The brain structure and function abnormalities of migraineurs: A systematic review and neuroimaging meta-analysis

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**Objectives:** To quantitatively summarize the specific changes in brain structure and function in migraine patients.

**Methods:** A literature screening of migraine was conducted from inception to Sept 1, 2022, in PubMed, Web of Science, Cochrane Library, and Medline databases using the keyword combination of "migraine and MRI." Activation likelihood estimation (ALE) was performed to assess the differentiation of functional connectivity (FC), regional homogeneity (ReHo), and gray matter volume (GMV) of migraine patients.

**Results:** Eleven voxel-based morphometry (VBM) studies and 25 resting-state fMRI (rs-fMRI) studies (16 FC and 9 ReHo studies) were included in this study. ALE analysis revealed the ReHo increase in the brainstem and left thalamus, with no decreased area. Neither increased nor decreased regions were detected in FC and GMV of migraine patients.

**Conclusions:** The left thalamus and brainstem were the significantly activated regions of migraine. It is a meaningful insights into the pathophysiology of migraine. The consistent altered brain areas of morphometrical and functional in migraine patients were far from reached based on current studies.

**Keywords**

migraine, magnetic resonance imaging, meta-analysis, systematic review, function, structure

**Introduction**

Migraine is a complex neurological dysfunction characterized by recurrent attacks and pulsating headaches susceptible to physical or environmental factors. Broad clinical symptoms, such as nausea, vomiting, photophobia, and phonophobia etc., have been complained by sufferers, with a headache duration ranging from 4 to 72 h (1). The
estimated 1-year prevalence of migraine is about 15%, with a female-to-male ratio of 3:1 (2).

However, the underlying neuroimaging alterations in migraine patients have previously been studied using functional and structural MRI techniques, with inconsistent conclusions (3–5). Some studies reported the increased functional connectivity (FC) in prefrontal cortex, anterior cingulate cortex (ACC) (6), superior frontal gyrus, and temporal pole (7), while decreased FC in periaqueductal gray (PAG) (6), hypothalamus (8), ACC (9), temporal lobe (10), insular cortex (11) and amygdala (12). Among migraine patients, regional homogeneity (ReHo) was significantly increased in bilateral thalami, middle frontal gyrus and left insula (13), and decreased in putamen (14), cerebellum (15), and posterior cingulate cortex (PCC) (16). Meanwhile, voxel-based morphometry (VBM) studies suggested that brain gray matter volume (GMV) increased in PAG, bilateral fusiform gyri, and cingulate gyri (17), and decreased in cerebellar culmen (18), ACC, hippocampus (17), and orbitofrontal cortex (19).

If there are regions that both function and structure altered in migraine patients. Based on ReHo, amplitude low-frequency fluctuation (ALFF) and positron emission tomography (PET), meta-analysis demonstrated decreased activity in the angular gyrus, visual cortex, and cerebellum, while increased in the caudate, thalamus, pons, and prefrontal cortex (20). On the other hand, GMV decrease in posterior insular-opercular regions, the bilateral prefrontal cortex, and the anterior cingulate cortex were revealed with AES-SDM (3, 5). It is frustrating that a consistent conclusion was not drawn. Meanwhile, there still a lacks meta-analysis on the brain FC alterations in migraine patients. As more studies on the brain structure and function alterations in migraine patients have been published, it is urgent to perform a meta-analysis to draw a comprehensive conclusion including functional and structural studies.

Therefore, we conduct the current neuroimaging meta-analysis on brain structure and function changes in migraine patients, with the hope of drawing a solid conclusion.

Materials and methods

This study was registered on the PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), with the registration number CRD42021257300.

Search strategy

A systematic literature search was conducted in the database of PubMed, Web of Science, Cochrane Library, and MEDLINE from inception to Sept 2022, according to Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) (21). The subject terms and keywords, (“migraine” OR “primary headache”) AND (“magnetic resonance imaging” OR “neuroimaging” OR “fMRI”) AND (“structure” OR “voxel-based morphometry” OR “morphometrical” OR “functional connectivity” OR “regional homogeneity” OR “function”), were used to identify candidate VBM and rs-fMRI studies. Then, manual screening was conducted in the references of the retrieved studies and reviews.

Inclusion and exclusion criteria

Studies that meet the following criteria were eligible for inclusion in this meta-analysis: (1) migraine patients diagnosed according to the International Classification of Headache Disorders (ICHD) (1); (2) MRI studies employed morphometric approaches of VBM, or functional metrics of FC and ReHo; (3) seed-based FC to whole-brain compared patients with migraine with health controls (HC) group; (4) coordinates were reported in Montreal Neurological Institute space (MNI), or Talairach space, and (5) peer-reviewed. Multiple papers published by the same author were included following the criteria: including the largest number of participants, latest published ones, and reported coordinates underwent stringent correction.

Exclusion criteria were as follows: (1) no HC group, (2) study was neither VBM nor FC and ReHo, (3) studies on the region of interest (ROI)-ROI, seed-ROI or independent component analysis (ICA), (4) intervention studies (pre/post-treatment contrasts such as transcranial magnetic stimulation or acupuncture), (5) seed-points or peak effect coordinates could not be retrieved, or (6) other types of migraine (e.g., vestibular migraine) and studies for comorbidities (Figure 1).

We also excluded those studies that adopted lax statistical methods, like small volume correction (SVC) and uncorrected multiple comparisons.

Data extraction

Articles retrieval, assessment, and data extraction were independently implemented by two authors (CZH and SJT)
FIGURE 1
The flowchart of literature screening.

according to the data extraction protocol. Any vagueness or disagreements were discussed with a third author (CYL), and a consensus was reached. The data information was sequentially collected, such as author, published year, sample size, characteristics of participants (e.g., age, gender, disease duration, and attacks), classification of migraine, and technical details (MRI scanner, seed regions, and correction methods, etc.). The peak coordinates of included studies were edited as available files according to the guidelines of AES-SDM 5.15 (http://www.sdmproject.com/) (22) or ALE 3.02 (http://www.brainmap.org/) (23). Talairach coordinates were translated into MNI via a toolbox provided by Ginger ALE.

Literature quality assessment

There is no consensus on the quality evaluation of neuroimaging studies up to now. We performed a customized checklist to assess the quality of included studies based on the assessment items of the Newcastle Ottawa Quality Assessment Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). The detailed items and scores of included studies are listed in Supplementary Tables S1, S2.

Activation likelihood estimation (ALE) analysis

ALE evaluated the significant convergence between peak effect foci from different trials (e.g., migraine > controls, migraine < controls) for a given study in comparison with a random distribution of foci. It treated reported significant foci as spatial probability distributions centered on given coordinates rather than as single points. ALE assesses the cumulative probabilities of each voxel based on reported foci. ALE map was acquired after calculating the union probabilities of each voxel. The true convergence of foci and random clustering was tested by permutation tests. Based on the sample size and random effect model, the likelihood of consensus among different experiments is attained. Each focus is modeled as the center of a Gaussian probability distribution. Then, the modeled activation (MA) map for each study is generated. We employed the recommendation setting of cluster-level family-wise error (FWE) ($p < 0.05$) to carry out multiple comparisons, using an initial cluster threshold of uncorrected $p < 0.001$, and permutation tests were 5,000 (23).

Sensitivity analysis

To assess the reliability and replicability of main results, we conducted a jackknife sensitivity analysis. The method was to repeat the process of removing one study and performing the others with the same meta-analysis at same threshold. If the main results remains significant in all or most of the combinations of the analysis, then it was regarded as rigorous.

Subgroup analysis

Subgroup analyses were performed to evaluate the consistency of findings and to eliminate latent factors affecting main results. We conducted subgroup analysis of patients with migraine without aura to exclude clinical and methodological heterogeneity.

Result

Thirty-nine MRI studies were included in this analysis, covering 11 VBM (Table 1), 16 FC (Table 2), and 9 ReHo studies (Table 3). It was comprised of 1,355 migraine patients (314 males and 1,041 females) and 1,149 (305 males and 844 females) HCs. Among them, VBM studies recruited 430 migraine patients (120 males, 328 females), and 317 HCs (93 males, 224 females); ReHo studies enrolled 337 migraine patients (77 males, 260 females), and 288 HCs (69 males,
### TABLE 1  Demographic and clinical characteristics of migraine in the VBM studies.

| Authors (years) | Migraine types | Patients | Disease attacks | Health controls |
|----------------|----------------|----------|----------------|----------------|
|                |                | M/F      | Age            | Duration years | M/F      | Age          |
| Neeb et al. (24) | EM             | 21 (6/15) | 49.36 ± 7.62   | 26.71 ± 14.42 | NA       | 5.33 ± 1.59  |
|                | CM             | 21 (6/15) | 49.04 ± 7.46   | 24.43 ± 8.3  | 17.38 ± 2.66 |
| Zhang et al. (16) | MWoA           | 32 (8/24) | 38.3 ± 10.16   | 9.5 ± 6.23   | 32 (8/24) | 38.8 ± 10.2  |
| Bonanno et al. (25) | MWA         | 14 (0/14) | 42.36 ± 2.95   | 5.21 ± 1.31  | NA       | 14 (0/14)   |
|                | MWoA           | 14 (0/14) | 43.5 ± 3.25    | 6.78 ± 3.66  | 22.75 ± 10.03 |
| Li et al. (26)  | MWoA           | 72 (15/57) | 21.3 (20.89, 21.73) | 66.75 (32.19, 101.31) | NA       | 5.89 (2.62, 9.16) |
| Yu et al. (17)  | EM             | 39 (9/30) | 39.74 ± 11.59  | NA           | 3.75 ± 2.64 |
| Chen et al. (19) | EM             | 56 (19/37) | 37.5 ± 7.6     | 194.6 ± 116.7 (month) | NA       | 13.8 ± 10.5 |
|                | CM             | 17 (9/8)  | 49.59 ± 14.64  | NA           | 3.75 ± 2.64 |
| Chou et al. (27) | Migraine       | 40 (8/32) | 39.2 ± 10.05   | 14.7 ± 10.2  | NA       | 9.9 ± 6.5    |
| Masson et al. (4) | Migraine      | 19 (6/13) | 32.7 ± 8.7     | 16.8 ± 7.4   | NA       | 3.3 ± 1.1    |
| Hubbard et al. (28) | Migraine    | 17 (4/13) | 41.71 ± 12.20  | >3 (month)   | NA       | 4.15         |
| Cao et al. (29) | MWoA           | 44 (11/33) | 34.93 ± 10.66  | 10.34 ± 8.98 | NA       | 10.14 ± 9.68 |
| Schading et al. (30) | Migraine   | 24 (1/23) | 38.1 ± 12.5    | 20 ± 12.0    | NA       | 5.7 ± 2.5    |

The technique details and main findings.

| Authors (years) | Diagnose criteria | Corrections | Scanners | Method | FWHM | Main findings |
|----------------|-------------------|-------------|----------|--------|------|---------------|
| Neeb et al. (24) | ICHD-III beta     | FWE         | 3.0T     | VBM    | 10   | Increased: right amygdala and right putamen, left putamen, right pallidum, right hippocampus, right PHG, right superior parietal lobule, left insula, right cerebellum, left superior occipital gyrus and cuneus. Decreased: frontal lobe, right angular gyrus. |
| Zhang et al. (16) | ICHD-III beta     | FDR         | 3.0T     | VBM    | 8    | Increased: bilateral cerebellar culmen, lingual gyrus, thalamus, fusiform and PHG |
| Bonanno et al. (25) | IHS               | FWE         | 3.0T     | VBM    | 8    | Increased: right superior parietal gyrus and left thalamus Decreased: right cerebellum, left postcentral and precentral gyrus, right inferior frontal gyrus, and left lingual gyrus |
| Li et al. (26)   | ICHD-II           | FWE         | 3.0T     | VBM    | 8    | Decreased: bilateral superior and inferior colliculus, PAG, LC, median raphe nuclei (MRN) and dorsal pons medulla |
| Yu et al. (17)   | ICHD-III beta     | AlphaSim    | 3.0T     | VBM    | 8    | Increased: PAG dIPFC, left hippocampus/PHG Decreased: ACC, bilateral dIPFC, left hippocampus/PHG |
| Chen et al. (19) | ICHD-III beta     | FWE         | 3.0T     | VBM    | 8    | Decreased: right orbitofrontal cortex |

(Continued)
TABLE 1 (Continued)

| Authors                          | Diagnose criteria | Corrections | Scanners | Method | FWHM | Main findings                                                                 |
|---------------------------------|-------------------|-------------|-----------|--------|------|--------------------------------------------------------------------------------|
| Chou et al. (27)                | ICHD-3            | FWE         | 3.0 T     | VBM    | 8    | Increased: left PCG                                                            |
|                                 |                   |             |           |        |      | Decreased: right PCG, left precentral gyrus, and cerebellum                    |
| Masson et al. (4)               | NA                | FWE         | 3.0 T     | VBM    | 15   | Decreased: superior temporal areas and postcentral gyrus                       |
| Hubbard et al. (28)             | ICHD-II           | GRF         | 3.0 T     | VBM    | 8    | Increased: left hippocampus                                                   |
| Cao et al. (29)                 | ICHD-III beta     | FWE         | 3.0 T     | VBM    | 8    | Decreased: middle frontal cortex                                               |
| Schading et al. (30)            | ICHD-III          | FWE         | 3.0 T     | VBM    | 3    | Increased: left lingual gyrus                                                  |

ACC, anterior cingulate cortex; MWA, migraine with aura; MWoA, migraine without aura; EM, episodic migraine; CM, chronic migraine; FWHM, full width at half maximum; GRE, Gaussian random field theory; FEW, family wise error; FDR, false detect rate; SVC, small volume correction; mM, menstrual migraine; LF, low frequency; HF, high frequency; PAG, periaqueductal gray; LC, locus coeruleus; MRN, median raphe nuclei; dlPFC, bilateral dorsolateral prefrontal cortex; PHG, parahippocampal gyrus; ICHD-3 beta, international classification of headache disorders, 3rd edition (beta version); PCG, postcentral gyrus; HIS, international headache society; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; T, Tesla; VBM, voxel-based morphometry.

219 females); FC studies included 588 migraine patients (135 males, 453 females), and 544 HCs (143 males, 401 females). All included structural and functional studies were performed statistical analyses for age and sex of included patients and controls (t-test or ANOVA, p < 0.05), individually. There were no significant differences in age and ratio of gender between migraine and HC, when the data were independently assessed. The preprocessing of fMRI images in all studies was performed by several steps, such as slice timing, realigning, normalizing, regressing nuisance covariates, filtering, and smoothing.

Brain function alterations

Using the coordinates of functional MRI studies to conduct ALE analysis, the ReHo values of left thalamus (MNI: −10, −24, 2; cluster volume 560 mm³) and brainstem (MNI: 6, −30, −44; 4, −28, −34; cluster volume 600 mm³) were increased, no decreased found. The changes of FC were not found (Figure 2, Table 4).

Brain structure alterations

No VBM alterations were found in this analysis.

Sensitivity analysis

ALE sensitivity analysis repeated the process of removing one study and performing the rest. We found that increased ReHo in brainstem and left thalamus was preserved throughout all studies, in spite of the most coordinates (80 foci) that reported by the Zhao’s study (13) were not led to the instability of results (Table 5).

Subgroup analysis

According to the diagnosis classification of migraine, we performed subgroup meta-analysis of migraine patients and migraine without aura to establish the consistency of findings. No clusters were above the threshold.

Discussion

To our knowledge, this is the first study adopting functional and structural fMRI metrics to verify brain alterations (VBM, FC, and ReHo) in migraine patients. The solid conclusion is that the ReHo values of left thalamus and brainstem were consistently increased. While GMV and FC were not illustrated alterations in migraine in terms of current evidence.

Migraine is associated with various central nervous system disorders (2). Profoundly prolonged duration and recurrently attacked headache are the main complaints of migraine sufferers (51). Thalamus is thought to have an essential role in the pathophysiology of migraine and has been investigated extensively (52–55). Meanwhile, the migraine genesis is more likely within brainstem, involving dysfunction and plasticity changes (56).

In migraine patients, pain information is transmitted from the meninges to the brain via the trigeminovascular pathway starting from trigeminal ganglion neurons (37). Specifically, the spinal trigeminal nucleus (SpV) neurons convey nociceptive signals to the brainstem (such as periaqueductal gray, reticular formation), hypothalamic, and basal ganglia. Then, the relay thalamic neurons project to the somatosensory, insular, motor, parietal association, auditory, visual, and olfactory cortices to construct the specific properties of migraine pain (58), for instance, nausea, vomiting, lacrimation, anxiety, and hypothalamic-regulated functions like appetite loosing and fatigue (56).
### TABLE 2  Demographic and clinical characteristics of FC studies in migraine.

| Author (years) | Migraine types | Patients | Disease | HC |
|----------------|----------------|----------|---------|----|
|                | Number (M/F)   | Age (years) | Duration (years) | Attacks (month) |
| Niddam et al. (31) | MwoA | 26 (9/17) | 32.3 ± 9.8 | 13.5 ± 8.0 | 26 (9/17) | 31.2 ± 5.8 |
|                 | MWA | 26 (9/17) | 28.3 ± 7.5 | 13.1 ± 7.8 | 22 (9/13) | 42.0 ± 10.3 |
| Zhang et al. (32) | MwoA | 22 (9/13) | 41.8 ± 10.2 | 9.8 ± 7.3 | 18 (4/14) | 39.11 ± 9.99 |
| Chen et al. (33) | EM | 18 (4/14) | 33.39 ± 10.69 | 12.44 ± 8.07 | NA | 46 | 21.24 (20.98;21.50) |
| Li et al. (34)  | MwoA | 72 (15/57) | 21.3 (20.89; 21.73) | NA | 26 (9/17) | 31.2 ± 5.8 |
| Yu et al. (35)  | MwoA | 48 (11/37) | 35.47 ± 9.91 | 9.38 ± 6.86 | NA | 48 | 35.12 ± 9.45 |
| Meylakh et al. (36) | Migraine | 26 (4/22) | 30.6 ± 2.1 | NA | NA | 78 | 30.7 ± 1.3 |
| Ke et al. (37)  | MwoA | 39 (9/30) | 39.74 ± 11.59 | NA | 3.75 ± 2.64 | 35 | 34.91 ± 10.89 |
| Meylakh et al. (38) | Migraine | 34 (10/24) | 32 ± 1.8 | NA | NA | 26 (4/22) | 32.3 ± 2.3 |
| Qin et al. (39) | MwoA | 48 (14/34) | 38.1 ± 10.4 | 8.5 ± 6.0 | 3.8 ± 3.3 | 48 | 39.0 ± 11.0 |
| Zhang et al. (40) | MwoA | 30 (4/26) | 39.87 ± 10.43 | 9.37 ± 7.77 | 5.17 ± 6.17 | 22 (8/14) | 34.27 ± 8.34 |
| Huang et al. (41) | MwoA | 45 (12/33) | 38.62 ± 10.11 | 13.8 ± 6.07 | 4.31 ± 1.8 | 35.45 ± 7.53 |
| Wei et al. (42) | MwoA-A (27) | 49 (7/42) | 34.41 ± 9.75 | 7.11 ± 5.51 | 4.22 ± 2.19 | 20 (3/17) | 33.4 ± 7.43 |
|               | MwoA-OA (22) | 34.91 ± 12.14 | 7.50 ± 6.77 | 4.45 ± 3.00 | NA | 40 | 36.88 ± 14.97 |
| Cao et al. (43) | Migraine | 30 (6/24) | 36.1 ± 13.28 | 85.23 ± 54.78* | NA | 27 (6/21) | 25.6 ± 4.0 |
| Gecse et al. (44) | MwoA | 27 (6/21) | 25.9 ± 4.6 | NA | NA | 27 (6/21) | 25.6 ± 4.0 |
| Gollion et al. (45) | MWA | 21 (4/17) | 39 (12) | 25 | 15* | 18 (5/13) | 39 (9.5) |
| Yang et al. (46) | migraine | 27 (2/25) | 34.89 9.070 | 11.11 ± 10.165 | NA | 30 (4/26) | 35.53 ± 12.53 |

### Technique details and main findings of included FC studies.

| Author (years) | Seeds | Studies | MRI scanners | Diagnose criteria | Correction | Main findings |
|----------------|-------|---------|--------------|-------------------|------------|---------------|
| Niddam et al. (31) | MFG/AI/MPC | FC | 3.0T | ICHD-II | FDR | Increased: left MFG, posterior cingulate and precuneus. Decreased: bilateral occipital lobes, right AI and basal ganglia. |
| Zhang et al. (32) | Precuneus/PCC | FC | 3.0T | ICHD-II | FDR | Decreased: left occipital gyrus, bilateral cuneus, bilateral parietal lobules, bilateral postcentral gyrus, bilateral dorsolateral prefrontal gyrus, pons, bilateral cerebellar posterior lobes, right paracentral lobule, right middle cingulate gyrus and bilateral SMA. |
| Chen et al. (33) | PAG | FC | 3.0T | ICHD-III beta | FDR | Decreased: left precentral gyrus, left MFG, left inferior parietal gyrus, bilateral middle temporal gyrus, right SFG, right SMA, right inferior frontal gyrus and medial SFG. |
| Li et al. (34) | Right precuneus | FC | 3.0T | ICHD-II | FWE | Decreased: left precuneus, supramarginal gyrus and ITG. |

(Continued)
| Author (years) | Seeds | Studies | MRI scanners | Diagnose criteria | Correction | Main findings |
|---------------|-------|---------|--------------|------------------|------------|---------------|
| Yu et al. (35) | Insulas | FC | 3.0 T | ICHD-III beta | FWE | Increased: the frontal lobe, the caudate nucleus, and the THA |
| Meylakh et al. (36) | PAG | FC | 3.0 T | ICHD-III beta | FDR | Increased: temporal lobe, parietal lobe, cingulate gyrus, precuneus, PHG, and caudate nucleus |
| Ke et al. (37) | Insula/cerebellum | FC | 3.0 T | ICHD-III beta | FDR | Increased: hypothalamus, THA |
| Meylakh et al. (38) | Hypothalamus | FC | 3.0 T | ICHD-III beta | Bonferroni | Increased: bilateral SMA/PCL, right postcentral gyrus, left orbitofrontal gyrus and fusiform gyrus, bilateral temporal pole, and cerebellum |
| Qin et al. (39) | ADN/VPN | FC | 3.0 T | ICHD-III beta | FWE | Decreased: right hippocampus and bilateral ACC |
| Zhang et al. (40) | LGN | FC | 3.0 T | ICHD-III beta | GRF | Increased: left cerebellum, left LG, left inferior frontal gyrus |
| Huang et al. (41) | Amygdala | FC | 3.0 T | ICHD-III beta | GRF | Decreased: bilateral STG and right precentral gyrus |
| Wei et al. (42) | LG | FC | 3.0 T | ICHD-III beta | Bonferroni | Increased: right PCC/precuneus, left MFG and left ITG |
| Cao et al. (43) | Thalamus | FC | 3.0 T | ICHD-III beta | FDR | Increased: left frontal gyrus |
| Gecce et al. (44) | PAG | FC | 3.0 T | ICHD-III | FWE | Increased: cerebellum |
| Gollion et al. (45) | Insula | FC | 3.0 T | ICHD-III | FDR | Increased: cerebellum |
| Yang et al. (46) | Thalamus | FC | 3.0 T | ICHD-III | FWE | Decreased: precuneus, ACC, frontal gyrus |

*R/F: arithmetic mean; 1/f: median; ^: pooled data; **: measures over less than 6 months; #: measures over 6 months. Wireless or # indicates the presence of a temporal trend.

Although, the regions exhibited FC alteration among those studies, involving cortex about pain processing, visual, auditory, affective, and cognitive evaluation, there is no solid conclusion of pain information projecting of migraine temporarily according to our analysis.

Meanwhile, the GMV changes of migraine assessed by VBM were heterogeneous between previous studies and meta-analysis (3–5). Now, a tendentious consensus of no structural brain alterations is more acceptable by researchers (60, 61). Furthermore, after rigorous literature screening, no morphometrical changes were detected with meta-analysis using different software.

**Conclusion**

The first quantitative coordinates meta-analysis of whole-brain neuroimaging studies for migraine that synthesized functional and structural MRI metrics, with the aim of providing
TABLE 3 Demographic and clinical characteristics of migraine in the ReHo studies.

| Author (years) | Migraine types | Patients | Disease | Health control |
|----------------|----------------|----------|---------|----------------|
|                |                | Number (M/F) | Age     | Duration (years) | Attacks (month) | Number (M/F) | Age     |
| Zhao et al. (13) | MWoA | Total:40 (12/28) | 30.5 ± 10.8 | 10.15 ± 7.01* | NA | 20 (5/15) | 28.4 ± 8.9 |
| Zhao et al. (14) | MWoA | ST:20 (5/15) | 27.12 ± 8.18 | 4.05 ± 1.64* | 4.5 ± 3.5 | 20 (0/20) | 22.4 ± 3.1 |
| Zhang et al. (47) | Migraine | MWoA:23 (6/17) | 34 ± 8 | 9 ± 7 | 5.9 ± 9.4 | 25 | 35 ± 8 |
| Zhang et al. (14) | MWoA | LT:20 (7/13) | 37.52 ± 10.2 | 16.25 ± 1.47* | 5.38 ± 5.8 | 78 (12/66) | 30.7 ± 1.3 |
| Zhao et al. (13) | MWoA | MWoA:12 (3/9) | 32 ± 9 | 8 ± 6 | 2.5 ± 1.3 | 31 | 42.0 ± 10.3 |
| Zhang et al. (13) | MWoA | 30 (8/22) | 41.0 ± 10.4 | 9.6 ± 6.83 | 3.3 ± 2.7 | 78 | 30.7 ± 1.3 |
| Meylakh et al. (36) | Migraine | 26 (4/22) | 30.6 ± 2.1 | 14.56 ± 2.22 | 2.63 ± 0.64 | 31 | 49.77 ± 13.69 |
| Chen et al. (49) | MWoA | IEM:19 (5/14) | 42.0 ± 11.0 | 9.37 ± 3.62 | 1.56 ± 0.61 | 25 | 21.21 (20.98;21.50) |
| Chen et al. (49) | MWoA | FEM:20 (4/16) | 38.0 ± 12.01 | 9.80 ± 3.61 | 5.82 ± 2.06 | 46 | 34.88 ± 6.66 |
| Li et al. (26) | MWoA | CM:17 (9/8) | 49.59 ± 14.64 | 7.41 ± 3.20 | 25.15 ± 6.87 | 22 (6/16) | 34.59 ± 7.99 |
| Liu et al. (15) | MWoA | 37 (6/31) | 37.97 ± 9.82 | 16.19 ± 12.81 | NA | 15 (2/13) | 34.88 ± 6.66 |
| Lei and Zhang (50) | Migraine | 22 (5/17) | 33.32 ± 10.27 | NA | NA | 22 (6/16) | 34.59 ± 7.99 |

The technique details and main findings.

| Author (years) | Diagnose criteria | Study | MRI scanner | Corrections | Main findings |
|----------------|-------------------|-------|-------------|-------------|---------------|
| Zhao et al. (13) | IHS | ReHo | 3.0T | FDR | Increased: bilateral thalamus, IFG, MOG, left insula, caudate, MFG, MTG, IOG, right ACC, MeFG, superior temporal gyrus, bilateral ACC, amygdala, thalamus, caudate, lentiform nucleus, uncus, SFG, temporal pole, cerebellum, brain stem, left hippocampus |
| Meylakh et al. (36) | ICHD-III beta | ReHo | 3.0T | FDR | Increased: right occipital lobe |
| Zhang et al. (48) | ICHD-II | ReHo | 3.0T | FWE | Decreased: bilateral S1 and the right PMC |
| Meylakh et al. (5) | ICHD-III beta | ReHo | 3.0T | FDR | Increased: PAG, hypothalamus, and somatosensory thalamus |

(Continued)
TABLE 3 (Continued)

The technique details and main findings.

| Author (years) | Diagnose criteria | Study | MRI scanner | Corrections | Main findings |
|----------------|------------------|-------|-------------|-------------|---------------|
| Chen et al. (49) | ICHD-III | ReHo | 3.0T | FDR | Increased: bilateral thalami, right central anterior gyrus, left central posterior gyrus, right insular lobe, right sacral gyrus, bilateral central posterior gyri, right middle temporal gyrus, left olfactory cortex, right hippocampus, parahippocampal gyrus, suboccipital gyrus, cuneus, occipital gyrus. Decreased: bilateral prefrontal cortex, left angular gyrus, bilateral anterior cingulate cortex, prefrontal cortex, putamen and right supplementary motor area, bilateral prefrontal cortex, precuneus, putamen, anterior cingulate cortex. |
| Li et al. (26) | ICHD-II | ReHo | 3.0T | FWE | Increased: bilateral MRN. Decreased: right middle occipital gyrus, inferior occipital gyrus, left middle occipital gyrus. |
| Liu et al. (15) | ICHD-III | ReHo | 3.0T | FWE | Decreased: cerebellum. |
| Lei and Zhang (50) | ICHD-III | ReHo | 3.0T | GRF | Increased: bilateral paracentral lobule. Decreased: bilateral ACC, cuneus, and lingual gyrus. |

ST, short-term; LT, long-term. MWoA, migraine without aura; IEM, infrequent episodic migraine; FEM, frequent episodic migraine; CM, chronic migraine.

Figure 2
The spontaneous activity of ReHo in migraine patients. Using whole-brain overview and axial, sagittal, and coronal view, (A) illustrates the brainstem activating cluster (MNI: 6, − 30, − 44, 600 mm³); (B) shows the left thalamus activating cluster (MNI: − 10, − 24, 2, 560 mm³).

TABLE 4 The ReHo values changings of migraine patients by ALE analysis.

| Cluster | Volume (mm³) | Coordinate (MNI) | ALE value | z values | Brain regions |
|---------|-------------|-----------------|-----------|----------|---------------|
|         |             | x   y   z       |           |          |               |
| 1       | 600         | 6   −30 −44     | 1.65 × 10⁻² | 4.70     | Brainstem     |
| 2       | 560         | −10 −24 2       | 1.70 × 10⁻² | 4.83     | Left thalamus |

MNI, montreal neurological institute space.
the most comprehensive insights into brain impairments of migraine patients. Our meta-analysis suggested spontaneous cerebral activity in the left thalamus and brainstem, with no FC and GMV alterations. The findings may be served as the brain dysfunction clue of the underlying pathophysiology of migraine. In addition, neuroimaging meta-analysis, for reliable and robustness results, rigorous literature screening is prerequisite.

Limitation

Firstly, the heterogeneity analysis, and correlation analysis were not carried out due to the ALE software restriction. The number of included studies was insufficient to perform subgroup analysis. Secondly, unpublished studies ("gray studies") were not included in our meta-analysis, which inevitably leads to publication bias. And the coordinates-based meta-analysis also has inherently biased, as it employs pooled stereotactic coordinates that are statistically significantly different, rather than raw data. Thirdly, this meta-analysis was limited to seed-based to whole-brain fMRI studies of FC, the studies using independent component analysis (ICA) and positron emission tomography (PET) approach not included.

Strengths and limitations of this study

- Functional and structural changes were evaluated simultaneously.
- Robust results were attributed to the rigorous processing analyses.
- More studies are needed to verify the changes in GMV.

Author contributions

Z-HC, Y-LC, J-TS, Y-TL, and CZ devoted to this study equally as the co-first authors. Z-HC wrote the original draft. Y-MZ, Z-YL, Y-XS, and M-HN were constructive for data abstraction and software analysis for this study. BH and L-FY monitored the analysis procedure. WW supervised the overall procedure. All authors revised and approved the final manuscript.

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).

Acknowledgments

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

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1022793/full#supplementary-material

References

1. Arnold M. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edn. New York, NY: Cephalalgia (2018), pp. 1–211.

2. Ashina M. Migraine, N Engl J Med. (2020) 383:1866–76. doi: 10.1056/NEJMrat1915327

3. Jia Z, Yu S. Grey matter alterations in migraine: a systematic review and meta-analysis. Neuroimage Clin. (2017) 14:130–40. doi: 10.1016/j.nicl.2017.01.019

4. Masson R, Demarquay G, Meunier D, Leveque Y, Hansoun S, Bidet-Caulet A, et al. Is migraine associated to brain anatomical alterations? New data and coordinate-based meta-analysis. Brain Topogr. (2021) 34:384–401. doi: 10.1007/s10548-021-00824-6

5. Dai Z, Zhong J, Xiao P, Zhu Y, Chen F, Pan P, et al. Gray matter correlates of migraine and gender effect: a meta-analysis of voxel-based morphometry studies. Neuroscie. (2015) 299:88–96. doi: 10.1016/j.neuroscience.2015.04.066

6. Mainero C, Boshyan J, Hadjikhani N. Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. Ann Neurol. (2011) 70:838–45. doi: 10.1002/ana.22537

7. Testore A, Russo A, Giordano A, Conte F, Corbo D, De Stefano M, et al. Disrupted default mode network connectivity in migraine without aura. J Headache Pain. (2013) 14:89. doi: 10.1186/1129-2377-14-89

8. Qiu E, Tian I, Wang Y, Ma L, Yu S. Abnormal coactivation of the hypothalamus and salience network in patients with cluster headache. Headache. (2015) 55:1163. doi: 10.1111/1526-4050.12442

9. Jia Z, Chen X, Tang W, Zhao D, Yu S. Atypical functional connectivity between the anterior cingulate cortex and other brain regions in a rat model of recurrent headache. Mol Pain. (2019) 15:1744806919842483. doi: 10.1177/1744806919842483

10. Schwedt TJ, Berisha V, Chong CD. Temporal lobe cortical thickness correlations differentiate the migraine brain from the healthy brain. PLoS ONE. (2015) 10:e116673. doi: 10.1371/journal.pone.0116673

11. Ellingsen DM, Garcia RG, Lee J, Lin RL, Kim J, Thurler AH, et al. Cyclic vomiting syndrome is characterized by altered functional brain connectivity of the insular cortex: a cross-comparison with migraine and healthy adults. Neurogastroenterol Motil. (2017) 29:e13004. doi: 10.1111/nmo.13004

12. Hadjikhani N, Ward N, Boshyan J, Napadow V, Maeda Y, Trumi A, et al. The missing link: enhanced functional connectivity between the anterior cingulate cortex and other brain regions in a rat model of recurrent headache. J Clin Neurophysiol. (2014) 30:229–35. doi: 10.1097/CNP.00000000000001442

13. Zhao L, Liu JX, Dong XL, Peng YL, Yuan K, Wu FM, et al. Differential modulating effect of acupuncture in patients with migraine without aura: a resting functional magnetic resonance study. Front Neurol. (2021) 12:680896. doi: 10.3389/fneur.2021.680896

14. Zhang YX, Chen H, Zeng M, He JW, Qi GQ, Zhang SJ, Liu RB. Abnormal whole brain functional connectivity pattern homogeneity and couplings in migraine without aura. Front Hum Neurosci. (2020) 14:19839. doi: 10.3389/fnhum.2020.619839

15. Yu Y, Zhao HR, Dai LL, Su YJ, Wang XM, Chen C, Zhang YL, et al. Headache frequency associates with brain microstructure changes in patients with migraine without aura. Brain Imag Behav. (2015) 1:650–7. doi: 10.1007/s11682-014-00232-2

16. Zhang J, Wu L, Su JY, Qao Y, Wang MX, Li F, et al. Assessment of gray and white matter structural alterations in migraineurs without aura. J Headache Pain. (2017) 18:1–7. doi: 10.1186/s10194-017-0783-5

17. Chen WT, Chou KH, Lee PL, Hsiao FJ, Niddam DM, Lai KL, et al. Comparison of gray matter volume between migraine and "strict-criteria“ tension-type headache. J Headache Pain. (2019) 19:4. doi: 10.1186/s10194-018-0834-6

18. Cai M, Liu J, Wang X, Ma J, Ma L, Liu M, et al. Spontaneous brain activity abnormalities in migraine: a meta-analysis of functional neuroimaging. Hum Brain Mapp. (2022). doi: 10.1002/hbm.26085

19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. (2009) 339:b535. doi: 10.1136/bmj.b535

20. Albajes-Ezragirre A, Solanes A, Fullana MA, Ioannidis JPA, Pajar-Poli P, Torrent C, et al. Meta-analysis of voxel-based neuroimaging studies using seed-based d mapping with permutation of subject images (SDM-P). J Vis Exp. (2019) 153:e59841. doi: 10.3791/59841

21. Ecklof SB, Bredal D, Laird AR, Kurth F, Fox PT. Activation likelihood estimation meta-analysis revisited. Neuroimage. (2012) 59:2349–61. doi: 10.1016/j.neuroimage.2011.09.017

22. Neub L, Bastian K, Villringer K, Israel H, Reuter U, Fiebach JB. Structural gray matter alterations in chronic migraine: implications for a progressive disease? Headache. (2017) 57:400–16. doi: 10.1111/head.13012

23. Benonno L, Lu Boono V, De Salvo S, Ruvelo C, Torre V, Bramanti P, et al. Brain morphologic abnormalities in migraine patients: an observational study. J Headache Pain. (2020) 21:25. doi: 10.1186/s10194-020-01109-2

24. Li Z, Zhou J, Lan L, Cheng S, Sun R, Gong Q, et al. Concurrent brain structural and functional alterations in patients with migraine without aura: an fMRI study. J Headache Pain. (2020) 21:141. doi: 10.1186/s10194-020-01203-5

25. Chou KH, Lee PL, Liang CS, Lee JT, Kao HW, Tsai CL, et al. Identifying neuroanatomical signatures in insomnia and migraine comorbidity. Sleep. (2021) 44:2202. doi: 10.1093leep/s2202
31. Niddam DM, Lai KL, Fuh JL, Chuang CY, Chen WT, Wang SJ. Reduced functional connectivity between salience and visual networks in migraine with aura. Cephalalgia. (2016) 36:53–66. doi: 10.1177/0333102415583144

32. Zhang JL, Su JJ, Wang MX, Zhao Y, Yao Q, Zhang QT, et al. Increased default mode network connectivity and increased regional homogeneity in migraineurs without aura. J Headache Pain. (2016) 17:1–9. doi: 10.1186/s10194-016-0692-z

33. Chen ZY, Chen XY, Liu MQ, Liu SF, Ma L, Yu SY. Disrupted functional connectivity of periaqueductal gray subregions in episodic migraine. J Headache Pain. (2017) 18:1–9. doi: 10.1186/s10194-017-0747-9

34. Li ZL, Lan L, Zeng F, Makris N, Hwang J,Guo T, et al. The altered right frontoparietal network functional connectivity in migraine and the modulation effect of treatment. Cephalalgia. (2017) 37:161–76. doi: 10.1177/0333102416641665

35. Yuan ZB, Lv YB, Song LH, Liu DH, Huang XL, Hu YY, et al. Functional connectivity differences in the insular sub-regions in migraine without aura: a resting-state functional magnetic resonance imaging study. Front Behav Neurosci. (2017) 11:124. doi: 10.3389/fnhbeh.2017.00124

36. Meylahk N, Marciszewski KK, Di Pietro F, Macfie VG, Macey PM, Henderson LA. Deep in the brain: changes in subcortical function immediately preceding a migraine attack. Hum Brain Mapp. (2018) 39:2051–63. doi: 10.1002/hbm.24030

37. Ke J, Yu Y, Zhang XD, Su YY, Wang XM, Hu S, et al. Functional alterations in the posterior insula and cerebellum in migraine without aura: a resting-state MRI study. Front Behav Neurosci. (2020) 14:567588. doi: 10.3389/fnhum.2020.567588

38. Meylahk N, Marciszewski KK, Di Pietro F, Macfie VG, Macey PM, Henderson LA. Altered regional cerebral blood flow and hypothalamic connectivity immediately prior to a migraine headache. Cephalalgia. (2020) 40:448–60. doi: 10.1177/0333102420911623

39. Qin ZX, Su JJ, He XW, Zhou Q, Cui YY, Zhang JL, et al. Altered resting-state functional connectivity between subregions in the thalamus and cortex in migraine without aura. Eur J Neurotol. (2020) 27:2233–41. doi: 10.1111/ejn.14411

40. Zhang D, Huang XB, Su W, Chen YC, Wang P, Mao CN, et al. Altered lateral geniculate nucleus functional connectivity in migraine without aura: a resting-state functional MRI study. J Headache Pain. (2020) 21:1–9. doi: 10.1186/s10194-020-01086-6

41. Huang X, Zhang D, Wang P, Mao C, Miao Z, Liu C, et al. Altered amygdala effective connectivity in migraine without aura: evidence from resting-state fMRI with Granger causality analysis. J Headache Pain. (2021) 22:25. doi: 10.1186/s10194-021-01240-8

42. Wei HI, Li J, Guo X, Zhou GP, Wang JJ, Chen YC, et al. Functional connectivity of the visual cortex differentiates anxiety comorbidity from episodic migraineurs without aura. J Headache Pain. (2021) 22:40. doi: 10.1186/s10194-021-01259-x

43. Cao ZM, Chen YC, Liu GY, Wang X, Shi AQ, Xu LF, et al. Abnormalities of thalamic functional connectivity in patients with migraine: a resting-state fMRI study. Pain Ther. (2022) 11:561–74. doi: 10.1007/s40122-022-00365-1

44. Gece K, Dobos D, Aranyi CS, Galambos A, Baksa D, Kocsel N, et al. Association of plasma tryptophan concentration with periaqueductal gray matter functional connectivity in migraine patients. Sci Rep. (2022) 12:739. doi: 10.1038/s41598-021-04647-0

45. Gellion C, Lerebourcs F, Nemmi F, Arrbarat G, Bonneville F, Larrieu V, et al. Insular functional connectivity in migraine with aura. J Headache Pain. (2022) 23:106. doi: 10.1186/s10194-022-01473-1

46. Yang Y, Xu H, Deng Z, Cheng W, Zhao X, Wu Y, et al. Functional connectivity and structural changes of thalamic subregions in episodic migraine. J Headache Pain. (2022) 23:119. doi: 10.1186/s10194-022-01491-z

47. Zhang X, Wang Z, Zhang Y, Zhang L, Geng Z, Ren L, et al. [Altered cortical and subcortical local coherence in migraine with and without aura.evidence from resting-state fMRI]. Zhonghua Yi Xue Za Zhi. (2015) 95:3196–200.

48. Zhang J, Su J, Wang M, Zhao Y, Zhang QT, Yao Q, et al. The sensorimotor network dysfunction in migraineurs without aura: a resting-state fMRI study. J Neuroil. (2017) 26:654–63. doi: 10.1007/s00415-017-8044-4

49. Chen C, Yan M, Yu Y, Ke J, Xu C, Guo X, et al. Alterations in regional homogeneity assessed by fMRI in patients with migraine without aura. J Med Sydst. (2019) 43:298. doi: 10.1007/s10916-019-1425-z

50. Lei M, Zhang J. Brain function state in different phases and its relationship with clinical symptoms of migraine: an fMRI study based on regional homogeneity (ReHo). Ann Transl Med. (2021) 9:928. doi: 10.21037/atm-21-2097

51. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev. (2017) 97:553–622. doi: 10.1152/physrev.00034.2015

52. Zhang L, Yu W, Xu M, Cui F, Song W, Yan M, et al. The hypothalamus may mediate migraine and ictal photophobia evidence from Granger causality analysis. Neuril Sci. (2022) 43:6021–30. doi: 10.1007/s10072-022-06245-y

53. Tu Y, Fu Z, Zeng F, Maleki N, Lan L, Li Z, et al. Abnormal thalamocortical network dynamics in migraine. Neurology. (2019) 92:e2706–16. doi: 10.1212/WNL.0000000000007607

54. Coppola G, Di Renzo A, Petolcchio R, Tinelli E, Di Lorenzo C, Serrao M, et al. Increased neural connectivity between the hypothalamus and cortical resting-state functional networks in chronic migraine. J Neuroil. (2020) 267:185–91. doi: 10.1007/s00415-019-09571-y

55. Wei Hl, Zhou X, Chen YC Yu YS, Guo X, Zhou GF, et al. Impaired intrinsic functional connectivity between the thalamus and visual cortex in migraine without aura. J Headache Pain. (2019) 20:1–9. doi: 10.1186/s10194-019-1086-1

56. Ashina M, Hansen JM, Do TP, Meo-Carrillo A, Burststein R, Moskovitz MA. Migraine and the trigeminovascular system—40 years and counting. Lancet Neurol. (2019) 18:795–804. doi: 10.1016/S1474-4422(19)30185-1

57. Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol. (2018) 17:174–82. doi: 10.1016/S1474-4422(17)30435-0

58. Burststein R, Noseda R, Borsok D. Migraine: multiple processes, complex pathophysiology. J Neurosci. (2015) 35:6619–29. doi: 10.1523/JNEUROSCI.0573-15.2015

59. Canetto E, Chen D, Biswal B, A. review of resting-state fMRI and its use to examine psychiatric disorders. Psychonobuiol. (2021) 1:42–53. doi: 10.1093/psychon/ikk003

60. Mehner J, Schulte I, May A. No grey matter alteration in longitudinal data of migraine patients. Brain. (2020) 143:e93. doi: 10.1093/brain/awaa300

61. Naegel S, Zeller J, Hougard A, Wese CM, Hans Christoph D, Zuelow S, et al. No structural brain alterations in new daily persistent headache: a cross sectional VBM/SMI study. Cephalalgia. (2022) 42:335–44. doi: 10.1177/0333102421945653

62. Chang Z, Wang Q, Wang Y, Zhang XT, et al. The pathogenesis of migraine with aura. J Headache Pain. (2018) 19:81–91. doi: 10.1186/s10194-017-0846-2