Journal of Neuroimaging

WILEY

JOURNAL OF NEUROIMAGING
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF NEUROIMAGING

REVIEW ARTICLE OPEN ACCESS

Aberrant Spontaneous Low-Frequency Brain Activity in Migraine: A Meta-Analysis of Resting-State fMRI Studies

Qiuyi Chen | Yuhan Liu | Xin Yang | Bin Li | Lu Liu

Department of Acupuncture and Moxibustion, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing Key Laboratory of Acupuncture Neuromodulation, Beijing, China

Correspondence: Bin Li (libin@bjzhongyi.com) | Lu Liu (lululalavictor1985@126.com)

Received: 18 February 2025 | **Revised:** 25 March 2025 | **Accepted:** 7 April 2025

Funding: This study was supported by the China National Natural Science Foundation (82374575), the Beijing Natural Science Foundation (7232270), the Capital's Funds for Health Improvement and Research (CFH2024-2–2235), the Outstanding Young Talents Program of Capital Medial University (B2207), and the Beijing Hospital Management Center "Peak" Talent Training Plan Team (DFL20241001).

Keywords: amplitude of low-frequency fluctuations | functional MRI | migraine | neuropathology | Seed-based d Mapping

ABSTRACT

Background and Purpose: Resting-state functional MRI has revealed abnormal brain activity in patients with migraine, though findings have been inconsistent. This meta-analysis utilized Seed-based d Mapping to assess variations in amplitude of low-frequency fluctuations (ALFF) and fractional amplitude of low-frequency fluctuations (fALFF). The aim was to identify common brain regions with altered spontaneous brain activity in migraine patients.

Methods: A systematic search was conducted in PubMed, Web of Science, and Embase for studies published up to August 2023, comparing spontaneous low-frequency brain activity between migraine patients and healthy controls (HCs). Jackknife sensitivity, heterogeneity, publication bias, and meta-regression analyses were performed to ensure the robustness and reliability of our findings.

Results: Nine studies, including 708 migraine patients and HCs, were included in the analysis. Applying a highly conservative family-wise error rate correction, no significant findings were observed. However, when a less conservative threshold was used, migraine patients exhibited increased ALFF/fALFF in the left anterior thalamus and the corticospinal tract but showed decreased values in the right middle frontal gyrus. Jackknife sensitivity analysis confirmed the reproducibility of these results, while heterogeneity analysis revealed significant variability across studies, likely due to differences in study design and patient populations.

Conclusions: This meta-analysis provides a comprehensive synthesis of neuroimaging evidence, linking migraine to abnormal spontaneous brain activity in regions associated with pain processing and nociceptive emotional modulation. These findings enhance our understanding of migraine pathophysiology and highlight potential targets for neuromodulation therapies, offering new directions for future research and clinical interventions.

Qiuyi Chen and Yuhan Liu contributed equally to this work.

1 | Introduction

Migraine is a recurrent neurological disorder characterized by pain, photophobia, phonophobia, vomiting, or nausea [1]. The Global Burden of Disease 2021 study estimates that migraine affects approximately 14% of the global population, translating to around 1.16 billion prevalent cases [2]. The World Health Organization ranks migraine attacks among the highest disability categories, contributing to 43.4 million years lived with disability (YLDs), making it the third leading cause of YLDs worldwide [2, 3]. In addition, migraines impose a significant socioeconomic burden. MRI has long been used to identify biomarkers that distinguish migraine from healthy individuals or other headaches types, as well as to identify neuroimaging features [4]. Although the pathology and physiology of migraine are not fully understood, impaired brain structures and altered brain functions have been shown to play critical roles in its development [5, 6].

Amplitude and fractional amplitude of low-frequency fluctuations (ALFF/fALFF) are indicators of spontaneous neuronal activities in specific brain regions and have been increasingly applied in neuroimaging studies to explore the potential pathological and physiological mechanisms of various diseases, including migraine [7]. The ALFF/fALFF technique measures spontaneous brain activity with high specificity and sensitivity [8, 9], capturing resting-state brain function changes in migraine patients and identifying abnormal activity related to pain processing and emotion regulation [10, 11]. This technique is particularly well-suited for large-scale analysis and cross-study comparisons, making it a widely used neuroimaging indicator [12].

Previous resting-state functional MRI studies in migraine patients have revealed aberrant brain activity primarily in pain-related regions (e.g., insula, hypothalamus) and pain-processing regions (e.g., anterior cingulate cortex, medial prefrontal cortex) [13–16]. However, results from functional imaging research often show high heterogeneity and poor reproducibility [17]. Small sample sizes in individual studies as well as heterogeneity in baseline data (e.g., age, gender, regions, duration, and migraine subtypes) may contribute to variations across published reports.

Therefore, our study aims to identify common brain regions with altered spontaneous brain activity through a meta-analysis of published articles. We systematically reviewed and synthesized fMRI studies on migraine to identify robust loci of altered spontaneous brain activity across nine neuroimaging studies. To this end, we employed Seed-based d Mapping with Permutation of Subject Images (SDM-PSI), a statistical technique to identify spatially consistent fMRI changes in migraine patient [18]. By analyzing a large body of fMRI literature on migraine, our meta-analysis aims to enhance understanding of its central mechanisms and identify potential biomarkers for migraine diagnosis and treatment.

2 | Methods

2.1 | Literature Search Strategy

We conducted a literature search in the PubMed, Web of Science, and Embase databases for articles published by August 2023 without restriction on regions or publication types. The search terms used included "migraine" or "headache" and "neuroimaging" or "fMRI" or "functional magnetic resonance imaging" or "amplitude of low-frequency fluctuations" or "ALFF" or "fractional amplitude of low-frequency fluctuations." Additionally, we manually searched registration websites and reference lists of included studies and relevant systematic reviews to identify other qualifying research. Two authors (Q.Y.C. and Y.H.L.) independently assessed the articles and resolved any disputes through consensus, with a third senior investigator (L.L.) available for adjudication if necessary. This meta-analysis was registered in PROSPERO (No. CRD42022347879).

2.2 | Selection Criteria and Data Extraction

Studies were included if they met the following inclusion criteria: (1) involved patients diagnosed with migraine; (2) conducted whole-brain voxel-level ALFF/fALFF analysis comparing migraine patients and healthy controls (HCs); (3) reported results registered in a standard space (Montreal Neurological Institute [MNI] or Talairach coordinates); (4) applied a statistical threshold for declaring statistical significance that was either corrected for multiple comparisons or based on an uncorrected intensity threshold; (5) included studies with larger sample sizes, even if the data overlapped with those of previously published studies; and (6) were original research articles published in English-language journals. The exclusion criteria were as follows: (1) patients with tension-type headache, cluster headache, other primary headaches, or secondary headache; (2) animal experiments; (3) studies where either the migraine or control group had fewer than seven participants [19]; and (4) only baseline data were included in longitudinal studies. If the information provided by the included studies was insufficient, the corresponding author would be contacted via email. Our study adhered to the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [20]. The process of literature search and selection is shown in Figure 1.

2.3 | Data Extraction

After excluding ineligible records, two authors (Q.Y.C. and X.Y.) independently extracted the relevant information and outcome data from the included studies. Any disagreements were resolved by consensus. The following information was extracted: demographics (e.g., sample size, average age, gender) and baseline characteristics (e.g., migraine types, migraine duration, visual analogue scale [VAS], anxiety and depression scale, medication status), diagnostic criteria, interventions, imaging methodology, peak coordinates, and *t*-values or other equivalents. Studies reporting null results were not included in the statistical analysis; for these, we used the notation "not reported (NR)."

2.4 | Quality Assessment

Currently, there are no official guidelines for evaluating the quality of fMRI research. Therefore, in our meta-analysis, we based the quality assessment on the fMRI evaluation criteria outlined by Wolters et al. [21], which consists of nine

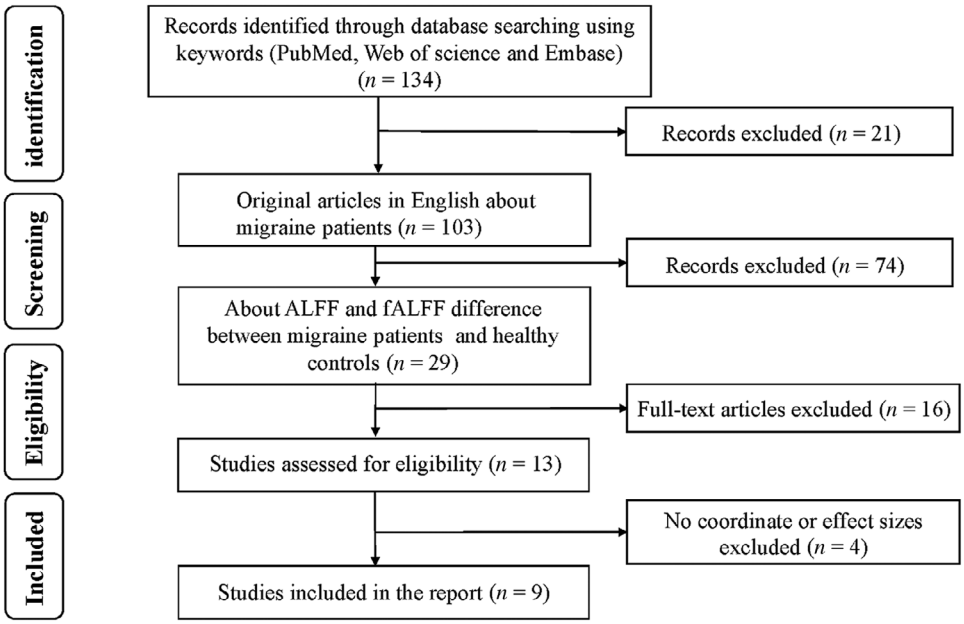

FIGURE 1 | Flow diagram of literature search and selection process. ALFF, amplitude of low-frequency fluctuations; fALFF, fractional amplitude of low frequency fluctuations; *n*, number.

domains: (1) Inclusion and exclusion procedure and patient demographics; (2) fMRI procedure and patient instructions; (3) Spatial normalization method; (4) Determination of the regions of interest; (5) Reproducibility of the analysis; (6) Statistical tests used to substantiate the results; (7) Correction for the multiple testing problem; (8) Figures and tables; and (9) Quality control measures. Each study was evaluated using a checklist, where each domain was rated 0, 0.5, or 1 point, with a maximum score of 9. Studies were classified as good (≥7.5), fair (4–7.5), or poor (≤4) in quality. These cutoffs were carefully chosen to ensure clear differentiation between high, moderate, and low-quality studies and were applied consistently across all neuroimaging studies. The assessments were independently conducted by two authors (Q.Y.C. and Y.H.L.) with discrepancies resolved by a third author (L.L.), who made the final decision.

2.5 | Data Analysis

2.5.1 | Voxel-Based Meta-Analysis

SDM-PSI is a statistical technique that uses the peak coordinates and corresponding effect sizes reported in the original study as data sources while also considering other key factors (e.g., sample size) that may influence the results of the study [22]. Our meta-analysis employed the SDM software package (version 6.21, the SDM Project, London, UK, http://www.sdmproject.com) to analyze spontaneous brain activity alterations in low-frequency fluctuation in migraine patients. The SDM technique has been validated and explained in previous studies [23, 24]. First, we extracted the peak coordinates and corresponding effect size for statistically significant region. These values were then converted using the SDM online transformation tool (https://www.sdmproject.com/utilities/?show=Statistics) to convert a *z*- or *p*-value to a *t*-value. Additionally, Talairach coordinates were transformed into MNI coordinates. Next, for each study, a standard MNI map of ALFF/fALFF differences was created using an anisotropic Gaussian kernel [24, 25]. The SDM software then generated a mean map through voxel-wise calculation within a random-effects model, combining the maps of all included studies while accounting for sample size, intrastudy variability, and heterogeneity [26]. The default SDM kernel size and thresholds (parameter settings: full width at half maximum = 20 mm, uncorrected voxel-level p <0.005, peak height Z >1, cluster extent >10 voxels) were applied to best balance false positives and negatives.

2.5.2 | Jackknife Sensitivity Analysis

We performed a jackknife sensitivity analysis to assess the robustness of our findings. This approach systematically removes one study at a time to ensure that no single study biases the combined results, and recalculates the stability of the remaining studies. If a brain region remains significant across all studies, the finding is considered highly replicable.

2.5.3 | Analysis of Heterogeneity and Publication Bias

Heterogeneity among studies was assessed using the random-effects model and the Q-statistic to evaluate the variability in the results. To identify potential publication bias, we conducted Egger's test and generated funnel plots based on values extracted from statistically significant peaks. All analyses were carried out using Stata/SE software (version 12.0, StataCorp LLC, College Station, TX, USA, http://www.stata.com). A p-value <0.05 was considered statistically significant.

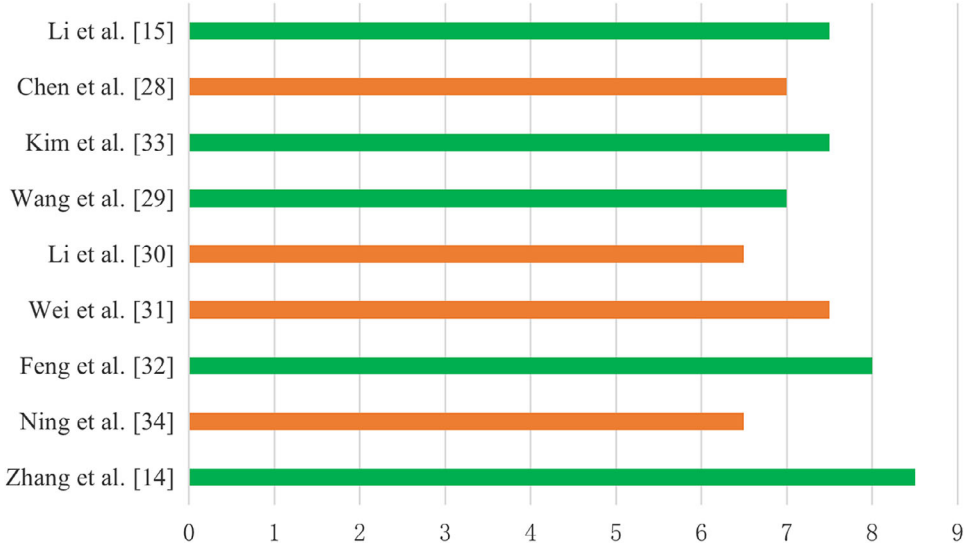

FIGURE 2 | Quality assessment derived from the guidelines of Wolters et al. [21]. Total score was based on nine criteria. For each item, 0, 0.5, or 1 point could be scored. An overall score of ≥7.5 was considered as good (green), 4–7.5 as fair (orange), and ≤4 as poor quality.

2.5.4 | Meta-Regression Analysis

We conducted a meta-regression analysis to examine the relationship between age, migraine duration, VAS score, gender, and the brain regions identified in the meta-analysis. Consistent with previous studies, the meta-regression analysis employed a stringent threshold of $p < 0.0005$ and a cluster extent ≥10 voxels to define statistical significance [27, 28].

3 | Results

3.1 | Included Studies and Sample Characteristics

A total of 134 articles were identified through preliminary screening. After reviewing the title, abstract, and full text, nine articles ultimately met the inclusion criteria [14, 15, 29–35], with a total of 708 samples included in the analysis. The literature selection process is illustrated in Figure 1. Among the nine studies, 388 migraine patients and 318 HCs were included in the meta-analysis. In each study, HCs were matched with migraine patients for age and gender. The quality score of all the studies was not less than 6.5 (Figure 2), indicating that the included studies were of acceptable quality. Table 1 provides a summary of the demographics, baseline characteristics, and imaging methods of the included studies.

3.2 | ALFF/fALFF Differences Among Included Studies

As shown in Figure 3, the voxel meta-analysis revealed both increases and decreases in ALFF/fALFF in the brain regions of migraine patients compared to HCs. Specifically, a significant decrease in ALFF/fALFF was observed in the right middle frontal gyrus, while a significant increase was found in the left anterior thalamic projections and left corticospinal tract in migraine patients. The detailed differences in ALFF/fALFF between migraine patients and HCs are provided in Table 2. These differences were not significant after applying family-wise error rate correction.

3.3 | Jackknife Sensitivity Analysis

The whole-brain jackknife sensitivity analysis demonstrated that the reduction in ALFF/fALFF in the right middle frontal gyrus was highly reproducible, showing consistency across five of the nine datasets. However, the ALFF/fALFF increases in the left anterior thalamic projections and left corticospinal tract were less reproducible, as they were consistent across only four dataset combinations (Table 3).

3.4 | Heterogeneity and Publication Bias

The heterogeneity analysis revealed significant interstudy variability in the ALFF/fALFF alteration in the right middle frontal gyrus, left anterior thalamic projections, and left corticospinal tract ($p < 0.005$) (Table 2). According to the Egger's test (Table 2), no publication bias was detected in the identified significant region of ALFF/fALFF differences in the standard meta-analysis when all datasets were considered.

3.5 | Meta-Regression Analyses

No significant relationship was found between age, migraine duration, gender, or VAS score and ALFF/fALFF in migraine patients. Due to limited data and the use of various inconsistent pain-related scales, we were unable to investigate migraine-specific scales (such as the Headache Impact Test-6 and the Migraine-Specific Quality of Life Questionnaire).

TABLE 1 | Characteristics of low-frequency fluctuation/fractional low-frequency fluctuation studies included in the meta-analysis.

	Sample (female)		Age (years)											
Study	**HC**	**Migraine**	**HC**	**Migraine**	**Migraine types**	**Migraine duration (months)**	**VAS score**	**Anxiety and depression scale**	**Medication (%)**	**Diagnostic criteria**	**Interventions**	**Modality**	**Software**	**fMRI scanner**
Li et al. [15]	42/34	62/48	21.21	21.29	MWoA	66.10	5.46	SDS, SAS	Drug free	ICHD-II	Acupuncture	ALFF	SPM12	3.0T Siemens
Chen et al. [29]	21/13	21/16	30.19 ± 6.30	31.19 ± 6.38	MWoA	44.69 ± 61.13	4.33 ± 1.46	NR	NR	ICHD	NR	ALFF	DPARSF2.3	3.0T Siemens
Kim et al. [34]	31/31	44/44	35.20 ± 9.20	36.20 ± 8.80	MWoA	163.20 ± 69.10	7.50 ± 1.70	NR	100.00	ICHD-III	NR	fALFF	SPM12	3.0T Siemens
Wang et al. [30]	NR	NR	NR	NR	NR	NR	NR	NR	NR	ICHD	NR	fALFF	DPARSF	3.0T GE
Li et al. [31]	43/34	70/56	21.23	21.51	MWoA	63.53	5.48	SDS, SAS	Drug free	ICHD-II	Acupuncture	fALFF	SPM12	3.0T Siemens
Wei et al. [32]	50/44	55/48	37.2 ± 10.28	33.58 ± 10.88	MWoA	86.64 ± 72.12	6.49 ± 1.35	GAD-7	Drug free	ICHD-III	NR	ALFF	SPM12	3.0T Philips
Feng et al. [33]	60/45	60/47	29.25 ± 7.26	31.72 ± 6.65	MWoA	61.50 ± 69.20	4.91 ± 1.66	SDS, SAS	Drug free	ICHD-II	Transcutaneous auricular vagus nerve stimulation	fALFF	SPM12, DPABI 3.0	3.0T Siemens
Ning et al. [35]	16/13	16/13	27.10 ± 4.80	28.30 ± 6.00	MWoA	5.90 ± 3.10	5.40 ± 1.60	NR	NR	ICHD	Acupuncture	ALFF	SPM8, DPARSF	3.0T Siemens
Zhang et al. [14]	31/22	30/22	40.20 ± 10.30	41.00 ± 10.40	MWoA	115.20 ± 81.96	7.20 ± 1.90	NR	NR	ICHD-II	NR	ALFF	SPM12	3.0T Siemens

Note: All the data represent mean ± standard deviation unless otherwise indicated.

Abbreviations: ALFF, amplitude of low-frequency fluctuations; fALFF, fractional amplitude of low-frequency fluctuations; fMRI, functional MRI; GAD-7, seven-item Generalized Anxiety Disorder questionnaire; GE, General Electric; HC, healthy controls; ICHD, International Classification of Headache Disorders; MWoA, migraine without aura; NR, not reported; SAS, self-rating anxiety scale; SDS, self-rating depression scale; SPM, statistical parametric mapping; VAS, visual analogue scale.

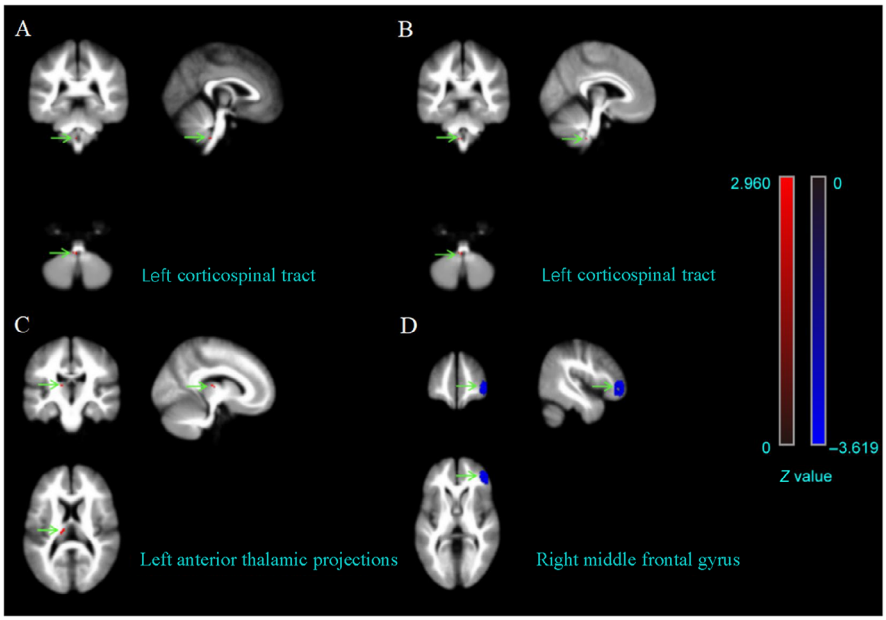

FIGURE 3 | Differences in low-frequency fluctuation (ALFF)/fractional ALFF (fALFF) between migraine patients and healthy controls. The red area (green arrow) highlights increased ALFF/fALFF in the left corticospinal tract (A and B) and left anterior thalamic projections (C) in migraine patients compared to healthy controls. The blue area (green arrow) shows decreased ALFF/fALFF in the right middle frontal gyrus (D) in migraine patients relative to healthy subjects. Red and blue regions represent areas of increased and decreased ALFF/fALFF, respectively, in migraine patients compared to healthy controls. Green arrows indicate clusters where ALFF/fALFF differences were observed between migraine patients and healthy controls. The color bar indicates the maximum and minimum Seed-based d Mapping *Z* values.

TABLE 2 | Clusters of low-frequency fluctuation/fractional low-frequency fluctuation differences in migraine compared to healthy participants.

	Anatomy label	Peak MNI coordinate (*x*, *y*, *z*)	Cluster size (voxels)	SDM *Z*-value	*p*-value	Egger's test (*p*-value)
Decreased ALFF/fALFF	Right middle frontal gyrus, BA 46	44, 50, 2	382	−3.619	0.000147939	0.114
Increased ALFF/fALFF	Left anterior thalamic projections	−12, −20, 12	9	2.960	0.001537621	0.252
	Left corticospinal tract	−2, −36, −50	2	2.666	0.003835618	0.074
	Left corticospinal tract	−6, −34, −50	1	2.577	0.004980922	0.074

Abbreviations: ALFF, amplitude of low-frequency fluctuations; BA, Brodmann area; fALFF, fractional amplitude of low-frequency fluctuations; MNI, Montreal Neurological Institute; SDM, seed-based mapping.

4 | Discussion

This study presents a large-scale data analysis of aberrant low-frequency fluctuation in spontaneous brain activity in migraine patients. Our meta-analysis clarified the most consistent and credible ALFF/fALFF changes associated with migraine. In addition to the voxel-based morphometry meta-analysis, we conducted several supplementary analyses, such as jackknife sensitivity and heterogeneity analyses, to verify the stability of the results. The quantitative meta-analysis using the SDM method revealed consistent differences in whole-brain ALFF/fALFF between migraine patients and HCs. Specifically, migraine patients exhibited increased ALFF/fALFF in the left anterior thalamic and left corticospinal tract while showing decreased ALFF/fALFF in the right middle frontal gyrus. These findings were highly reproducible based on the jackknife sensitivity and heterogeneity analyses. However, the generalizability of our findings may be limited to patients with migraines without aura, as the majority of the studies included in this analysis (eight out of nine) primarily focused on this type of migraine. Several factors contribute to this outcome. First, migraine without aura is the most prevalent type of migraine, with meta-analysis showing an overall migraine prevalence of 11%, of which 8% are migraine without aura and 3% are migraine with aura [36]. Second, the diagnostic criteria for migraine without aura are well-established, and high-quality treatment guidelines exist, enabling standardized research with strong clinical relevance [37, 38]. Finally, migraine without aura carries significant health risks and

TABLE 3 | Jackknife sensitivity analysis.

All studies	Right middle frontal gyrus	Left anterior thalamic projections	Left corticospinal tract
Li et al. [15]			✓
Chen et al. [29]	✓		
Kim et al. [34]		✓	✓
Wang et al. [30]	✓		✓
Liang et al. [31]		✓	✓
Wei et al. [32]	✓		
Feng et al. [33]	✓	✓	
Ning et al. [35]		✓	
Zhang et al. [14]	✓		
Total	5 out of 9	4 out of 9	4 out of 9

numerous complications [39]. Studies have shown that patients with migraine without aura are at risk of developing chronic migraine [40], which is defined by headaches occurring 15 or more days per month, leading to a considerable economic burden on society.

The thalamus plays a key role in the transmission and regulation of sensory and motor information in the peripheral nervous system and various cortical areas, including pain regulation, sleep/wake cycle, consciousness, cognitive functions, and vision [41, 42]. Converging evidence suggests that migraine patients experience increased functional connectivity between the left thalamus and pain-related brain areas, as well as visual cortex [43, 44]. This suggests that migraine patients undergo changes in the functional connectivity of brain regions involved in pain processing and modulation as well as visual perception. These alterations may be linked to functional impairments in pain processing [42]. Our results revealed that the low-frequency fluctuation of spontaneous brain activity in left anterior thalamic was overactivated. Although we can only speculate, this hyperactivation of the left anterior thalamus in migraine patients might be related to an increase in thalamic volume. Notably, changes in thalamic volume are known to predict the transition from episodic to chronic migraine [45].

In addition to the thalamus, our meta-analysis also revealed an increase in low-frequency fluctuation of spontaneous brain activity in the left corticospinal tract. The corticospinal tract, a descending fiber pathway, plays a crucial role in painful awareness [46]. Studies have demonstrated that pain can inhibit corticospinal excitability, which is thought to be an evolutionary adaptation designed to downregulate cortical activity in order to facilitate rapid protective spinal reflexes [47, 48]. The discrepancy between the findings in the literature and those of our meta-analysis might stem from the fact that all patients in the MRI scans were in the intermittent period of migraine attacks, during which the corticospinal tract excitability was not inhibited. Diffusion tensor imaging has shown that both mean diffusion and radial diffusion in the left corticospinal tract are greater in migraine patients [49]. Based on these findings, the increased low-frequency fluctuation in the corticospinal tract observed in our analysis may be associated with impaired white matter integrity. However, future research is needed to clarify the physiological role of the corticospinal tract in migraine and pain disorders. The different roles of the right and left corticospinal tracts in migraine and pain disorders remain unclear.

Furthermore, we found abnormal low-frequency fluctuation in the right middle frontal gyrus, which is now understood to be integral to emotion regulation. Recent functional imaging studies have linked lesions of this area to anxiety and depression [50–52]. Among the nine studies included in our analysis, five did not assess migraine patients using anxiety and depression scale. Contemporary research suggests that long-term migraine sufferers are particularly susceptible to developing anxiety and depression, with abnormal brain function observed in the middle frontal gyrus [13, 53, 54]. In our meta-analysis, we noted a reduction in low-frequency fluctuation of spontaneous brain activity in the right middle frontal gyrus in migraine patients compared to HCs. This finding suggests that functional abnormalities in the middle frontal gyrus in migraine patients may contribute to impaired emotional regulation.

This quantitative meta-analysis investigates the abnormal low-frequency fluctuation in spontaneous brain activity between migraine patients and HCs. Previous voxel-based morphometry meta-analyses on anatomical changes have reported varied findings. Dai et al. and Jia et al. observed decreased gray matter volume in the posterior insular–opercular regions, the prefrontal cortex, the left middle frontal gyrus, and the cingulate cortex when compared to HCs [6, 55]. However, Masson et al. found nonsignificant results [56]. Interestingly, some studies have reported significant reduction in structures of the middle frontal cortex in migraine patients, which overlap with some of the regions identified in our analysis [6, 57]. This suggests the possibility of functional and structural abnormalities in the right middle frontal cortex. However, whether these structural changes contribute to the abnormal spontaneous brain activity in migraine patients, whether functional deficits lead to these structural changes, or whether there is no correlation between the two remains unclear and requires further investigation. Thus,

the special role of the middle frontal gyrus in the neurologic mechanisms of migraine warrants more research.

Furthermore, a recently published meta-analysis summarized the functional alterations in migraine patients, including ALFF, fALFF, regional homogeneity, PET, and arterial spin labeling. The analysis reported a reduction in brain activity in the visual cortex and cerebellum, alongside increased activity in the thalamus and prefrontal cortex in migraine patients when compared to HCs [58]. The results of its ALFF/fALFF subgroup analysis indicated a significant increase in functional activity in the left thalamus, which partially aligns with our findings. However, due to difference in the algorithm behind the anisotropic effect size SDM and our previous SDM, the results remain somewhat divergent [18].

Previous studies have demonstrated that specific migraine treatments, such as preventive medications, acute pain relievers, or neuromodulation therapies, can induce changes in brain activity, especially in brain regions related to pain processing and emotional modulation [59–61]. In this context, exploring whether treatment status can serve as a modulating factor for observed ALFF/fALFF changes is of great significance. It is crucial to analyze treatment as a covariate because the type and duration of treatment may significantly affect brain activity patterns and, to some extent, explain individual differences in ALFF/fALFF changes [62, 63]. Considering the impact of treatment not only provides more accurate results for research but also helps identify which treatment methods have more pronounced modulating effects on the function of specific brain regions. Future research should focus on incorporating treatment data to understand how various treatment methods modulate brain activity in migraine patients, thereby guiding the development of personalized treatment strategies.

This paper provides a foundation for understanding the central mechanism of migraines, but there are still some limitations. First, our meta-analysis has publication bias, as unpublished and inaccessible studies were not included. Second, our analysis is based on summary data (such as coordinate values from published studies) rather than raw data, which may result in the omission of results with small or moderate effect sizes, potentially reducing the precision of the meta-analysis. Third, some studies did not provide details on the gender ratio, age, and VAS score of the subjects, and the sample size and analysis methods varied across studies. These potential confounding factors may reduce the comparability of the results. Fourth, most studies included in our metanalysis lacked treatment data. This prevents assessing the potential influence of treatment on brain activity changes in migraine patients, affecting the generalizability and interpretation of our findings. Future research that includes treatment data and uses it as a covariate would help clarify its impact on brain activity in migraine patients. Fifth, many subjects self-administered analgesics, and it is unclear whether the changes in brain activity observed in migraine patients are due to the disease itself or medication. Finally, all the included studies were cross-sectional, so the causal relationship between migraine and abnormal low-frequency fluctuation in spontaneous brain activity cannot be determined from this meta-analysis. Longitudinal studies should be conducted in the future to investigate whether these abnormal low-frequency fluctuations can serve as a diagnostic or predictive marker for migraine.

The current meta-analysis using SDM indicates that migraine patients exhibit a wide range of regional spontaneous brain activity abnormalities, mainly involving the anterior thalamic, corticospinal tract, and middle frontal gyrus. These findings provide evidence for the pathological and physiological changes underlying migraine brain dysfunction. Future studies should explore whether the abnormal patterns of low-frequency fluctuation in spontaneous brain activity can be used as early marker for migraine diagnosis or prediction. However, these conclusions remain tentative, as they did not withstand a potentially overly conservative family-wise error correction. In any case, it is evident that further and much larger studies are necessary to more robustly identify the key brain low-frequency fluctuations associated with migraine.

Acknowledgments

We thank all the authors of the included studies. We also express our gratitude to Professor Wendy Zhang for reviewing the language and grammar of our manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. E. Loder and W. Renthal, "Calcitonin Gene-Related Peptide Monoclonal Antibody Treatments for Migraine," *JAMA Internal Medicine* 179 (2019): 421–422.

2. GBD 2021 Nervous System Disorders Collaborators, "Global, Regional, and National Burden of Disorders Affecting the Nervous System, 1990–2021: A Systematic Analysis for the Global Burden of Disease Study 2021," *Lancet Neurology* 2024;23:344–381.

3. J. A. Salomon, T. Vos, D. R. Hogan, et al., "Common Values in Assessing Health Outcomes From Disease and Injury: Disability Weights Measurement Study for the Global Burden of Disease Study 2010," *Lancet* 380 (2012): 2129–2143.

4. R. Messina, C. H. Sudre, D. Y. Wei, et al., "Biomarkers of Migraine and Cluster Headache: Differences and Similarities," *Annals of Neurology* 93 (2023): 729–742.

5. A. May and R. Burstein, "Hypothalamic Regulation of Headache and Migraine," *Cephalalgia* 39 (2019): 1710–1719.

6. Z. Jia and S. Yu, "Grey Matter Alterations in Migraine: A Systematic Review and Meta-Analysis," *NeuroImage: Clinical* 14 (2017): 130–140.

7. R. Qi, L. Zhang, S. Wu, et al., "Altered Resting-State Brain Activity at Functional MR Imaging During the Progression of Hepatic Encephalopathy," *Radiology* 264 (2012): 187–195.

8. Q. H. Zou, C. Z. Zhu, Y. Yang, et al., "An Improved Approach to Detection of Amplitude of Low-Frequency Fluctuation (ALFF) for Resting-State fMRI: Fractional ALFF," *Journal of Neuroscience Methods* 172 (2008): 137–141.

9. X. N. Zuo, A. Di Martino, C. Kelly, et al., "The Oscillating Brain: Complex and Reliable," *Neuroimage* 49 (2010): 1432–1445.

10. H. Zheng, T. Zhai, X. Lin, et al., "The Resting-State Brain Activity Signatures for Addictive Disorders," *Med* 5 (2024): 201.e6–223.e6.

11. X. Xiong, L. Dai, W. Chen, et al., "Dynamics and Concordance Alterations of Regional Brain Function Indices in Vestibular Migraine: A Resting-State fMRI Study," *J Headache Pain* 25, no. 1 (2024): 1.

12. J. Gong, J. Wang, S. Qiu, et al., "Common and Distinct Patterns of Intrinsic Brain Activity Alterations in Major Depression and Bipolar Disorder: Voxel-Based Meta-Analysis," *Translational Psychiatry* 10 (2020): 353.

13. H. L. Wei, J. Li, X. Guo, et al., "Functional Connectivity of the Visual Cortex Differentiates Anxiety Comorbidity From Episodic Migraineurs Without Aura," *Journal of Headache and Pain* 22 (2021): 40.

14. J. Zhang, J. Su, M. Wang, et al., "The Sensorimotor Network Dysfunction in Migraineurs Without Aura: A Resting-State fMRI Study," *Journal of Neurology* 264 (2017): 654–663.

15. Z. Li, F. Zeng, T. Yin, et al., "Acupuncture Modulates the Abnormal Brainstem Activity in Migraine Without Aura Patients," *NeuroImage: Clinical* 15 (2017): 367–375.

16. T. Xue, K. Yuan, P. Cheng, et al., "Alterations of Regional Spontaneous Neuronal Activity and Corresponding Brain Circuit Changes During Resting State in Migraine Without Aura," *NMR in Biomedicine* 26 (2013): 1051–1058.

17. K. Skorobogatykh, W. S. van Hoogstraten, D. Degan, et al., "Functional Connectivity Studies in Migraine: What Have We Learned?," *Journal of Headache and Pain* 20 (2019): 108.

18. J. Radua, K. Rubia, E. J. Canales-Rodríguez, et al., "Anisotropic Kernels for Coordinate-Based Meta-Analyses of Neuroimaging Studies," *Frontiers in Psychiatry* 5 (2014): 13.

19. M. Tahmasian, A. A. Sepehry, F. Samea, et al., "Practical Recommendations to Conduct a Neuroimaging Meta-Analysis for Neuropsychiatric Disorders," *Human Brain Mapping* 40 (2019): 5142–5154.

20. D. F. Stroup, J. A. Berlin, S. C. Morton, et al., "Meta-Analysis of Observational Studies in Epidemiology: A Proposal for Reporting. Meta-Analysis of Observational Studies in Epidemiology (MOOSE) Group," *JAMA* 283 (2000): 2008–2012.

21. A. F. Wolters, S. C. F. van de Weijer, A. F. G. Leentjens, et al., "Resting-State fMRI in Parkinson's Disease Patients With Cognitive Impairment: A Meta-Analysis," *Parkinsonism & Related Disorders* 62 (2019): 16–27.

22. S. J. Iwabuchi, R. Krishnadas, C. Li, et al., "Localized Connectivity in Depression: A Meta-Analysis of Resting State Functional Imaging Studies," *Neuroscience and Biobehavioral Reviews* 51 (2015): 77–86.

23. A. Albajes-Eizagirre, A. Solanes, E. Vieta, et al., "Corrigendum to 'Voxel-Based Meta-Analysis via Permutation of Subject Images (PSI): Theory and Implementation for SDM' [Neuroimage 186 (2019) 174–184/YNIMG_15396]," *Neuroimage* 231 (2021): 117859.

24. A. Albajes-Eizagirre, A. Solanes, M. A. Fullana, et al., "Meta-Analysis of Voxel-Based Neuroimaging Studies Using Seed-Based D Mapping With Permutation of Subject Images (SDM-PSI)," *Journal of Visualized Experiments: JoVE* no. 158 (2019): e59841.

25. X. Xu, Q. Li, Y. Qian, et al., "Genetic Mechanisms Underlying Gray Matter Volume Changes in Patients With Drug-Naive First-Episode Schizophrenia," *Cerebral Cortex* 33 (2023): 2328–2341.

26. M. Sussman, J. Benner, P. Neumann, and J. Menzin, "Cost-Effectiveness Analysis of Erenumab for the Preventive Treatment of Episodic and Chronic Migraine: Results From the US Societal and Payer Perspectives," *Cephalalgia* 38 (2018): 1644–1657.

27. Q. Han, Y. Hou, and H. Shang, "A Voxel-Wise Meta-Analysis of Gray Matter Abnormalities in Essential Tremor," *Frontiers in Neurology* 9 (2018): 495.

28. S. Zhang, W. Wang, X. Su, et al., "White Matter Abnormalities in Anorexia Nervosa: Psychoradiologic Evidence from Meta-Analysis of Diffusion Tensor Imaging Studies Using Tract Based Spatial Statistics," *Frontiers in Neuroscience* 14 (2020): 159.

29. H. Chen, G. Qi, Y. Zhang, et al., "Altered Dynamic Amplitude of Low-Frequency Fluctuations in Patients with Migraine Without Aura," *Frontiers in Human Neuroscience* 15 (2021): 636472.

30. J. J. Wang, X. Chen, S. K. Sah, et al., "Amplitude of Low-Frequency Fluctuation (ALFF) and Fractional ALFF in Migraine Patients: A Resting-State Functional MRI Study," *Clinical Radiology* 71 (2016): 558–564.

31. Z. Li, J. Zhou, S. Cheng, et al., "Cerebral Fractional Amplitude of Low-Frequency Fluctuations May Predict Headache Intensity Improvement Following Acupuncture Treatment in Migraine Patients," *Journal of Traditional Chinese Medicine* 40 (2020): 1041–1051.

32. H. L. Wei, T. Tian, G. P. Zhou, et al., "Disrupted Dynamic Functional Connectivity of the Visual Network in Episodic Patients With Migraine Without Aura," *Neural Plasticity* 2022 (2022): 9941832.

33. M. Feng, Y. Zhang, Z. Wen, et al., "Early Fractional Amplitude of Low Frequency Fluctuation Can Predict the Efficacy of Transcutaneous Auricular Vagus Nerve Stimulation Treatment for Migraine Without Aura," *Frontiers in Molecular Neuroscience* 15 (2022): 778139.

34. Y. E. Kim, M. K. Kim, S. I. Suh, and J. H. Kim, "Altered Trigeminothalamic Spontaneous Low-Frequency Oscillations in Migraine Without Aura: A Resting-State fMRI Study," *BMC Neurology* 21 (2021): 342.

35. Y. Ning, K. Li, Y. Zhang, et al., "Effect of Acupuncture at Zulinqi (GB41) on the Amplitude of Low Frequency Fluctuations in Migraine Without Aura Patients: A Resting-State Functional Magnetic Resonance Imaging Study," *International Journal Clinical and Experimental Medicine* 10 (2017): 3038–3048.

36. A. Onofri, U. Pensato, C. Rosignoli, et al., "Primary Headache Epidemiology in Children and Adolescents: A Systematic Review and Meta-Analysis," *Journal of Headache and Pain* 24 (2023): 8.

37. "Headache Classification Committee of the International Headache Society (IHS) the International Classification of Headache Disorders, 3rd Edition," *Cephalalgia* 2018;38:1–211.

38. M. Ashina, D. C. Buse, H. Ashina, et al., "Migraine: Integrated Approaches to Clinical Management and Emerging Treatments," *Lancet* 397 (2021): 1505–1518.

39. J. Gupta and S. S. Gaurkar, "Migraine: An Underestimated Neurological Condition Affecting Billions," *Cureus* 14 (2022): e28347.

40. M. E. Bigal and R. B. Lipton, "Clinical Course in Migraine: Conceptualizing Migraine Transformation," *Neurology* 71 (2008): 848–855.

41. R. Noseda, M. Jakubowski, V. Kainz, D. Borsook, and R. Burstein, "Cortical Projections of Functionally Identified Thalamic Trigeminovascular Neurons: Implications for Migraine Headache and Its Associated Symptoms," *Journal of Neuroscience* 31 (2011): 14204–14217.

42. S. Younis, A. Hougaard, R. Noseda, and M. Ashina, "Current Understanding of Thalamic Structure and Function in Migraine," *Cephalalgia* 39 (2019): 1675–1682.

43. H. L. Wei, X. Zhou, Y. C. Chen, et al., "Impaired Intrinsic Functional Connectivity Between the Thalamus and Visual Cortex in Migraine Without Aura," *Journal of Headache and Pain* 20 (2019): 116.

44. Z. M. Cao, Y. C. Chen, G. Y. Liu, et al., "Abnormalities of Thalamic Functional Connectivity in Patients With Migraine: A Resting-State fMRI Study," *Pain and Therapy* 11 (2022): 561–574.

45. X. Y. Chen, Z. Y. Chen, Z. Dong, M. Q. Liu, and S.-Y. Yu, "Regional Volume Changes of the Brain in Migraine Chronification," *Neural Regeneration Research* 15 (2020): 1701–1708.

46. I. Tracey and P. W. Mantyh, "The Cerebral Signature for Pain Perception and Its Modulation," *Neuron* 55 (2007): 377–391.

47. C. Fossataro, D. Burin, I. Ronga, et al., "Agent-Dependent Modulation of Corticospinal Excitability During Painful Transcutaneous Electrical Stimulation," *Neuroimage* 217 (2020): 116897.

48. A. Rohel, J. Bouffard, P. Patricio, et al., "The Effect of Experimental Pain on the Excitability of the Corticospinal Tract in Humans: A

Systematic Review and Meta-Analysis," *European Journal of Pain* 25 (2021): 1209–1226.

49. C. D. Chong and T. J. Schwedt, "Migraine Affects White-Matter Tract Integrity: A Diffusion-Tensor Imaging Study," *Cephalalgia* 35 (2015): 1162–1171.

50. P. Zhao, R. Yan, X. Wang, et al., "Reduced Resting State Neural Activity in the Right Orbital Part of Middle Frontal Gyrus in Anxious Depression," *Frontiers in Psychiatry* 10 (2019): 994.

51. J. N. Pannekoek, S. J. van der Werff, P. H. Meens, et al., "Aberrant Resting-State Functional Connectivity in Limbic and Salience Networks in Treatment–Naïve Clinically Depressed Adolescents," *Journal of Child Psychology and Psychiatry and Allied Disciplines* 55 (2014): 1317–1327.

52. L. Yang, A. Xiao, Q. Y. Li, et al., "Hyperintensities of Middle Frontal Gyrus in Patients With Diabetic Optic Neuropathy: A Dynamic Amplitude of Low-Frequency Fluctuation Study," *Aging* 14 (2022): 1336–1350.

53. K. L. Lai, D. M. Niddam, J. L. Fuh, et al., "Cortical Morphological Changes in Chronic Migraine in a Taiwanese Cohort: Surface- and Voxel-Based Analyses," *Cephalalgia* 40 (2020): 575–585.

54. E. Szabó, A. Galambos, N. Kocsel, et al., "Association Between Migraine Frequency and Neural Response to Emotional Faces: An fMRI Study," *NeuroImage: Clinical* 22 (2019): 101790.

55. Z. Dai, J. Zhong, P. Xiao, et al., "Gray Matter Correlates of Migraine and Gender Effect: A Meta-Analysis of Voxel-Based Morphometry Studies," *Neuroscience* 299 (2015): 88–96.

56. R. Masson, G. Demarquay, D. Meunier, et al., "Is Migraine Associated to Brain Anatomical Alterations? New Data and Coordinate-Based Meta-Analysis," *Brain Topography* 34 (2021): 384–401.

57. W. Hu, J. Guo, N. Chen, J. Guo, and L. He, "A Meta-Analysis of Voxel-Based Morphometric Studies on Migraine," *International Journal of Clinical and Experimental Medicine* 8 (2015): 4311–4319.

58. M. Cai, J. Liu, X. Wang, et al., "Spontaneous Brain Activity Abnormalities in Migraine: A Meta-Analysis of Functional Neuroimaging," *Human Brain Mapping* 44 (2023): 571–584.

59. H. Basedau, L. M. Sturm, J. Mehnert, et al., "Migraine Monoclonal Antibodies Against CGRP Change Brain Activity Depending on Ligand or Receptor Target—An fMRI Study," *eLife* 11 (2022): e77146.

60. L. Liu, T. L. Lyu, M. Y. Fu, et al., "Changes in Brain Connectivity Linked to Multisensory Processing of Pain Modulation in Migraine With Acupuncture Treatment," *NeuroImage: Clinical* 36 (2022): 103168.

61. M. Lim, D. J. Kim, T. D. Nascimento, and A. F. DaSilva, "High-Definition tDCS Over Primary Motor Cortex Modulates Brain Signal Variability and Functional Connectivity in Episodic Migraine," *Clinical Neurophysiology* 161 (2024): 101–111.

62. G. Chen, Z. S. Saad, J. C. Britton, D. S. Pine, and R. W. Cox, "Linear Mixed-Effects Modeling Approach to FMRI Group Analysis," *Neuroimage* 73 (2013): 176–190.

63. T. Johnstone, K. S. Ores Walsh, L. L. Greischar, et al., "Motion Correction and the Use of Motion Covariates in Multiple-Subject fMRI Analysis," *Human Brain Mapping* 27 (2006): 779–788.