCA patients, comparing to MWoCA ones, in the present study, possibly suggests that dysfunction of the descending circuitry could play a role in reducing pain inhibition and facilitating pain perception, thus introducing CA or hyperalgesia. In a previous fMRI experiment, Moulton and colleagues also measured brainstem function interictally in migraineurs who had demonstrable allodynia during migraine attacks. Consistent with our results, they found hypofunction of pain descending modulatory circuits in such migraineurs, and supported the postulation that a brainstem dysfunction could precipitate migraine attacks. In their study, however, participants with allodynia or other manifestations suggesting central sensitization were not distinguished using any validated instrument. Besides, subjects with allodynia were compared with normal controls only, but not with migraineurs without allodynia, so their results could not directly find out the altered cerebral regions specific to central sensitization [28].

Meanwhile, the other significantly weaker activated cerebral region, inferior parietal lobe, is near the somatic sensory cortex. It belongs to the posterior parietal cortex, which is generally considered to be an integration center for different aspects of somatosensory signals, and also participate in information process during central pain sensitization. Although its functional meaning is not known in detail yet, it has been demonstrated in previous studies to involve in spatial discrimination and attention to pain [31–33]. We speculated that dysfunction of inferior parietal lobule may disturb the regulation of process to intentionally direct attention away from pain, thus leading suffering subjects to be more susceptible to nociceptive stimuli. Such inverse relationships between pain sensitivity and structural alterations of cerebral regions, including inferior parietal lobule, have also been found by Emerson and colleagues using VBM [34]. Further, pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” [35]. Inferior parietal lobule also plays a role in emotional and cognitive processing [26], so its dysfunction may impact on pain sensation and promote the establishment of central sensitization in migraine patients from the emotional level.

Central Sensitization

Central sensitization is not a new concept. During the past two decades, plenty of experimental and clinical
studies have proved that central sensitization is an important component of the sensory abnormalities in patients with painful disorders, such as fibromyalgia, temporomandibular disorders, complex regional pain syndrome, rheumatoid arthritis, osteoarthritis, as well as the primary headaches [3]. However, specific cerebral alternations contributing to central sensitization have not been clearly recognized. Findings from animal models suggested it was associated with abnormal changes in the brainstem, thalamus, and cortical centers [4,36]. Previous imaging studies have also found increased activity in brainstem, thalamus, cerebellum, insula, cingulate cortex, and somatosensory cortex, which were speculated to lead to central sensitization in subjects with hyperalgesia or allodynia [37,38]. However, just as the definition of hyperalgesia and allodynia, the pain perception may be stronger in such patients than in normal subjects or patients without sensory dysfunction with an identical stimulus, thus, resulting in increased activity of cerebral areas relevant to increasing pain experience [39]. So it is still unclear whether those cerebral activation changes reflect the experience of increased pain perception or the dysfunctional regions leading to central sensitization. Therefore, to determine functional changes specifically related to CA in migraineurs, we compare cerebral signals between participants of the same intensity of pain sense, instead of the same stimulus intensity could collecting imaging data under the identical pain perception as there remain limitations within the study. First, only common migraineurs without aura were enrolled, because migraine with and without aura may be distinct disorders [40]. Then we set strict inclusion and exclusion criteria for each group of subjects. The demographic and clinical features were balanced among groups, except the 24-HAMD and 14-HAMA scores between each migraine group and controls. It is in line with previous clinical findings that patients with migraine often have mood disorders as comorbidities [41]. Studies revealed that psychological factors like mood, attention, and controllability could significantly affect subjects’ perceived pain intensity [42,43]. In the present study, however, the design of collecting imaging data under the identical pain perception instead of the same stimulus intensity could decrease the risk of bias from participants’ mood conditions. More than that, the mood scores were not statistically different between the two migraine groups, thus, not influencing the primary result of our study. We further limited the timing of MRI scanning to interictal phase, avoiding the impact on BOLD signals from spontaneous pain itself.

We distinguished migraineurs with CA using ASC, a validated questionnaire for assessing allodynia in migraine patients [9]. Although quantitative sensory testing (QST) is the gold standard for the assessment of CA, it is hardly to be implemented in our tentative study, as we evaluated migraine patients during the interictal phase, when they usually do not exhibit allodynia. It has been found that sensory hypersensitivity and allodynia could be detected even in the headache-free period in migraineurs [8,44]. However, as opposed to what had been expected initially, the intensity of applied electrical stimulation to introduce similar pain perception in the present study was not significantly different between groups. It means the enrolled participants with MWCA might not be hypersensitive to electrical stimuli comparing to those ones with MWoCA or normal controls during the experiments phase. It may be because that we only recruited episodic migraine subjects, in whom allodynia was less persistent and temporarily related to headache attacks. What’s more, the range and mean values of ASC scores of participants in MWCA group suggested they were all with mild to moderate allodynia, although there have already been functional abnormalities during pain processing, as demonstrated in the MR images. It might also explain why only a few cerebral regions with significantly different activation between the two migraine groups were found in our study. But the indifference of stimulation intensity between groups further reduced the impact on cerebral imaging data. In further studies, we will use QST to evaluate the actual sensation of participants to get more precise results. We will also include patients with more severe CA, and try to analysis the relationship between cerebral alterations and the severity of allodynia.

CA is currently considered to be a common symptomatic manifestation of central sensitization, but it is not a necessary condition. Patients with central sensitization can also present hyperalgesia or other sensory disturbances [3,4]. In spite of this, CA has been suggested as a risk factor for migraine progression [14], so our findings can at least reflect that those functional changes in CNS of MWCA subjects are associated with the progression of migraine.

Limitations

Nevertheless, our findings must be interpreted with caution as there remain limitations within the study. First, the sample of subjects is small. The length of disease course, severity of migraine and CA, and other characteristics of headache may vary patients’ CNS alterations, but we did not make any subgroup comparisons due to the few participants, although the general comparisons
about the above feature were similar among groups in the present study. Second, whether the migraineurs had allodynia or hyperalgesia at the moment they underwent MRI scanning could make an effect on the BOLD signals. We did not evaluate their pain sensation this time, and not selected out those subjects for further analysis. Third, we assessed participants’ pain intensity using a simple VAS instrument only, although it has been widely validated and established in both clinical work and scientific researches. In addition, we have not performed a long-term evaluation or rescanned the subjects yet, so the changes demonstrated could also be the result of repetitive migraine attacks, rather than the cause. Whether the functional alteration is a predictor or a consequence of central sensitization cannot be determined by the present study.

In summary, the present study demonstrates that the interictal dysfunction of pain processing pathway may be responsible for (at least relevant to) central sensitization in migraine patients, via abnormal modulations of nociceptive transmission. Future studies of central sensitization in migraine and other primary headaches are required, as deeper understanding in such area may shed light on the mechanism of these disorders and provide a firm basis for novel pathogenesis-based methods of treatment.

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References


