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Review

Symptomatic Migraine Patients: A Systematic Review and Meta-Analysis Protocol on Functional Connectivity and Regional Homogeneity Alterations

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ABSTRACT

Goal: A large body of functional magnetic resonance imaging (fMRI) research has used functional connectivity (FC) and regional homogeneity (ReHo) measures to investigate how migraineurs' brains work. Nevertheless, the results of these investigations are sometimes contradictory. We will conduct a comprehensive literature review and meta-analysis to find commonalities in the findings of functional alterations in the brains of migraine sufferers and to outline possible avenues for further research. The methodology involves two researchers working separately to search all articles published between the beginning of the databases (i.e., Medline, Cochrane Library, PubMed, and Web of Science) up to June 1, 2021. If there is a dispute, it may be addressed and resolution reached by consulting with a third investigator. Afterwards, an ALE random-effects model will be used to conduct a coordinate-based meta-analysis. This meta-analysis will provide light on the regions of the brain that are changed in migraine sufferers, namely in the areas of cerebral FC and ReHo. Based on the existing literature, this study will uncover functional abnormalities in the brains of migraine sufferers, drawing conclusions and outlining possible directions for future research.

Keywords
Functional magnetic resonance imaging; Neuroimaging; Meta-analysis; Protocol; Migraine.

INTRODUCTION

Recurrent, unilateral, pulsing headaches ranging in severity from mild to severe are hallmarks of migraine, an idiopathic illness. Photophobia, nausea, vomiting, and smell sensitivity are common symptoms of this disorder, and they tend to become worse when you exercise or are around certain environmental elements [1]. According to the 2017 Global Burden of Disease Study, around 15% of adults suffer from migraines.

Globally, and that the female-to-male prevalence rate is around 3:1 [2]. One of the leading causes of neurologic impairment, migraine has imposed heavy costs on individuals and society at large [2]. It is still unclear what causes migraines, while theories involving the trigemino-vascular system and cortical spreading depression (CSD) have been advanced [3, 4].

Evidence suggesting migraine sufferers have changed white matter (WM) or gray matter (GM) volumes has been mounting over the last few decades, thanks to advancements in magnetic resonance imaging (MRI) [5, 6]. Using two metrics—regional homogeneity (ReHo) and functional connectivity (FC)—resting-state functional magnetic resonance imaging (rs-fMRI) may identify functional abnormalities in the brains of migraine sufferers. This technique is based on blood oxygenation level-dependent (BOLD) data.

As a data-driven approach, ReHo determines how comparable the BOLD signals are by comparing the activity of individual voxels to that of their nearby neighbors when they are at rest [7]. Several disorders, including tension-type headache, idiopathic trigeminal neuralgia, chronic shoulder pain, bipolar disorder, and schizophrenia, have been studied using this technique to examine changes in brain function [8–12]. Multiple rs-fMRI studies have demonstrated that compared to healthy controls (HC), migraine patients' ReHo values are lower in the ACC, putamen, cerebellum, and posterior cingulate cortex (PCC), and higher in the thalamus, insula, and central gyrus

[13–18].

A seed or ROI's signal time-course may be determined by connecting it with voxels throughout the complete brain, allowing one to estimate the FC across the brain [19]. However, the statistical power and ease of interpretation of the seed-based analysis are much higher. At the same time, several neuroimaging investigations have shown that migraine sufferers have significant alterations in FC. People who suffer from migraines tend to have higher FC values in some brain regions, such as the hypothalamus, temporal lobe, insular cortex, and amygdala, and lower values in others, including the prefrontal and anterior cingulate, superior frontal gyrus, and temporal pole [20-26]. Migraine sufferers' changed FC regions are scattered over several brain regions, with few consistently summarized areas.

Acute attack symptoms may differentiate between the interictal and ictal phases of migraine, but when a migraine starts, no one knows for sure, and MRI scans aren't always an option for patients during the acute attack period [27]. The findings of functional magnetic resonance imaging (fMRI) might be influenced by analytical and experimental processes, and this technology has low reproducibility [28].

Finding strong functional changes in the brain using a neuroimaging meta-analysis might help fill the underlying knowledge gap. In the past, several studies and a meta-analysis thoroughly examined the idea that aberrant brain function varies during migraines [29–31]. In migraine sufferers, for example, a meta-analysis indicated that the somatosensory cortex, cingulate cortex, and fMRI studies based on heat or ammonia stimulation

There was activation in the limbic lobe, basal ganglia, and midbrain areas [29]. Another finding from the brain anatomy meta-analysis that relied on voxel-based morphometry (VBM) was that there wasn't enough strong evidence of particular structural alterations in the brain that were consistently linked to migraine [32].

In conclusion, it is clear that functional changes in migraine patients are shown by changes in FC and ReHo. To further our understanding of migraine diseases, we want to conduct a meta-analysis and systematic review of rs-fMRI studies that have been published. In order to explore functional changes in migraine patients, we want to conduct a coordinate-based activation likelihood estimate (ALE) meta-analysis [33]. In light of the existing literature, this study will shed light on the functional alterations in the brains of migraine sufferers, drawing conclusions about these alterations and outlining possible avenues for further research.

Methods And Analysis

This meta-analysis protocol complies with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement, and will have been registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) at the beginning of the study (registration number: CRD42021257300) [34].

Selection criteria Inclusion criteria

The published studies will satisfy the following inclusion criteria:

1. Peer reviewed,
2. Patients diagnosed with migraine according to the International Classification of Headache Disorders (ICHD),
3. Original rs-fMRI studies with ReHo and FC analysis,
4. Compare migraine patients with HC by whole-brain seed-based FC, and
5. Written in English. If the peak coordinates are not provided in the full-text or appendix material, the corresponding authors will be contacted for this information.

Exclusion criteria

The exclusion criteria are as follows:

1. No seed-to-whole-brain FC studies,
2. No comparative HC group,
3. Comorbidity or secondary with other diseases,
4. Other types of migraine (e.g., vestibular migraine),
5. The results of significant effect cluster coordinates missing stringent correction information (e.g., $p < 0.05$),
6. Duplicate studies,
7. Systematic reviews, and
8. Case reports. The detailed screening process is exhibited as a flow diagram in Figure 1.

Search method

The following terms will be searched in the title, abstract, and full-text: "migraine" OR "migraine with aura" OR "migraine without aura" OR "chronic migraine", AND "magnetic resonance imaging" OR "functional magnetic resonance imaging" OR "fMRI". In addition, keywords such as "functional connectivity"

Table 1: Cochrane library search strategy.

OR "regional homogeneity" will be used to screen the articles in the online databases (i.e., PubMed, Web of Science, Cochrane library, and Medline) published from inception to June 1, 2021. The reference list of retrieved studies will also be screened to include more feasible studies (Table 1).

The search strategy will be revised to be suitable for other online databases. MeSH: Medical Subject Headings; fMRI: functional magnetic resonance imaging.

Quality Evaluation

At present, there is no consensus on the quality evaluation of neuroimaging research. In this study, the quality of included studies will be assessed with the Newcastle-Ottawa Quality Assessment Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) as published in previous meta-analyses [35, 36]. (Table 2)

Each item was scored as a 1 or 0 if it fully or partially fitted the bill, respectively. IHS: International headache society; FC: functional connectivity; ROI: region of interest; FWE: family-wise error; FDR: false discovery rate; T: tesla; rs-fMRI: resting-state functional magnetic resonance imaging.

The quality score of each study will be assigned as high (10-12), medium (5-9), or low (0-4). Two investigators will evaluate the qual-

ity of all included studies independently based on this scale. Any disagreement will be resolved by consensus with a third investigator (CZH).

Data Collection

Two investigators (CYL and XQ) will extract data from all included studies. Any uncertainty or disagreement will be settled through consensus with a third investigator (CZH). The extracted data will comprise all authors' names, publication year, sample size, demographic and clinical characteristics of subjects, as well as the main findings. The parameters of the MRI scan, seed point, statistical correction methods, and the main findings will also be included.

ALE Meta-Analysis

The coordinate-based meta-analysis will be carried out using the Brainmap Ginger ALE 3.0.2 program, which can be found at http://www.brainmap. org/. By analyzing each article's spatial uncertainty and convergence of coordinates—which are considered as a tridimensional Gaussian probability distribution—the technique employs the kernel approach. The next step is to analyze the consistency of reported coordinates across studies using a random-effects model of ALE. This will help to compensate for within-experiment and within-group effects.

To create the modeled activation (MA) maps, we will use the reported locations in the space of the Montreal Neurological Institute (MNI). In order to calculate the MA maps, the sample-size-dependent coordinates will undergo Gaussian kernel smoothing.

In order to determine where to activate, we will use a 3D probability distribution with the coordinate MA score as its center. After that, we'll use each MA map to get the union ALE map's likelihood. Using random spatial clustering, we can find out how the activation foci really converge [37, 38].

The multiple comparison correction will be performed using a cluster-level family-wise error (FWE) with a corrected threshold of $p < 0.05$ and an uncorrected threshold of $p < 0.001$ for the first cluster. The permutation tests will be repeated 5,000 times [37]. By using cluster-level FWE thresholding, we may achieve a balance between sensitivity and specificity. The Ginger ALE program will be used to convert the Talairach coordinates to MNI coordinates.

A meta-regression or subgroup study

Patients will be categorized into subgroups based on factors such as the length of the condition, the frequency of episodes, the type of migraine (chronic, with or without aura), the age or gender of the patients, and the trial procedures [33, 39]. We will also examine the possibility of heterogeneity in the meta-analysis.

Analysis of sensitivity

Using the leave-one-out technique, we will do a sensitivity analysis to assess whether the findings can be replicated. With the exception of one research, all other trials will undergo the same examination. The procedure will be repeated after removing another research. This method's strength lies in its capacity to assess the consistency of meta-analysis results while excluding the impact of individual outlier research. The findings are now more credible and repeatable thanks to the sensitivity analysis.

Presentation of findings

Following the guidelines laid forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, the findings will be provided. In addition, the study selection flow diagram will be shown [40]. Data will be presented in tables that detail the participants' demographics, clinical features, and inclusion/exclusion criteria as well as the factors that were considered. Visuals and tabular data will showcase the outcomes of the ALE. Additional information on the procedures may be found in the appendices. Included studies' quality and bias assessments will be shown.

Conclusion

Objective and quantitative tools (activation likelihood estimate) will be used in this study. The research on migraine will be comprehensively reviewed and evaluated with a customized checklist. Meanwhile, several metrics of fMRI will be combined to perform a coordinate-based meta-analysis, identify robust brain functional changes of migraine and to describe potential future direction.

Limitation

A limitation is the inconsistency in pre-processing procedures of fMRI data across all included studies, and the exclusion of unpublished research may cause potential biases.

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