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Grey matter alterations in migraine: A systematic review and meta-analysis

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ABSTRACT

Objectives: To summarize and meta-analyze studies on changes in grey matter (GM) in patients with migraine. We aimed to determine whether there are concordant structural changes in the foci, whether structural changes are concordant with functional changes, and provide further understanding of the anatomy and biology of migraine.

Methods: We searched PubMed and Embase for relevant articles published between January 1985 and November 2015, and examined the references within relevant primary articles. Following exclusion of unsuitable studies, meta-analysis were performed using activation likelihood estimation (ALE).

Results: Eight clinical studies were analyzed for structural changes, containing a total of 390 subjects (191 patients and 199 controls). Five functional studies were enrolled, containing 93 patients and 96 controls. ALE showed that the migraineurs had concordant decreases in the GM volume (GMV) in the bilateral inferior frontal gyri, the right precentral gyrus, the left middle frontal gyrus and the left cingulate gyrus. GMV decreases in right claustrum, left cingulated gyrus, right anterior cingulate, amygdala and left parahippocampal gyrus are related to estimated frequency of headache attack. Activation was found in the somatosensory, cingulate, limbic lobe, basal ganglia and midbrain in migraine patients.

Conclusion: GM changes in migraineurs may indicate the mechanism of pain processing and associated symptoms. Changes in the frontal gyrus may predispose a person to pain conditions. The limbic regions may be accumulated damage due to the repetitive occurrence of pain-related processes. Increased activation in precentral gyrus and cingulate opposed to GMV decrease might suggest increased effort duo to disorganization of these areas and/or the use of compensatory strategies involving pain processing in migraine. Knowledge of these structural and functional changes may be useful for monitoring disease progression as well as for therapeutic interventions.

1. Introduction

Migraine is a primary headache that is characterized by mostly unilateral pulsating head pain, is aggravated by routine physical activity, and is associated with nausea and/or photophobia and phonophobia (Headache Classification Committee of the International Headache, 2013). Migraine may be accompanied by a variety of autonomic, cognitive, and emotional disturbances (Grassini and Nordin, 2015). Epidemiological studies have documented its high prevalence and high socioeconomic and personal impact. Migraine has a 1-year prevalence of 14% in the general population (Vos et al., 2012) and 9.3% in China (Yu et al., 2012). It was ranked as the sixth greatest cause of disability worldwide in the Global Burden of Disease Survey 2013 (2015). It is generally believed that migraine is abnormal brain function that depends on the activation and sensitization of the trigeminovascular pathway (Borsook and Burstein, 2012; Noseda and Burstein, 2013). Cortical spreading depression (CSD) is the electrophysiological correlate of migraine aura (Ferrari et al., 2015; Pietrobon and Moskowitz, 2013). Questions remain, however, concerning the mechanisms of initiation, continuation, and termination of migraine.

Neuroimaging has led to advances in the understanding of primary headache mechanisms, and to better identification of the causes of headache, as well as the structures that are responsible for initiation of the pain. Co-localization of structural changes (i.e., an increase in voxel-based morphometry [VBM]) as well as changes in localized brain activity characterized using positron emission tomography (PET) have been found in the same area of the brain (hypothalamus) in cluster headache patients (May et al., 1999). Hypothalamus is undoubtedly crucial for the pathogenesis of the trigeminal autonomic syndromes, so anatomical co-localization of functional and structural changes (especially increase in GM) raises the possibility that the observed changes may be causal—as opposed to a consequence—of pain (May, 2009).

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Combined analysis of structural and functional changes in migraine may be urgent to elaborate the pathophysiological mechanism.

Because of the episodic nature and unpleasantness of migraine attacks, imaging during spontaneous migraine has proven difficult. Therefore, most magnetic resonance imaging (MRI) studies of migraine have focused on the migraineurs between attacks, during the so-called interictal phase. In recent years, grey matter (GM) morphology based on MR, particularly VBM, has been carried out on migraineurs. VBM involving statistical voxel-wise testing of the local concentration of GM is a whole-brain method for analysis of automatically pre-processed structural high-resolution MRI data (Draganski and May, 2008). However, not all the studies reported entirely consistent findings. Some researchers have meta-analyzed VBM studies in migraine, but they did not combine them with functional changes and had not taken frequency of migraine attacks into account (Dai et al., 2015; Wenting Hu et al., 2015).

There have been several studies on the functional changes that occur in interictal migraineurs. However, variations like nociceptive, olfactory and visual stimuli in the methods used complicate a meta-analysis of all studies showing brain regions with atypical activation in migraine sufferers (Chen et al., 2015; Schwedt et al., 2015). Interictal cutaneous pain thresholds are lower in migraine patients compared to controls, so we chose articles used nociceptive stimuli for a meta-analysis (Schwedt et al., 2011; Weissman-Fogel et al., 2003). Here, we systematically summarize and meta-analyze the voxel-wise changes and functional changes in GM in patients with migraine. Combined with previously published studies on pain disorders, we aimed to answer the following questions. i) Are there concordant structural changes in the foci (increase or decrease) in migraine? ii) Are these changes concurrent with changes in function? iii) What can be deduced from GM changes in migraine? We describe how these studies have helped our understanding of the anatomy and biology of migraine, discuss their limitations, and propose avenues for future research using MRI to study migraine.

2. Materials and methods

2.1. Search strategy

We searched PubMed and Embase for manuscripts published between January 1985 and November 2015 using the following search terms: ("MRI" OR "magnetic resonance imaging") AND "migraine" AND "structur*" for VBM analysis. Search words: ("fMRI" OR "functional magnetic resonance imaging") AND ("migraine disorders" OR ("migraine" AND "disorders") OR "migraine") were used for functional studies. Literatures were screened from the title, abstract, intensive reading full-text. We limited the search to studies published in the English language and where the subjects were human. We also examined the references of relevant primary articles and review articles to identify studies that may have been missed in the search.

2.2. Inclusion and exclusion criteria

The meta-analysis included only articles (i) that evaluated the association of grey matter changes and migraine based on a case-control or cohort design; (ii) that contained information on the sample sizes, disease conditions; (iii) patients with migraine were diagnosed according to the International Classification of Headache Disorders (ICHD); (iv) reported whole-brain results of changes in stereotactic coordinates; v) nociceptive stimuli (either heat or ammonia) were used for functional studies and (vi) used thresholds for significance corrected for multiple comparisons or uncorrected with special extent thresholds. We excluded the following: a) non-original studies; b) studies in which the field of view was confined to a restricted region of the cortex; c) studies in which the comparisons between patients with migraine and healthy subjects did not include changes in GM; d) comorbidity with other diseases; e) migraine-like syndromes that were secondary to other diseases; f) articles that concerned other types of headache or a special subtype of migraine (like vestibular migraine); g) articles that reported no significant results; h) articles in which there was no healthy control (HC) group or no comparison with HC; i) studies with unspecified VBM analyses; j) grey matter functional changes due to other stimuli (like visual or olfactory) or combined with other tasks or intervention; k) only functional connectivity was conducted; l) resting-state functional studies in migraineurs; m) duplicate articles; and n) case reports. The selection process is shown as a flow chart in Fig. 1.

2.3. Data extraction

The two authors (ZJ and SY) independently extracted data from each study using a predefined data extraction form, any lack of clarity or disagreement was resolved through discussion. The investigators abstracted data from each study to obtain information on author, publication year, sample size, characteristics of the study population (age, gender), types of migraine, disease information and technical details (MRI scanner, region studied, timing, methods and main findings). The coordinates in each study were independently extracted according to the ALE Method.

2.4. Statistical analysis

We used Ginger ALE 2.3.5 (http://www.brainmap.org/) to evaluate the presence of common patterns of GM alterations. Ginger ALE is a BrainMap application that can be used to perform an ALE meta-analysis on coordinates in a Talairach or MNI space. ALE is probably the most widely used algorithm for coordinate-based meta-analyses. The approach treats activation foci reported in neuroimaging studies as spatial probability distributions centered at given coordinates rather than as single points. For each voxel, Ginger ALE estimates the cumulative probabilities that at least one study reports activation for that locus. ALE maps are then obtained by computing the union of activation probabilities for each voxel. Differentiation between true convergence of foci and random clustering is tested using a permutation procedure (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2012). With version 2.0, Ginger ALE switched the ALE methods from fixed effects to random effects, and incorporated variable uncertainty based on the sample size (Eickhoff et al., 2012). A random effects model assumes a higher than chance likelihood of consensus between different experiments, but not in relation to activation variance within each study. During an ALE analysis, each activation focus is modeled as the center of a Gaussian probability distribution, and is used to generate a modeled activation (MA) map for each study. Where we used data that were not expressed in Talairach coordinates, these were transformed into Talairach space using icbm2tal, as implemented in Ginger ALE 2.3.5 (Lancaster et al., 2007). A very conservative threshold of $P < 0.001$ was chosen, and the minimum cluster size was 100 mm^3. All of these steps combined help to control for publication bias with regard to reported foci.

3. Results

Lots of studies have been performed on grey matter (structural or functional) changes in migraine patients, but the results were not consistent and different areas were found in them. After a careful screen, we identified 8 clinical studies that used VBM to assess changes in GM regions in migraineurs and controls, containing a total of 390 subjects (191 patients and 199 controls). The patient group was comprised of 24 men and 167 women, where 155 cases of migraine were without aura and 36 were with aura. The control group comprised 28 men and 171 women. There were 11 subjects diagnosed as chronic migraineurs. The clinical manifestations and technical details of the structural