Original Article
A meta-analysis of voxel-based morphometric studies on migraine

Wenting Hu, Jian Guo, Ning Chen, Jiang Guo, Li He

Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China

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Abstract: Purpose: To identify consistent results of voxel-based morphometry (VBM) studies in migraine. Methods: Whole-brain VBM studies comparing migraine patients with healthy controls (HC) were systematically searched in PubMed, ISI Web of Science, Embase, and Medline databases from January 1990 to Dec 2014. Coordinates were extracted from clusters with significant difference in gray matter volume (GMV) between migraine patients with healthy controls (HC). Meta-analysis was performed using activation likelihood estimation (ALE). Results: A total of 5 studies, comprising 126 migraineurs, including 23 migraine with aura, 41 migraine without aura, 11 epidemic migraine and 16 chronic migraine as well as 19 Mm and 16 nmM, and 134 HC, were enrolled. The included studies report GMV reduction at 84 coordinates in migraine, as well as GMV increase at 2 coordinate in migraine. However, due to only two included studies have classified patients into these two phenotypes and one stated they included only migraine with aura patients, we were not able to perform a subgroup analysis and separate meta-analyses on each phenotype. Conclusion: There were significant reductions in Middle frontal cortex (BA6, 9) structures and the Inferior frontal cortex (BA44) in migraine. These changes of GMV may indicate the mechanisms of the associated symptoms such as cognitive dysfunction, emotion problems and autonomic dysfunction. But whether this is the characteristics of the subtypes of migraine or can distinguish the types of migraine or primary headache, further studies examining larger samples may better elucidate the changes related to the illness and highlight its pathological mechanism.

Keywords: Migraine, voxel-based morphometry (VBM), voxel, voxel-wise, voxel-based or morphometry, meta-analysis

Introduction

Migraine is a form of episodic primary neurovascular headache that is probably based fundamentally on dysfunction in the brain [1]. Migraine headaches cause significant individual and societal burden due to pain, environmental sensitivities, resulting disability, and lost productivity. Migraine costs much directly and indirectly and results in substantial pain, disability, and a decreased overall quality of life [2-6]. A better understanding of migraine mechanisms will lead to improved treatments and a reduction in the negative impact of migraine [7-10].

Advances in our understanding of the neurobiology of migraine have provided considerable insights into the problem. Neuroimaging has led to advances in the description of migraine mechanisms and to the identification of secondary structural and functional effects of migraine [11]. However, due to the episodic and generally unpredictable nature of individual migraine attacks, imaging during spontaneous migraine has proven difficult [12, 13]. New imaging techniques may have potential to identify mechanisms responsible for the transformation from infrequent to frequent headache patterns, and thus, lead to novel diagnostic and therapeutic interventions that will help to improve the lives of millions of patients with migraine [14]. Voxel-based morphometry (VBM) is a newer technique that aims to detect consistent structural differences between groups of subjects that can be related to functional correlates and thus further understanding of disease pathophysiology in the brains of patients with migraine and non-migraine controls [7, 9, 12]. In the past decade, VBM has been widely used in many types of cephalalgia, such as cluster headache [15], chronic tension type
headache [16], hypnic headache [17]. Moreover, in recent years, VBM also has been conducted in migraine. However, the results about these studies were full of contradictions. An initial VBM study of migraine found no differences in global or regional grey or white matter between patients and controls [18], but more recent studies have found differences. A separate VBM study confirmed that patients with migraine had decreased grey matter in the anterior cingulate cortex, insula, amygdala, parietal operculum, and middle and inferior frontal gyrus [19]. JH Kim and colleagues found those had regions of reduced grey matter density in the bilateral insula, motor premotor, prefrontal, cingulate cortex, as well as right posterior parietal cortex and orbitofrontal cortex [20], and increased density of the PAG and the dorsolateral pons [21].

Therefore, the present work aims to systematically and voxel wisely meta-analyze the GM changes in patients with migraine. We used Activation likelihood estimation (ALE) to do this analysis, which is a powerful voxel-based meta-analytic technique originally designed for functional neuroimaging studies [22, 23], and has been effectively applied in a number of disorders, such as idiopathic [21] Parkinson’s disease [24], amyotrophic lateral sclerosis [25], and obsessive-compulsive disorder [26-28], Neuromyelitis Optica Patients [29]. Though finding the core regions of structural changes, our work may be helpful in obtaining insights for further understanding of the pathophysiology underlying migraine [7-9, 30].

Materials and methods

Data source

A systematic search of the Medline database (from January 1990 to Dec 2014), PubMed, ISI Web of Science and Embase was conducted. The key words used were (“Migraine “; “Migraine with aura”; “Migraine without aura”; “Magnetic resonance imaging (MRI)”; “Voxel-based morphometry (VBM)”; “Meta-analysis”; “Activation likelihood estimation (ALE)”; “ voxel”; “voxel-wise”; “voxel-based” or “morphometry”). The references of the relevant articles were also searched for additional studies.

Selection of studies and extraction of data

A study was considered for inclusion: If it (1) reported a VBM (GMV or gray matter concentra-
tion) comparison between adult patients with migraine and healthy control (HC) subjects; (2) reported whole-brain results of changes in stereotactic coordinates; (3) used thresholds for significance corrected for multiple comparisons or uncorrected with special extent thresholds; (4) involved patients divided into migraine with aura and migraine without aura or episodic migraine and chronic migraine according to the Second Edition of International Classification of Headache Disorders (ICHD-II) [31]; (5) involved patients without intracranial surgery; (6) published in English with peer review. To avoid repetitive data, the study with the most complete description of data was recruited when the same name of author, similar characteristics of participants and data appeared in two or more publications. In cases where similar studies met the aforementioned inclusion criteria but had overlapping data with one author, the study with the largest sample size was selected.

A study was excluded: If (1) data were not sufficient even after contact with the authors by phone or e-mail; (2) fewer than seven subjects in any group were studied; (3) data overlapped with those of another article; (4) some results were uncorrected and the special extent threshold was not reported; (5) there was no HC group; (6) patients with other kinds of headache, such as cluster or hypnic headache, were involved. The method used in the current study was according to the Meta-analysis of observational studies in Migraine guidelines for meta-analyses of observational studies.

The coordinates in each study were independently extracted by neurologists (namely, Wenting Hu and Jian Guo) according to the ALE method [32-34].

Voxel-based meta-analysis

Voxel-based meta-analysis was performed on the selected studies using the ALE software (Ginger ALE 2.3.2, http://www.brainmap.org/) in a standard process to compare the VBM changes between the migraine group and the HC group. The listed coordinates in the Montreal Neurological Institute (MNI) space in those studies were transformed into Talairach space using icbm2tal [35] as implemented in Ginger ALE2.3.2. The listed coordinates in Talairach space in those studies were back-transformed.
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Table 1. Demographic and clinical characteristics of VBM studies on migraine in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Total migraine</th>
<th>HC</th>
<th>Disease</th>
<th>Mean frequency of migraine</th>
<th>Mean duration of migraine</th>
<th>Estimated Lifetime frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>JH Kim et al. [20] (2008)</td>
<td>20 (3)</td>
<td>33.7 ± 11.3</td>
<td>33 (4)</td>
<td>MA 5 (2)</td>
<td>NA</td>
<td>9.8 ± 6.0</td>
</tr>
<tr>
<td>Maria et al. [21] (2006)</td>
<td>16 (1)</td>
<td>42.7</td>
<td>15 (2)</td>
<td>MA 7 (1)</td>
<td>NA</td>
<td>42.7</td>
</tr>
<tr>
<td>Matharu et al. [18] (2003)</td>
<td>28 (2)</td>
<td>31</td>
<td>28 (2)</td>
<td>MA 11 (1)</td>
<td>NA</td>
<td>31</td>
</tr>
<tr>
<td>Walter et al. [19] (2007)</td>
<td>27 (6)</td>
<td>34.9 ± 8.4</td>
<td>27 (6)</td>
<td>MA 11 (2)</td>
<td>32.1 ± 8.7</td>
<td>20.6 ± 8.9</td>
</tr>
<tr>
<td>Schmidt et al. [37] (2008)</td>
<td>32 (0)</td>
<td>32.4 ± 9.2</td>
<td>31 (0)</td>
<td>mM 19 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Key: HC: healthy control. MA: migraine with aura; MO: migraine without aura; NA: not available; SD: standard deviation; VBM: voxel-based morphometry. Mm: menstrual migraine; nmM: not menstrual migraine.
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Table 2. Technique details of VBM studies on migraine in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>MRI scanner</th>
<th>Software</th>
<th>Smoothing (FWHM)</th>
<th>P-Value</th>
<th>Foci number</th>
<th>Greater GMV</th>
<th>Smaller GMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>JH Kim et al. (2008)</td>
<td>1.5 T</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>19</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Maria et al. (2006)</td>
<td>3 T</td>
<td>SPM2</td>
<td>12 mm</td>
<td>P &lt; 0.001 (uncorrected)</td>
<td>40</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Matharu et al. (2003)</td>
<td>2.0 T</td>
<td>SPM99</td>
<td>10 mm</td>
<td>P &lt; 0.005 (uncorrected)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walter et al. (2007)</td>
<td>1.5 T</td>
<td>SPM2</td>
<td>12 mm</td>
<td>NA</td>
<td>21</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Schmidt et al. (2008)</td>
<td>1.5 T</td>
<td>SPM2</td>
<td>12 mm</td>
<td>P &lt; 0.05</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: FDR: false discovery rate; FEW: family-wise error; FWHM: full width at half-maximum; MRI: magnetic resonance imaging; NA: not available; SPM: statistical parametric mapping; T: tesla; VBM: voxel-based morphometry.

Only GMV reduction was found in the patients in 2 studies [20, 37], whereas both GMV increased and reduction were found in the remaining 2 studies [19, 21]. The identified articles included 84 foci GM abnormalities among which 2 corresponded to a greater GMV and 82 corresponded to a smaller GMV in PFD patients compared to HC. The technical details of the included studies are shown in Table 2. Group analyses were performed between the migraine with or without aura group and HC subjects, respectively. The group analysis of GMV increase was not successfully performed because only two studies reported GMV increase and there were few coordinates reported. As shown in Table 3 and Figure 1.

We found no increase of GMV in migraine patients in our study. The reduction of GMV has been validated in ALE and JACKKNIFE sensitivity analysis, and that is independent of age and disease duration.

Nine clusters were identified in the ALE analysis under FDR < 0.05 and voxels > 100. As illustrated in Figure 1 and Table 3, smaller GMV in the middle frontal cortex (BA6, 9), inferior frontal cortex (BA44), pre-central cortex (BA44), sub-lobar insula (BA13), sub-gyral temporal cortex (BA20), temporal cortex (BA20), whereas, no greater GMV were identified in patients with PFD compared to healthy controls.
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Discussion

To the best of our knowledge, this is the first study to pool VBM studies for meta-analysis of brain structural differences between migraine and healthy subjects. The present voxel-based meta-analysis using ALE mainly found patients with migraine to have consistent structural changes of smaller GMV in the Middle frontal cortex (BA6, 9), Inferior frontal cortex (BA44), Pre-central cortex (BA44), sub-lobar insula cortex (BA13), Sub-Gyral cortex, temporal cortex (BA20), temporal cortex (BA21). These results were in line with the findings of other positron emission tomography [39, 40], Magnetic Resonance Imaging (MRI) [41, 42], and VBM study (not included in this meta-analysis due to involved mixed patients group of migraine with and without aura). In the current analysis, Middle frontal cortex (BA6, 9) was found in both migraine with and without aura patients, in accordance with a study that used MRI and regions of interest (ROI) [41]. Therefore, further studies are needed to elucidate the issue. Interestingly, Table 2 and Figure 1 show wider GMV reduction in the migraine with aura than in the migraine without aura. This finding was supported by the results of other studies.

The current meta-analysis utilizes the latest version of the ALE software, which has been successfully used in some coordinate based meta-analyses on imaging data [43-45], to identify the consistent regional changes among studies. This modified software overcomes several drawbacks of the original implementation, such as the need to manually set the FWHM value as well as the anatomical uniformed analysis space and its fixed effects inference. Consequently, the specificity of the ensuring results is increased without losing the sensitivity of the original approach [36].

However, due to that the included studies did not further classify the patients into migraine with aura and migraine without aura groups, except 3 have classified patients into these two phenotypes [18, 20, 21] and 2 stated they included only episodic migraine and chronic migraine [19], and the other included only menstrual migraine and not menstrual migraine [37], we were not able to perform separate meta-analyses on each phenotype. Taken together, the current results suggest that the VBM approach can be a useful method in estimating GM abnormalities in migraine.

In our analysis, we find no definite changes in the reported reduction of GMV in pre-central gyrus [20], left amygdala, Left Parietal Operculum [19], cingulate cortex [21]. Using VBM, JH Kim et al found that migraine patients had significant GMV reductions in the bilateral insula, motor/premotor, prefrontal, cingulate cortex, right posterior parietal cortex, and orbitofrontal cortex. The regions reported here were then recognized as being involved in general pain processing or the response to pain [46-48]. Moreover, such GM changes have also been demonstrated in other forms of chronic pain disorders, including back pain [49, 50] tension-type headache [51] and phantom limb pain [52]. We didn't find the same changes as reported in other studies. Even we set the minimum concentration value of 100 mm³, rather
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than 200 mm³, it is still difficult to find a greater concentration of related brain regions.

However, up to date, the precise mechanism of the reduction of GMV and different intracranial damages in the migraine remain unclear. A few studies have shown that the brain damages maybe related to age, whereas our systematic review also did not find this correlation. A case report showed functional MRI abnormalities in brain stem regions in a subject with migraine with aura. As shown in Table 3 and Figure 1, the reduction of GMV are susceptible to be in the right brain than the left, and it is supported by some studies.

Because of the deficiency of the included studies, we could not make the regression analysis to evaluate the effects of the drugs on gray matter changes. The notion that structural abnormalities of specific CNS regions might contribute to characterizing the different headache conditions, differentiate their clinical manifestations and guide therapeutic interventions has been postulated by several authors [6, 22, 23]. We are not clear that these changes of gray mater are specific for migraine and that if it can differentiate the subtypes of migraine including migraine with aura, migraine without aura, chronic tension type headache etc. In addition, we cannot predict the development of migraine. Therefore, it needs more profound and longitudinal on a group of homogeneous patients should be conducted in the future to confirm these findings.

Figure 1. ALE map investigating differences in GMV between Migraine patients and HC. Key: Significant clusters were overlain onto an MRlcron template for Windows for display purposes only. GMV: gray matter volume; HC: healthy control.
Nevertheless, in the present study, there were several limitations that could have affected the accuracy of the results. Firstly, the meta-analysis is subject to publication bias because unpublished international studies were not included and the studies were limited to those published in English, and the number of included studies was small. Second, the heterogeneity of the methodologies in the VBM studies, such as the different preprocessing protocols (traditional or optimized), smoothing kernels, and statistical thresholding methods, could not be entirely ruled out. Third, the voxel-wise meta-analysis was based on the pooling stereotactic coordinates with significant difference, rather than on raw data from the included studies, which may have led to less accurate results. Fourth, although this new version of the ALE accommodates the sample size of each includes study, it fails to take into account the different statistical parameters of each cluster (e.g., z scores and cluster size) in each study. Fifth, clinical variables, such as symptom dimensions, medication status and co-morbidity status, were not considered in this analysis. Sixth, a correlation analysis between GMV reduction and disease duration failed because the relative data were not available in some studies. Seventh and last, the analysis of GMV increase in migraine patients was not successfully performed because only two studies detected it. However, the fact that almost all of the studies contributed to the results argues in favor of the robustness of our findings despite the clinical heterogeneity of the study populations.

**Conclusion**

Whole-brain VBM studies identified consistent widespread GMV reduction in migraine, specifically in the Middle frontal cortex (BA6, 9), Inferior frontal cortex (BA44). These changes of GMV may indicate the mechanisms of the associated symptoms such as cognitive dysfunction, emotion problems and autonomic dysfunction. But whether this is the characteristics of the subtypes of migraine or can distinguish the types of migraine or primary headache, further studies examining larger samples may better elucidate the changes related to the illness and highlight its pathological mechanism.

**Disclosure of conflict of interest**

None.
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[43] Cauda F, Geda E, Sacco K, D’Agata F, Duca S, Geminiani G. Grey matter abnormality in au-
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