

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

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Submitted: 08 Feb 2022; Accepted: 14 Feb 2022; Published: 25 Feb 2022

Citation: Yu-Ling Cui, Qiang Xu, Yu-Ting Li, Yang-Ming Zhang, Mr. Jing-Ting Sun, Ze-Yang Li, Min-Hua Ni, Lin-Feng Yan, Guang-Bin Cui, Wen Wang, Zhu-Hong Chen (2022) Functional Connectivity and Regional Homogeneity Alterations in Migraine Patients: A Protocol of Systematic Review and Meta-Analysis. *Adv Mach Lear Art Inte*, 3(1), 33-39.

Abstract

Objective: There are numerous functional magnetic resonance imaging (fMRI) studies examining the cerebral function of migraine patients using regional homogeneity (ReHo) and functional connectivity (FC) measurements. However, these studies generally report inconsistent conclusions. We will perform a systematic review and meta-analysis of this body of literature, aiming to identify consistent conclusions regarding cerebral functional changes in migraine patients and to describe potential future directions.

Methods: Two investigators will independently screen studies published in online databases (i.e., Medline, Cochrane Library, PubMed, and Web of Science) from the database inception to June 1, 2021. By discussing with a third investigator, any disagreement will be resolved and will attain consensus. A coordinate-based meta-analysis will then be performed with an activation likelihood estimate (ALE) random-effects model.

Results: The cerebral FC and ReHo altered regions in migraine patients will be elucidated in this meta-analysis.

Conclusion: This study will reveal cerebral functional changes of migraine patients based on current literature to identify consistent conclusions and to describe potential future direction.

Keywords: Functional Magnetic Resonance Imaging, Neuroimaging, Meta-Analysis, Protocol, Migraine.

Introduction

Migraine is an idiopathic disorder characterized as recurrent, unilateral, pulsating, moderate-to-severe headaches. This condition is usually accompanied by photophobia, nausea, vomiting, and olfactory sensitivity, which are typically aggravated with physical activity or environment factors [1]. The Global Burden of Disease Study 2017 showed that migraine roughly affects 15% of adult's

world widely and that the prevalence rate of female-to-male is around 3:1 [2]. Migraine has caused significant individual and social burdens, and is considered one of the most important factors for neurologic disability [2]. The theory of the trigemino-vascular system and cortical spreading depression (CSD) are implicated in migraine, but the underlying mechanisms remain elusive [3, 4].

With the development of magnetic resonance imaging (MRI) in the past decades, increasing evidence has revealed that either the white matter (WM) or gray matter (GM) volumes are altered in migraine patients [5, 6]. Resting-state functional MRI (rs-fMRI) is based on blood oxygenation level-dependent (BOLD) signals and detects cerebral functional changes in migraine patients in the context of two metrics, regional homogeneity (ReHo) and functional connectivity (FC).

ReHo, which is a data-driven method, calculates the similarity of the BOLD signals in a voxel-wise way that compares the activity of a given voxel to that of its nearest neighbors during the resting state [7]. This measurement has been widely used to discuss cerebral functional changes in several diseases, such as tension-type headache, idiopathic trigeminal neuralgia, chronic shoulder pain, bipolar disorder, and schizophrenia [8-12]. A number of rs-fMRI studies have showed that, compared with healthy controls (HC), the ReHo values of migraine patients are significantly decreased in the anterior cingulate cortex (ACC), putamen, cerebellum, and posterior cingulate cortex (PCC), and are increased in the thalamus, insula, and central gyrus [13-18].

By extracting the signal time-course from a seed or region of interest (ROI) and correlating it with voxels spanning the whole-brain, the FC across the brain can be estimated [19]. Nevertheless, the seed-based analysis is easier to interpret and has greater statistical power. Meanwhile, many neuroimaging studies have revealed remarkable changes of FC in migraine patients. The FC values of the periaqueductal gray (PAG), hypothalamus, ACC, temporal lobe, insular cortex, and amygdala were increased in migraineurs, while those of the prefrontal and anterior cingulate, superior frontal gyrus, and temporal pole were decreased [20-26]. The altered areas of FC disperse throughout multiple cerebral regions of migraine patients, without many consistently summarized brain regions.

Although interictal and ictal periods of migraine can be distinguished by acute symptoms of attacks, the onset of a migraine is uncertain and patients are often unable to undergo a MRI scan during the acute attack period [27]. Furthermore, functional MRI (fMRI) results can be affected by experimental and analytical procedures, and the repeatability of this method is poor [28].

Using a neuroimaging meta-analysis approach to identify robust functional alterations of the brain may provide avenues to resolving the underlying gap in this field. Formerly, abnormal cerebral function that fluctuates during a migraine has been reported in many studies, and has also been comprehensively analyzed by meta-analysis [29-31]. For instance, for heat or ammonia stimulation-based fMRI analysis in migraine patients, a meta-analysis found that the somatosensory cortex, cingulate cortex,

limbic lobe, basal ganglia and midbrain regions were activated [29]. In addition, a meta-analysis based on brain anatomy using voxel-based morphometry (VBM) indicated a lack of powerful evidence of specific cerebral structural changes that were reliably associated with migraine [32].

Therefore, it can be summarized that FC and ReHo alterations reveal the underlying functional changes of migraine patients. We aim to perform a systematic review and meta-analysis of published rs-fMRI studies to enrich the knowledge about migraine disorders. Thus, we plan to perform a coordinate-based activation likelihood estimate (ALE) meta-analysis to investigate functional alterations in migraine patients [33]. This study will reveal cerebral functional changes of migraine patients based on the current studies to identify consistent conclusions regarding cerebral functional changes in migraine patients and to describe potential future directions.

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.

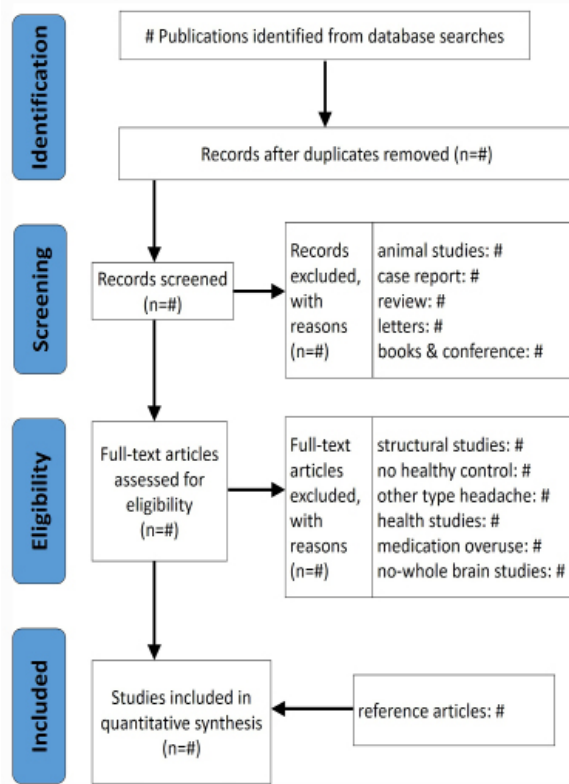


Figure 1. The flow diagram of study screening.

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”

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).

Table 1: Cochrane library search strategy.

#1	[MeSH] migraine
#2	[Title/Abstract/Keyword] migraine or chronic migraine
#3	[MeSH] migraine with aura
#4	[Title/Abstract/Keyword] migraine with aura
#5	[MeSH] migraine without aura
#6	[Title/Abstract/Keyword] migraine without aura
#7	1 or 2 or 3 or 4 or 5 or 6
#8	[Title/Abstract/Keyword] functional connectivity
#9	[Title/Abstract/Keyword] regional homogeneity
#10	8 or 9
#11	[MeSH] magnetic resonance imaging
#12	[Title/Abstract/Keyword] functional magnetic resonance imaging
#13	[Title/Abstract/Keyword] fMRI
#14	11 or 12 or 13
#15	7 and 10 and 14
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)

Table 2: Quality assessment checklist.

Subjects:	
1	Migraine was diagnosed according to the IHS criteria. Demographic data of patients were reported.
2	Healthy controls with medication overuse, psychiatric illness, and other types of headaches were excluded.
3	Age, gender, disease duration, attacks, and comorbidity were reported.
4	Patients with migraine and healthy controls came from the same general population.
5	The sample size of patients with migraine and healthy controls was more than 10.
Imaging data acquisition and analysis:	
6	MRI field strength $\geq 1.5T$.
7	The rs-fMRI studies were analyzed as FC between a seed point and the whole-brain. ROI and a priori regional analysis were excluded.
8	The procedure of imaging data processing and the software were clearly described.
9	Significant coordinates were reported in standard stereotactic space.
Results and conclusions:	
10	Adopted recommended statistics and corrected for multiple comparisons (FWE/FDR/AlphaSim) to achieve significance convergence.
11	The parameters (p, t, or z) of resulting coordinates were indicated.
12	The conclusion was consistent with the results. The limitations were discussed.

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 quality 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 Brainmap Ginger ALE 3.0.2 software (<http://www.brainmap.org/>) will be used to perform the coordinate-based meta-analysis. The algorithm uses the kernel method to evaluate the spatial uncertainty and convergence of coordinates, treated as a tridimensional Gaussian probability distribution, of the included individual articles. Then, a random-effects model of ALE will

be used to assess the consistency of reported coordinates across studies in order to correct for the within-experiment and within-group effects.

The modeled activation (MA) maps will be generated using reported coordinates in the Montreal Neurological Institute (MNI) space. When computing the MA maps, Gaussian kernel smoothing will be applied to coordinates based on the sample size.

The 3D probability distribution centered on the coordinate MA score will be the activation foci. Then, the union probability of the union ALE map will be calculated using individual MA maps. The actual convergence of the activation foci will be determined with random spatial clustering [37, 38]

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 initial cluster will be used for multiple comparison correction, and permutation tests will be repeated 5000 times [37]. The balance between the sensitivity and specificity will be provided with the cluster-level FWE thresholding. Talairach coordinates will be translated to the MNI coordinates using the Ginger ALE software.

Subgroup or meta-regression analysis

When enough studies (>10) are included, the duration of the disease, the frequency of the attacks, the types of migraine with or without aura or chronic migraine, the age or gender of patients, and the methods of the trials will be used to divide patients into different subgroups [33, 39]. The potential heterogeneity of the meta-analysis will also be analyzed.

Sensitivity analysis

To test the replicability of the results, we will perform a sensitivity analysis using the leave-one-out method. An identical analysis will be applied to all remaining studies, with only one study being removed. Then, the process will be repeated with another study being removed. The advantage of this method is that it can evaluate the stability of the meta-analysis outcomes and eradicate the influence from specific outlier studies. Overall, the sensitivity analysis improves the credibility and repeatability of the results.

Results presentation

The results will be presented in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. The flow diagram of study selection will also be shown [40]. The inclusion and exclusion criteria, the included parameters, and the demographic and clinical characteristics of subjects will be shown in tables. The ALE results will be presented in figures and tables. Other details in the methods will be provided in the supplementary materials. The quality and bias assessment of the included studies 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.

Acknowledgement

We would like to thank the authors of all included studies for their excellent work. Our gratitude also goes for Profs. Jin-Lian Li, Liang-Wei Chen and Jun-Ling Zhu from Department of Radiology of Tangdu Hospital for their constructive comments on this study.

Funding

This work was supported by the Hovering Program of Fourth Military Medical University (axjhww to WW), and the Talent Foundation of Tangdu Hospital (2018BJ003 to WW).

Abbreviations

ACC: anterior cingulate cortex
ALE: activation likelihood estimate
BOLD: blood oxygen level dependent
CSD: cortical spreading depression
FC: functional connectivity
fMRI: functional magnetic resonance imaging
FWE: family-wise error
GM: gray matter
HC: health controls
ICHD: International Classification of Headache Disorders
IHS: International Headache Society
MA: modeled activation
MNI: Montreal Neurological Institute
PAG: periaqueductal gray
PCC: posterior cingulate cortex
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
ReHo: regional homogeneity
ROI: region of interest
rs-fMRI: resting-state functional magnetic resonance imaging
WM: white matter.

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