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GRAY MATTER CORRELATES OF MIGRAINE AND GENDER EFFECT: A META-ANALYSIS OF VOXEL-BASED MORPHOMETRY STUDIES

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Abstract—*Background*: An increasing number of neuroimaging studies have revealed gray matter (GM) anomalies of several brain regions by voxel-based morphometry (VBM) studies in migraineurs. However, not all the studies reported entirely consistent findings. Our aim is to investigate concurrence across VBM studies to help clarify the structural anomalies underpinning this condition. *Methods*: A systematic search of VBM studies of patients with migraine and healthy controls (HC) published in PubMed and Embase databases from January 2000 to March 2014 was conducted. A quantitative meta-analysis of whole-brain VBM studies in patients with migraine compared with HC was performed by means of anisotropic effect size version of signed differential mapping (AES-SDM) software package. *Results*: Nine studies comprising 222 patients with migraine and 230 HC subjects were included in the present study. Compared to HC subjects, the patients group showed consistent decreased GM in the posterior insular-opercular regions, the prefrontal cortex, and the anterior cingulate cortex. Results remained largely unchanged in the following jackknife sensitivity analyses. Meta-regression analysis showed that a higher percentage of females in the patient sample was associated with decreased GM in the right dorsolateral prefrontal cortex. *Conclusions*: This is the first quantitative whole-brain VBM meta-analysis in migraine showing strong evidence of brain GM anomalies within the pain-processing neural network. Further longitudinal investigations are needed to determine whether these structural anomalies are reversible with effective treatment on migraine.

Key words: voxel-based morphometry, migraine, signed differential mapping, gray matter, meta-analysis.

INTRODUCTION

Migraine is a very common disorder, affecting millions of people at high cost in the world (Blumenfeld et al., 2011). Migraine is characterized by recurrent unilateral headaches accompanied by nausea, vomiting, photophobia and phonophobia (Headache Classification Subcommittee of the International Headache Society, 2004). Traditionally, migraine is conceptualized as a neurovascular disorder, but recent advances in several research areas have provided strong evidence for the involvement of neural network anomalies in the pathophysiology of migraine. In particular, brain imaging studies have revealed functional anomalies in a distributed pain network implicated in the pathophysiology of migraine (Maizels et al., 2012; Vecchia and Pietrobon, 2012). These regions involved are about the supraspinal nociceptive processing comprising the periaqueductal gray (PAG) and limbic system including the anterior cingulate cortex (ACC), amygdala, insula, orbitofrontal cortex (OFC) and prefrontal cortex (PFC), and the hypothalamus (Maizels et al., 2012). Anomalies in these areas are conceptualized as a consequence of brain functional and structural plasticity that is correlated with the central sensitization (May, 2011; Seifert and Maihofner, 2011; Vecchia and Pietrobon, 2012). The majority of migraine patients are female, suggesting that female hormones might play an important role in the pathophysiology of the disorder (Shyti et al., 2011; Borsook et al., 2014). However, the brain structural alternations underlying the pathophysiology remains incompletely understood.

Modern imaging technologies have made tremendous progress in detecting the structural and functional brain anomalies in migraine (Maizels et al., 2012; Lakhan et al., 2013). Voxel-based morphometry (VBM) is a magnetic resonance imaging (MRI) analytical technique that allows voxel-wise comparisons of the local density or volume of gray matter (GM) and white matter (WM) between groups (Ashburner and Friston, 2000). Compared with the manual method of drawing regions of interest (ROI) to

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Abbreviations: ACC, anterior cingulate cortex; AES-SDM, anisotropic effect size version of signed differential mapping; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; GM, gray matter; HC, healthy controls; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; ROI, regions of interest; SDM, signed differential mapping; VBM, voxel-based morphometry.

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measure the volume of the brain structures, VBM is a hypothesis-free and time-efficient tool to quantify structural differences over the whole-brain *in vivo* (Ashburner and Friston, 2000, 2001). VBM has been widely used to investigate structural changes in neurological and neuropsychiatric disorders in the last decade (Radua and Mataix-Cols, 2009; Via et al., 2011; Pan et al., 2012). With respect to migraine, a number of VBM studies were published that identified GM anomalies in multiple brain regions. However, findings regarding GM alterations were inconsistent across investigations. For example, some studies failed to find any regional GM anomalies (Matharu et al., 2003; Schmidt-Wilcke et al., 2008; Russo et al., 2012b; Tessitore et al., 2013), whereas other studies found widespread GM loss in brain regions (Rocca et al., 2006; Kim et al., 2008; Valfre et al., 2008; Schmitz et al., 2008a,b; Jin et al., 2013; Obermann et al., 2014). These divergencies could be attributed to small and heterogeneous samples of participants as well as substantial methodological differences. Thus, there has been increasing interest in using the meta-analysis approach to identify consistent results. Identifying robust alterations of brain structures may open new avenues in targeting the neural substrates in understanding the pathophysiology of migraine.

A newly developed meta-analytic tool for neuroimaging studies, namely signed differential mapping (SDM) (Radua and Mataix-Cols, 2009; Radua et al., 2012b), has been effectively applied in multiple disorders, such as obsessive-compulsive disorder (Radua and Mataix-Cols, 2009; Radua et al., 2014a), bipolar disorder (Bora et al., 2010), and others (Via et al., 2011; Pan et al., 2012; Radua et al., 2012a). The SDM method has been updated to the new version called anisotropic effect size version of signed differential mapping (AES-SDM) (Radua et al., 2014b). SDM was built and improved to incorporate the positive features of existing peak-probability methods, such as anatomical likelihood estimation (ALE) and multilevel kernel density analysis (MKDA) (Radua and Mataix-Cols, 2009; Radua et al., 2014b). AES-SDM combines both peak coordinates and statistical parametric maps. In addition, it employs anisotropic kernels during the recreation of effect size maps in order to account for the anisotropy in the spatial covariance, thus allowing more exhaustive and accurate meta-analyses (Radua et al., 2012b, 2014b). To date, no such quantitative meta-analysis of VBM studies on migraine has been conducted. Therefore, the present work aims at voxel-wisely meta-analyzing the GM changes in migraine using AES-SDM (Radua et al., 2014b). In addition, we intended to explore the effect of clinical variables (i.e., age, gender, disease duration, symptom severity, attack frequency) on the GM alternations in migraine if possible.

EXPERIMENTAL PROCEDURES

Data sources and study selection

Systematic and comprehensive searches were performed in PubMed and Embase database from January 2000 to March 2014 using a combination of keywords (‘‘voxel*’’ or ‘‘VBM’’ or ‘‘morphometry’’ or ‘‘gray matter’’) and migraine. The reference lists of the included studies and relevant scholarly reviews were then searched for additional studies. Studies were considered for inclusion if the following conditions were satisfied: (1) VBM (GM density or volume) comparison of adult patients with migraine *vs*. healthy controls (HC) was conducted; (2) Whole-brain results in three-dimensional coordinates (*x*, *y*, *z*) of changes in standard stereotactic space (Talairach or MNI) were reported; (3) Thresholds for significance corrected for multiple comparisons or uncorrected with spatial extent thresholds were used; and (4) Studies were published in English with peer review. In such cases, the publication with the largest group size and comprehensive information needed was selected if the patient-group data overlapped with the inter-subgroups in one study or with another study. The studies were excluded if they suffer from at least one of the following deficiencies: (1) studies that sufficient data for the meta-analysis could not be obtained from the original article or after contacting the authors; (2) studies with fewer than nine subjects in either the patients group or the HC group; (3) studies using the ROI methods. Study selection and data extraction were performed in a standardized form by two authors (ZY. Dai and JG. Zhong) and any disagreements were assessed by the third author (HC. Shi). The majority opinion was used for final analysis. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed in our study (Moher et al., 2009) (Fig. 1).

Meta-analysis of VBM studies

Regional differences in GM changes between migraineurs and the HC subjects were analyzed using the anisotropic effect size version of signed differential mapping (AES-SDM) software package (www.sdmproject.com), which employed a voxel-based meta-analytic approach that is based on, and improves on, other existing methods (Radua and Mataix-Cols, 2009; Radua et al., 2012b, 2014b).

SDM methods have been described in detail elsewhere (Radua and Mataix-Cols, 2009; Radua et al., 2012b, 2014b) and are briefly summarized here. First, peak coordinates and effect-sizes (derived from e.g. *t*-values) of GM differences between patients and controls were extracted from each data set. Second, a standard MNI map of the differences in GM was separately recreated for each study by means of an anisotropic Gaussian kernel, which assigns higher effect sizes to the voxels more correlated with peaks. This anisotropic kernel has been found to optimize the recreation of the effect-size maps while at the same time it is robust because it does not depend on a full width at half maximum (Radua et al., 2014b). Third, a map of the effect size variance was derived for each study from its map of effect size and its samples' sizes. Fourth, the mean map was obtained by voxel-wise calculation of the random-effects mean of the study maps, weighted by the sample size and variance of each study and the between-study heterogeneity.