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Meta-analytical evidence of functional and structural abnormalities associated with pain processing in migraine patients

An activation likelihood estimation

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Abstract

Background: Migraine is a primary headache disorder that causes debilitating throbbing pain. Several functional MRI (fMRI) and voxel-based morphometry (VBM) studies have been used to investigate the structural and functional alteration in migraine. Here, we aim to study the converged brain regions of functional and structural abnormalities in gray matter volume (GMV) associated with pain processing and management in migraineurs and healthy controls (HC).

Methods: A systematic search through PubMed and Sleuth was carried out for peer-reviewed functional and structural neuroimaging studies on migraine patients and HC yielded a total of 1136 studies. We performed an activation likelihood estimation (ALE) meta-analysis on VBM and pain stimulation task-based fMRI studies to investigate the converged areas of GMV and functional abnormalities between migraineurs and HC. We performed two subgroup analyses between migraine with aura (MwA) and migraine without aura (MwoA) relative to HC, and between chronic migraine (CM) and episodic migraine (EM) compared to HC.

Results: The total sample included 16 fMRI and 22 VBM studies, consisting of 1295 migraine patients, compared to 995 HC. In fMRI analysis, ALE maps for pain stimulation tasks revealed hyperactivation in migraineurs in the substantia nigra compared to HC, whereas hypoactivation was seen in the cerebellum. For the VBM analysis, ALE clusters of increased GMV in migraineurs were observed in the parahippocampus and putamen nucleus. Whereas clusters of reduced GMV in migraineurs were seen in the frontal gyri. Compared to HC, MwoA patients showed a GMV reduction in the insula, and anterior cingulate, whereas MwA patients showed GMV reduction in the cerebellum, cingulate gyrus, and insula. CM patients showed decreased GMV in the precentral gyrus, whereas EM patients showed decreased GMV in the parahippocampus, and inferior frontal gyrus when compared to HC.

Conclusions: Our findings represent a potential biomarker for the diagnosis and management of migraine, by showing clustered brain regions of abnormal patterns of activation and GMV changes between migraineurs and HC which might be associated with hyposensitivity to pain in migraineurs. Further studies are required to determine disease progression or therapeutic interventions' effect on migraine.

Abbreviations: ALE = activation likelihood estimation, BA = Brodmann area, CM = chronic migraine, EM = episodic migraine, fMRI = functional MRI, GMV = gray matter volume, HC = healthy controls, MNI = Montreal Neurological Institute, MwA = migraine with aura, MwoA = migraine without aura, NOS = Newcastle-Ottawa Scale, ROI = region-of-interest, SD = standard deviation, VBM = voxel-based morphometry.

Keywords: activation likelihood estimation, functional MRI, migraine, nociceptive stimulation, pain processing, voxel-based morphometry

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This study did not include human subjects thus ethical statement was not required.

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1. Introduction

Migraine is a primary headache disorder that causes throbbing pain usually on one side of the head. It is the most common neurological disease with predominance in females and the sixth-highest cause of disability worldwide.[1] The predominant symptom of migraine is severe headache attacks, which worsen during physical activity or stress, and may be accompanied by loss of appetite, nausea, and vomiting.[2]

Migraine can be classified according to The International Headache Society (IHS) into migraine with aura (MwA) and migraine without aura (MwoA) with specific symptoms associated with each one. In MwoA, which represents the most common type of migraine, patients suffer from moderate to severe headache attacks with an average duration between 4 to 72 hours that are felt as a unilateral pulsation, and usually increase in severity with physical activities and do not respond to treatment. These symptoms are usually accompanied by nausea, vomiting, and photophobia or phonophobia.[3] On the other hand, MwA is a less common type occurring in only 30% of migraineurs and is characterized by several reversible focal neurological symptoms that come before, with, or in the absence of headache. The visual aura phenomenon comes in the form of spots and zig-zag lines at the center of the visual field and is followed by motor, sensory, speech, and language symptoms.[4–6]

According to the frequency of headaches, migraine can be classified into episodic and chronic migraine. Episodic migraine (EM) has an average headache duration between 4 to 72 hours, and attack frequencies of <15 days per month. Whereas chronic migraine (CM) has a higher frequency of headaches for more than 3 months with an average of 15 days per month.[7]

Migraine can also be classified into four cycling phases: preictal, ictal, postictal, and interictal.[8] The preictal phase lasts up to 48 hours before the onset of a headache attack. Some evidence suggests an activation of the hypothalamus immediately before the headache attack which then leads to hypersensitivity and hypervigilance to incoming stimuli.[8] Whereas the ictal phase occurs during the headache attack and most symptoms can be seen in this phase, such as nausea, vomiting, and hypersensitivity to visual, olfactory, auditory, and somatosensory stimuli, and it can last for 4 to 72 hours.[9,10] In addition, the postictal phase begins after the headache attack and lasts up to 24 hours, then disappears, and is characterized by symptoms other than headaches such as cognitive deficits, fatigue, and others.[11] Finally, the interictal phase happens between migraine attacks, and patients in this phase are headache-free and asymptomatic.[12] Although most of the symptoms appear during migraine attacks, some ictal symptoms may also occur less predominantly in this phase.[13]

Although the mechanism and pathophysiology of migraine are not very well understood, several studies revealed structural and functional abnormalities in several brain regions, and magnetic resonance spectroscopy and positron emission tomography studies suggest mitochondrial dysfunction and defects in energy metabolism and other metabolic alterations in migraineurs.[14–16] Another proposed mechanism associated with pain processing and perception in migraine patients is a vasodilatory effect of intracranial and extracranial blood vessels near the trigeminal pathway, which will activate the release of vasoactive neuropeptides such as the substance P, calcitonin gene-related peptide and others.[3]

Neuroimaging modalities have recently been used to study the pathophysiology of migraine in different behavioral domains. Functional MRI (fMRI) has allowed researchers to study pain processing and perception in migraineurs during pain stimulation tasks, using noxious, visual, or auditory stimuli, and to investigate the relationship of atypical patterns of brain activation associated with migraine.[17] Another modality that has been used is voxel-based morphometry (VBM), which investigates volumetric changes in gray matter volume (GMV), white matter volume, and cerebrospinal fluid across the whole brain.[22,23] In this systematic review and meta-analysis, we aim to investigate the clustered and converged brain regions of activation and deactivation associated with pain processing in response to noxious stimuli in migraineurs compared to healthy controls (HC) and to assess the relationship between functional abnormalities and structural alterations in GMV across VBM studies.

2. Methods

2.1. Literature search and inclusion criteria

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The detailed study protocol is registered on PROSPERO and can be accessed through (CRD42022332314; URL: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=332314).

A systematic search through PubMed database was carried out for peer-reviewed English studies on the following keywords: "functional MRI", "task-based fMRI", "nociceptive stimuli", "pain perception", "migraine", "voxel-based morphometry", and "gray matter volume". The detailed search algorithm is shown in Supplemental Digital Content 1, http://links.lww.com/MD/H659. We also searched Sleuth (3.0.4) database from Brainmap (https://brainmap.org) for fMRI and VBM studies.[18,19]

A two-step screening process was done for the retrieved studies. First, two reviewers independently screened titles and abstracts for the following criteria: migraine patients and HC, task-based fMRI, and pain stimulation task. Studies were excluded if they: did not enroll HC, were on animal subjects, used resting-state fMRI, were on other types of headaches, or were case reports, reviews, or letters. Second, another two reviewers screened full texts of included studies for the following criteria: whole-brain coordinates are reported for task-based fMRI, coordinates reported for gray matter volume, and included between-group comparison HC and migraineurs. Studies were excluded if they: did not report coordinates, used region-of-interest (ROI) analysis, had no pain stimulation fMRI, or did not compare with HC. A third reviewer made the judgment in case of disagreement in both steps.

2.2. Data extraction

Data were extracted from each study for the first author's name, year of the study, demographic variables for the number of migraineurs and migraine type, number of HC, mean age (Standard Deviation [SD]), clinical information for disease duration, and attack frequency. Imaging variables were extracted for the software used for analysis, image acquisition, pain stimuli for fMRI task, and threshold settings.

2.3. Quality assessment

The quality of included studies was assessed by two reviewers based on The Newcastle-Ottawa Scale (NOS) for fMRI studies,[20] and the 12-checklist tool for VBM studies which has been previously described by Strakowski et al[21] The NOS tool evaluates the quality based on three domains: cohort selection, comparability between cases and controls, and exposure, with a total of 8 subcategories. The scale's overall score ranges from 0 to 8. The risk of bias was rated as high (1–3), moderate (4–5), and low (6–8). The 12-checklist tool evaluated 3 domains: sample characteristics, methods for image acquisition and analysis, in addition to limitations and conclusions, with a total of 12 subcategories in which a score of 1, 0.5, or 0 was set, if the criteria were fully, partially, or not met. Detailed information for

the 12-checklist tool is shown in Supplemental Digital Content 2, http://links.lww.com/MD/H660.

2.4. Activation likelihood estimation

The activation likelihood estimation (ALE) is a quantitative meta-analytical approach for structural and functional neuroimaging studies, it calculates where foci from multiple experiments converge, by treating the reported coordinates as a spatial probability center, rather than single points. The ALE approach uses a random-effect model to calculate the converged areas between studies, rather than a fixed-effect model which compares between foci.[22–24] Foci data for fMRI and VBM studies were extracted by two reviewers for the first author's name, year of study, the number of subjects, and coordinates of each experiment in a 3D stereotactic format (x, y, z). Then, foci were transformed into the Montreal Neurological Institute (MNI) space using the icbm2tal tool developed by Lancaster et al[30,31] and provided by GingerALE, which is a better fit than Brett transform mni2tal tool. The meta-analysis was conducted by applying threshold settings of uncorrected *P* value < .001 and a minimum volume of 250 mm^3.

To explore regional differences of reduced GMV across migraine subtypes, we performed two subgroup analyses, the first contrast between MwA and MwoA relative to HC. The second contrast was between CM and EM compared to HC. We used an uncorrected *P* value threshold < .001 and a minimum volume of 250 mm^3.

The thresholded ALE images were visualized using Mango version 4.1 software for Windows OS (Research Imaging Institute – Mango [uthscsa.edu]), and placed on the 1 × 1 × 1 mm T1-weighted ICBM 2009c nonlinear symmetric template, which represents an unbiased non-linear average of the MNI152 database with high-spatial-resolution and signal-to-noise.[32,33] Anatomical labels were shown using the MNI atlas provided in Mango.[28,29]

3. Results

3.1. Study selection and sample characteristics

Out of 1136 studies identified from PubMed search, 58 studies were retrieved for assessment after duplicate removal and title and abstract screening. A total of 16 task-based fMRI and 22 VBM studies were included in the ALE meta-analysis after the full-text screening. The detailed screening process is shown in the PRISMA flow diagram in Figure 1.

The full sample comprised 1259 migraine patients and 995 healthy headache-free controls. Study characteristics and demographic data for fMRI and VBM studies are shown in Tables 1 and 2, respectively. Imaging and experimental data for fMRI and VBM studies are shown in Tables 3 and 4, respectively.

3.2. Quality assessment

Eleven fMRI studies showed a low risk of bias according to the NOS tool and 5 showed a moderate risk of bias due to unreported controls recruitment and pain exposure were tested for migraineurs only. All studies compared migraineurs and HC

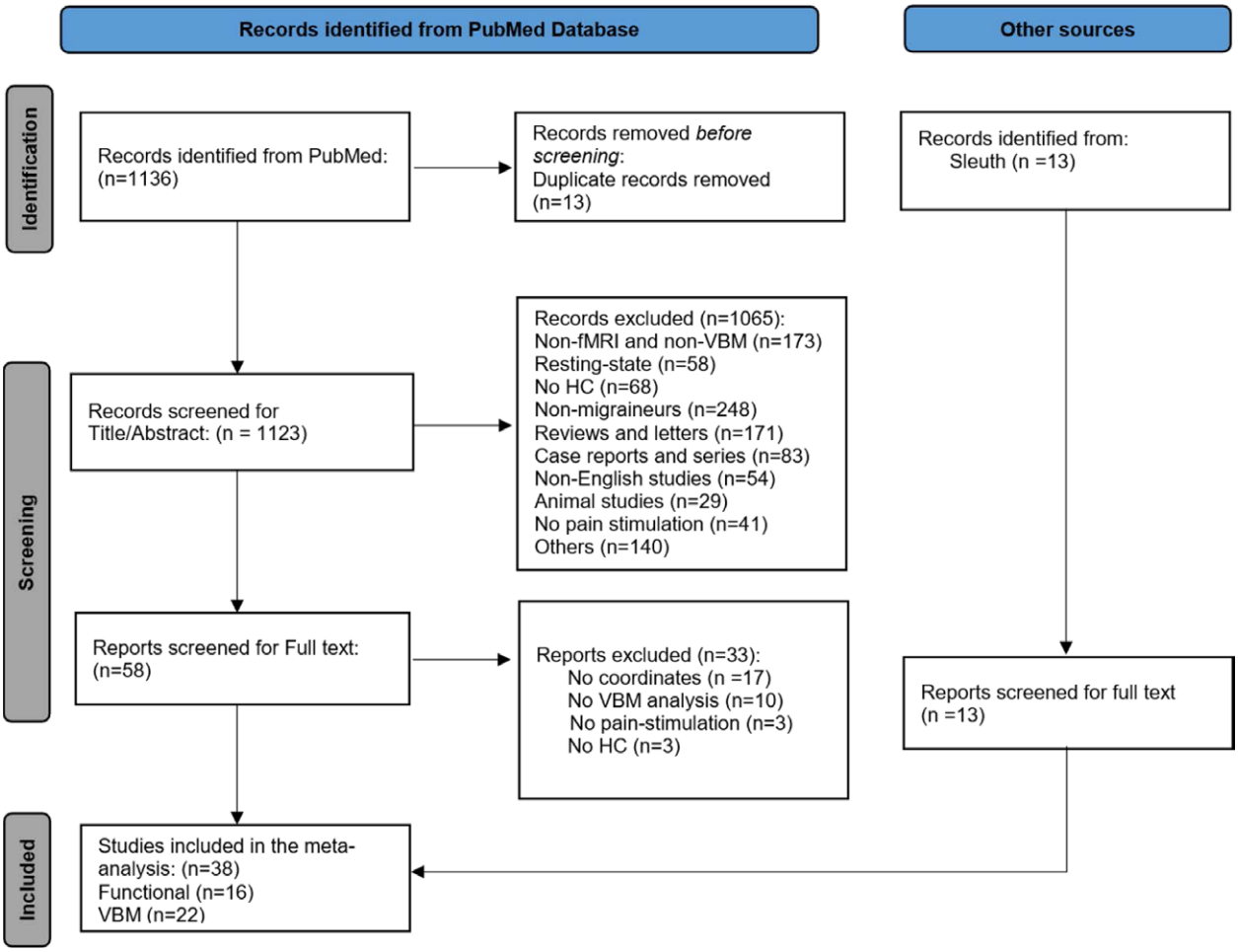

Figure 1. PRISMA flow diagram illustrating the screening process of included studies. fMRI = functional MRI, HC = healthy controls, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, VBM = voxel-based morphometry.

Table 1

Characteristics of included fMRI studies.

No.	First author (year)	Migraineurs	Males (N)	Mean age (SD)	Controls (M)	Mean age (SD)
1	Aderjan et al (2010)	6 MwA12 MwoA	9	32.13 (9.95)	15 (7)	28.8 (7.73)
2	Bogdanov et al (2019)	14 EM-MwoA5 MA7 CM-MOH	5	32.833.644.4	24	31.3
3	Chen et al (2015)	19 MwoA CA-15 MwoA CA+19 MwoCA	22	28.13 (8.03)26.47 (7.06)	20 (6)	28.10 (5.93)
4	Eck et al (2011)	4 MwA6 MwoA	1	37.9 (4.7)	10 (1)	37.8 (4.8)
5	Mehnert et al (2019)	40 MwoA14 MwA	9	34.3 (11.9)	54 (9)	32.6 (11.5)
6	Moulton et al (2008)	12 EM	3	42.2 (11.7)	12 (3)	42.3 (11.9)
7	Moulton et al (2011)	6 EM-MwoA5 EM-MwA	3	42.5 (11.9)	11 (3)	42.3 (11.9)
8	Mungoven et al (2022)	21 EM-MwoA4 EM-MwA	6	29.6 (2.0)	29 (10)	26.4 (1.4)
9	Russo et al (2016)	20 EM-MwoA CA+20 EM-MwoA CA-	10	32.1 (1.5)31.0 (1.8)	20 (5)	28.3 (1.4)
10	Russo et al (2012)	16 EM-MwoA	8	27.83 (1.26)	16 (8)	27.50 (1.70)
11	Russo et al (2017)	16 MwoA	1	31.31 (2.33)	16 (1)	29.13 (1.60)
12	Russo et al (2019)	18 EM-MwoA17 EM-MwA	15	32.47 (2.01)	15 (5)	27.40 (1.53)
13	Schwedt et al (2014)	8 EM-MwA16 EM-MwoA	5	36.2 (11.3)	27 (5)	33.7 (12.5)
14	Solstrands Dahlberg et al (2018)	21 EM	5	32.71 (8.3)	22 (5)	32.96 (8.9)
15	Stankewitz et al (2011)	10 MwA30 MwoA	9	20–46*	20 (5)	18–37*
16	Mathur et al (2016)	10 CM4 EM	3	40.8 (11.9)	14 (3)	38.9 (12.5)

CA = Cutaneous Allodynia, CM-MOH = chronic migraine medication overuse headache, MwA = migraine with aura, MwoA = migraine without aura, SD = standard deviation.
*Age in range.

Table 2

Characteristics of included VBM studies.

	Author (year)	Migraineurs	Males (N)	Mean age ± SD	Disease duration	Attack frequency	Controls	Mean age ± SD
1	Cao et al (2022)	34 MwoA-DI10 MwoA-DA	11	34.44 ± 10.0436.60 ± 13.02	10.68 ± 10.039.20 ± 3.79	9.61 ± 8.9811.90 ± 12.14	32 (16)	30.63 ± 9.56
2	Celle et al (2017)	19 EM-MwoA6 EM-MwA	23	75 ± 1.2	46.2 ± 16.4	7.4 ± 3.4	39 (9)	75.4 ± 0.9
3	Chen et al (2018)	31 EM-MwoA25 CM-MwoA	19	37.5 ± 7.6	194.6 ± 116.7	13.8 ± 10.5	43 (15)	36.2 ± 7.7
4	Chou et al (2020)	6 MwA34 MwoA	8	39.2 ± 10.5	14.7 ± 10.2	9.9 ± 6.5	27 (6)	41.3 ± 10.1
5	Coppola et al (2015)	24 EM-MwoA	5	31.6 ± 7.6	16.5 ± 6.6	3.4 ± 2.4	15 (4)	28.6 ± 4.0
6	Coppola et al (2017)	20 CM-MwoA	6	31.3 ± 10.2	15.0 ± 13.1	23.0 ± 6.8	20 (7)	28.5 ± 4.1
7	Hubbard et al (2014)	13 CM4 EM	4	41.71 ± 12.20	12.53 ± 8.41	11.65 ± 10.07	18 (4)	38.89 ± 11.25
8	Kim et al (2008)	5 EM-MwA15 EM-MwoA	3	33.7 ± 11.3	9.8 ± 6.0	32.7 ± 10.9/y	33 (4)	33.8 ± 10.5
9	Lai et al (2016)	66 CM-MwoA	27	40.2 ± 10.0	18.4 ± 10.4	32.2 ± 8.9	33 (6)	39.7 ± 11.1
10	Li Z et al (2020)	72 MwoA		21.30	66.75	5.89	46 (12)	21.24
11	Liu et al (2017)	80 MwoA		22.8 ± 0.3	59.8 ± 4.7	6.3 ± 0.81	50	22.6 ± 0.2
12	Liu h et al (2020)	44 CM-HFM12 EM-HFM	13	40.3 ± 10.5	17.2 ± 11.3	19.2 ± 7.1	37 (10)	39.93 ± 9.3
13	Messina et al (2016)	19 MwoA19 MwA19 VM	20	35.5135.140.0	16.513.615.7	526	20 (7)	36.9
14	Neeb et al (2016)	21 EM21 CM	12	49.36 ± 7.6249.04 ± 7.46	26.71 ± 14.4224.43 ± 8.3	5.33 ± 1.591715.9 ± 2.95	21 (6)	49.40 ± 7.79
15	Obermann et al (2014)	17 VM	3	42.71 ± 10.05	6.17 ± 4.51	3.79 ± 3.02	17 (3)	42.17 ± 9.26
16	Qin et al (2019)	50 MwoA	15	38.7 ± 11.2	8.6 ± 6.2	3.3 ± 2.8	50 (15)	39.5 ± 11.3
17	Rocca et al (2006)	7 MwA9 MwoA	1	42.7	24.8	20.3/y	15 (2)	38.6
18	Rocca et al (2013)	7 MwA5 MwoA	5	15.113.0	1.74.7	7/y23/y	15 (8)	13.3
19	Schmidt-Wilcke et al (2007)	32 EM3 CM	35	32.4 ± 9.2	N/A	N/A	31 (31)	32.2 ± 12.6
20	Valfrè et al (2008)	16 EM11 CM	6	32.1 ± 8.738.9 ± 6.4	20.6 ± 8.9	11.8 ± 9.7	27 (7)	34.9 ± 8.6
21	Yu et al (2021)	39 EM-MwoA17 CM-MwoA	18	39.74 ± 11.949.59 ± 14.64	N/A	3.75 ± 2.6419.56 ± 4.17	35 (15)	34.91 ± 10.89
22	Zhang et al (2017)	32 MwoA	8	38.3 ± 10.16	9.5 ± 6.23	3.36 ± 2.55	32 (8)	38.8 ± 10.02

CM = chronic migraine, DA = during attack, DI = during interictal, EM = episodic migraine, HFM = high-frequency migraine, MwA = migraine with aura, MwoA = migraine without aura, SD = standard deviation, VBM = voxel-based morphometry, VM = vestibular migraine.

Table 3

Image acquisition and experimental data for the included fMRI studies.

First author (year)	Pain stimuli	Imaging analysis	Image acquisition	Threshold settings
Functional studies				
Adrejan et al (2010)	Chemical	SPM5	3T Siemens Trio scanner	FWE-corrected *P* value < .05
Bogdanov et al (2019)	Thermal laser	SPM8	3T Siemens Magnetom Allegra scanner	FWE-corrected *P* value < .05
Chen et al (2015)	Electrical	SPM8	3T Siemens Trio Tim scanner	Uncorrected *P* value < .001
Eck et al (2011)	Verbal	SPM2	1.5T Siemens Magnetom Vision Plus scanner	Uncorrected *P* value < .005
Mehnert et al (2019)	Chemical	SPM12	3T Siemens Trio scanner	FWE-corrected *P* value < .01
Moulton et al (2008)	Thermal	FSL 4.0	3T Siemens Trio scanner	Uncorrected *z* = 1.6
Moulton et al (2011)	Thermal	FSL	3T Siemens Trio scanner	
Mungoven et al (2022)	Thermal	SPM12	3T Philips Achieva	FDR-corrected *P* value < .05
Russo et al (2016)	Thermal	BrainVoyager QX	3T GE Healthcare HDxt scanner	Uncorrected *P* value < .005
Russo et al (2012)	Thermal	BrainVoyager QX	3T GE Healthcare HDxt scanner	Uncorrected *P* value < .005
Russo et al (2017)	Thermal	BrainVoyager QX	3T GE Healthcare Signa HDxt scanner	Uncorrected *P* value < .005
Russo et al (2019)	Thermal	BrainVoyager QX	3T GE Healthcare Signa HDxt scanner	Uncorrected *P* value < .001
Schwedt et al (2014)	Thermal	SPM8	3T Siemens MAGNETOM Trio scanner	FWE-corrected *P* value < .05
Solstrands Dahlberg et al (2018)	Thermal	FEAT Version 6	3T Siemens Trio scanner	
Stankewitz et al (2011)	Chemical	SPM5	3T Siemens Trio scanner	Uncorrected *P* value < .001
Mathur et al (2016)	Thermal	SPM8	3T Siemens Trio Tim scanner	Corrected *P* value < .005

FDR = false-discovery rate, FWE = family-wise error, fMRI = functional MRI.

Table 4

Image acquisition for the included VBM studies.

First author (year)	Imaging analysis	Image acquisition	Threshold settings
VBM studies			
Cao et al (2022)	SPM12	3T MR (GE Discovery MR750 scanner)	FWE-corrected *P* value < .05
Celle et al (2017)	SPM8	1.5T Magnetom Avento, Siemens Healthcare	FWE-corrected *P* value < .05
Chen et al (2018)	SPM8	3T Siemens Magnetom Tim Trio	FWE-corrected *P* value < .05
Chou et al (2020)	SPM12	3.0T Discovery MR750 scanner	FWE-corrected *P* value < .05
Coppola et al (2015)	SPM8	3T Siemens Verio MRI scanner	Uncorrected *P* value < .05
Coppola et al (2017)	SPM12	3T Siemens Magnetom Verio scanner	FWE-corrected *P* value < .05
Hubbard et al (2014)	SPM8	3T Siemens Tim Trio MRI scanner	RFT-corrected *P* value < .05
Kim et al (2008)	SPM2	1.5T Siemens Sonata	SVC-corrected *P* value < .05
Lai et al (2016)	SPM8	1.5T GE Excite II MR system General Electric Healthcare	FWE-corrected *P* value < .05
Li et al (2020)	SPM12	3T Siemens Trio Tim system	FWE-corrected *P* value < .05
Liu et al (2017)	FSL	3T Signa GE Healthcare, Milwaukee, WI	FWE-corrected *P* value < .05
Liu et al (2020)	SPM12	3T GE Discovery MR750 scanner	FWE-corrected *P* value < .05
Messina et al (2016)	SPM12	3T Intera scanner	FWE-corrected *P* value < .05
Neeb et al (2016)	SPM8	3T Siemens Tim Trio	FWE-corrected *P* value < .05
Obermann et al (2014)	SPM8	1.55T Siemens Avanto scanner	FWE-corrected *P* value < .05
Qin et al (2019)	SPM12	3T Siemens Trio Tim system	FWE-corrected *P* value < .05
Rocca et al (2006)	SPM2	3T Philips Intera scanner	SVC-corrected *P* value < .05
Rocca et al (2013)	SPM8	3T Intera scanner	FWE-corrected *P* value < .05
Schmidt-Wilcke et al (2007)	SPM2	1.5T Siemens Symphony scanner	SVC-corrected *P* value < .05
Valfrè et al (2008)	SPM2	1T Siemens MAGNETOM IMPACT scanner.	FWE-corrected *P* value < .05SVC-corrected *P* value < .05
Yu et al (2021)	SPM8	3T MAGNETOM Skyra, Siemens Healthcare	Uncorrected *P* value < .05
Zhang et al (2017)	SPM12	3T Siemens Trio Tim MRI scanner	FDR-corrected *P* value < .05

FDR = false-discovery rate, FWE = family-wise error, SVC = small-volume correction, VBM = voxel-based morphometry.

for activation and deactivation. For the VBM studies, all studies reported a low risk of bias with scores > 8. Only 5 studies evaluated patients for a follow-up, 12 studies used sliced thickness for MRI > 3 mm or did not report full image acquisition. Detailed scores of each study are shown in the Supplemental Digital Content 3 and 4, http://links.lww.com/MD/H661.

3.3. ALE meta-analysis

3.3.1. ALE analysis of fMRI studies. Sixty-four foci from 30 fMRI pain stimulation experiments on 415 migraine patients and 325 HC showed increased activation in migraine patients in the right substantia nigra compared to HC (MNI coordinates [*x*, *y*, *z*]: 12, –12, –12). While showing decreased activation in the bilateral anterior lobe of the cerebellum through the culmen (MNI coordinates [*x*, *y*, *z*]: –8/10, –28, –20/–16]). Using a *P* value threshold < .003, migraineurs also showed increased activation in the middle frontal gyrus (Brodmann area [BA] 6) relative to controls (MNI coordinates [*x*, *y*, *z*]: –48, 10, 44). Peak MNI coordinates, cluster sizes, and *P* values are shown in Table 5. ALE maps of increased and decreased GMV are shown in Figure 2.

3.3.2. ALE analysis of VBM studies. A total of 50 experiments consisting of 845 migraine patients and 656 HC and 218 foci in which migraineurs showed an increase or decrease in GMV were entered in the ALE meta-analysis. ALE clusters of increased GMV in migraineurs compared to HC were observed in the left parahippocampus extending to the amygdala, left superior temporal gyrus (BA 22), left cuneus of the occipital

Table 5

ALE data for activation and deactivation, GMV increase and decrease in migraineurs versus HC.

Brain region	Brodmann area	MNI coordinates	Cluster size (mm^3)	*P* value ($\times 10^{-4}$)*
Increased activation				
R Substantia Nigra		12, −12, −12	169	.24301
L Middle frontal gyrus	BA 6	−48, 10, 44	115	.00015**
Decreased activation				
L Cerebellum-Culmen		−8, −28, −20	1009	.03075
R Cerebellum-Culmen		10, −28, −16	446	.00202
GMV increase				
L Amygdala		−26, −2, −14	534	.00103
R Cerebellar Tonsil		46, −46, −44	361	.00041
L Superior Temporal Gyrus	BA 22	−46, −54, 18	324	.00484
R Putamen		32, −2, −12	305	.00135
L Cuneus	BA 18	−18, −82, 28	201	.09347
GMV decrease				
L Inferior frontal gyrus	BA 44	−60, 12, 12	396	.00045
L Superior frontal gyrus	BA 6	−24, 16, 52	287	.02512
R Inferior frontal gyrus	BA 44	62, 14, 10	165	.38316
R Medial frontal gyrus	BA 25	4, 24, −24	159	.24263

ALE = activation likelihood estimation, BA = Brodmann area, GMV = gray matter volume, HC = healthy controls, L = left, MNI = Montreal Neurological Institute, R = right.

*Uncorrected *P* value < .001.

**Uncorrected *P* value < .003.

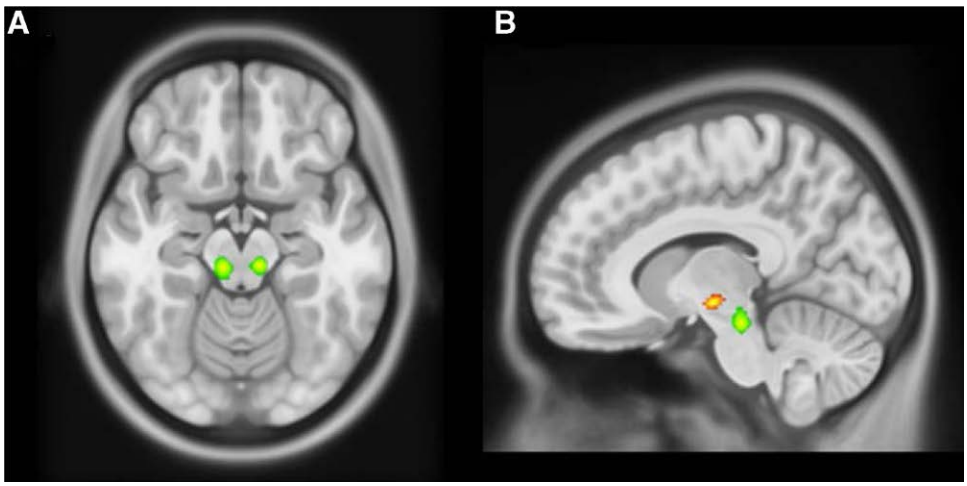

Figure 2. ALE maps of increased (red) or decreased (green) activation in migraineurs compared to healthy controls. (A) Left substantia nigra and right red nucleus of the midbrain. (B) Right subthalamic nucleus. ALE = activation likelihood estimation.

lobe (BA 18), and right posterior lobe of the cerebellum to the cerebellar tonsils, and right putamen nucleus (MNI coordinates: [−26, −2, −14], [−46, −54, 18], [−18, −82, 28], [46, −46, −44], [32, −2, −12], respectively). Whereas clusters of reduced GMV in migraineurs compared to controls were seen in the bilateral inferior frontal gyrus (BA 44), left superior frontal gyrus (BA 6), and right medial frontal gyrus (BA 25), (MNI coordinates: [−60/62, 12/14, 10/12], [−24, 16, 52], [4, 24, −24], respectively). Peak MNI coordinates, cluster sizes, and *P* values are shown in Table 5. ALE maps of increased and decreased GMV are shown in Figure 3. To exclude the confounding effect of age-related GMV reduction, a sensitivity analysis was performed for GMV reduction by excluding Celle et al study on elderly patients (mean age 75).[30] The results of the sensitivity analysis did not reveal different clustered areas than the pooled analysis, however, cluster size differed slightly as the following: bilateral inferior frontal gyrus (401 mm^3, 170 mm^3), left superior frontal gyrus (289 mm^3), and right medial frontal gyrus (165 mm^3).

3.3.3. Subgroup analysis of GMV in MwoA and MwA. A total of 59 foci from 12 experiments were included in the subgroup analysis of 756 subjects of MwoA and MwA relative to HC. When compared to HC, MwoA patients showed a decrease in GMV in the right insula, anterior cingulate, middle frontal gyrus, and left postcentral gyrus. While MwA patients showed GMV reduction in the right posterior lobe of the cerebellum, cingulate gyrus, insula, bilateral middle frontal gyrus, left fusiform gyrus, and inferior frontal and temporal gyri. Peak MNI coordinates, cluster sizes, and *P* values are presented in Table 6. ALE maps of increased and decreased GMV are shown in Figure 4.

3.3.4. Subgroup analysis of GMV in EM and CM. Seven experiments that consisted of 36 foci contributed to the subgroup analysis of 180 episodic migraineurs compared to HC, and 212 CM patients compared to HC. Chronic migraineurs showed decreased GMV in the left precentral gyrus (BA 13), whereas EM patients showed decreased GMV in the left uncus, precentral gyrus, parahippocampus, and right inferior frontal gyrus (BA 47). Peak MNI coordinates, cluster sizes, and *P* values are presented in Table 6. ALE maps of increased and decreased GMV are shown in Figure 5.

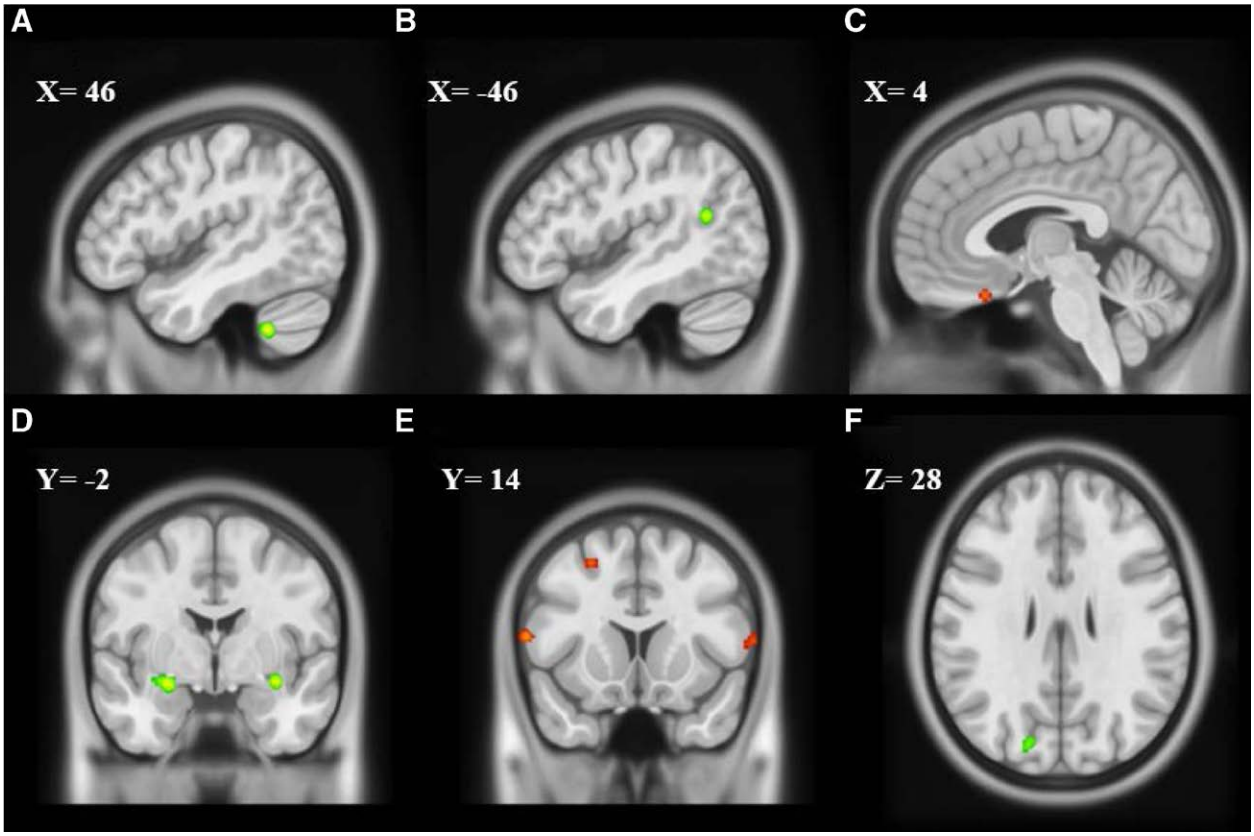

Figure 3. ALE maps of GMV increase (green) and decrease (red) in migraineurs versus HC. (A) Cerebellar tonsils, (B) Superior temporal gyrus (BA 22), (C) Medial frontal gyrus (BA 25), (D) Putamen and amygdala, (E) Bilateral inferior frontal gyrus and superior frontal gyrus, and (F) Cuneus of occipital lobe (BA 18). ALE = activation likelihood estimation, BA = Brodmann area, GMV = gray matter volume, HC = healthy controls.

Table 6

ALE data of subgroup analysis on GMV reduction in MwoA and MwA, CM, and EM.

Brain region	Brodmann area	MNI coordinates	Cluster size (mm^3)	*P* value ($\times 10^{-2}$)*
MwoA vs HC				
R insula	BA 47	36, 20, –8	298	.00255
R anterior cingulate	BA 32	4, 24, –14	267	.00662
L postcentral gyrus	BA 40	–36, –24, 48	212	.00855
R middle frontal gyrus	BA 11	22, 40, –20	149	.00926
MwA vs HC				
R posterior cerebellar lobe		10, –82, –20	437	.00069
L middle frontal gyrus	BA 6	–26, 14, 52	319	.00623
L inferior frontal gyrus	BA 44	–62, 12, 12	319	.00623
R cingulate gyrus	BA 32	2, 22, 44	305	.00242
R middle frontal gyrus	BA 9	40, 30, 24	305	.01737
L fusiform gyrus	BA 36	–50, –42, –22	305	.01737
R insula	BA 13	48, –18, 2	305	.00346
L inferior temporal gyrus	BA 20	–56, –16, –32	305	.00346
EM vs HC				
L precentral gyrus	BA 13	–52, –10, 10	165	.00555
CM vs HC				
L uncus	BA 28	–26, 8, –26	329	$.00087 \times 10^{-2}$
L parahippocampus	BA 34	–20, 2, –18	277	$.00776 \times 10^{-2}$
R inferior frontal gyrus	BA 47	38, 28, –20	262	$.00925 \times 10^{-2}$
L precentral gyrus	BA 6	–32, –12, 66	209	.00043

ALE = activation likelihood estimation, BA = Brodmann area, CM = chronic migraine, EM = episodic migraine, GMV = gray matter volume, HC = healthy controls, L = left, MwA = migraine with aura, MwoA = migraine without aura, MNI = Montreal Neurological Institute, R = right.

*Uncorrected *P* value < .003.

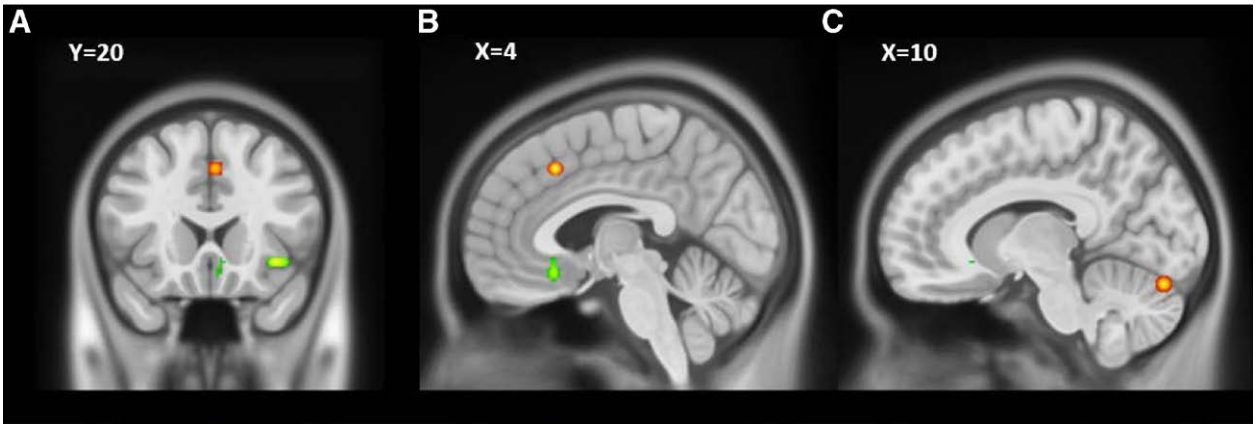

Figure 4. ALE maps of subgroup analysis of GMV reduction between MwA (red) and MwoA (green). (A) Insula and middle frontal gyrus, (B) Anterior cingulate and medial frontal gyrus, (C) Declive of the cerebellum. ALE = activation likelihood estimation, GMV = gray matter volume, MwA = migraine with aura, MwoA = migraine without aura.

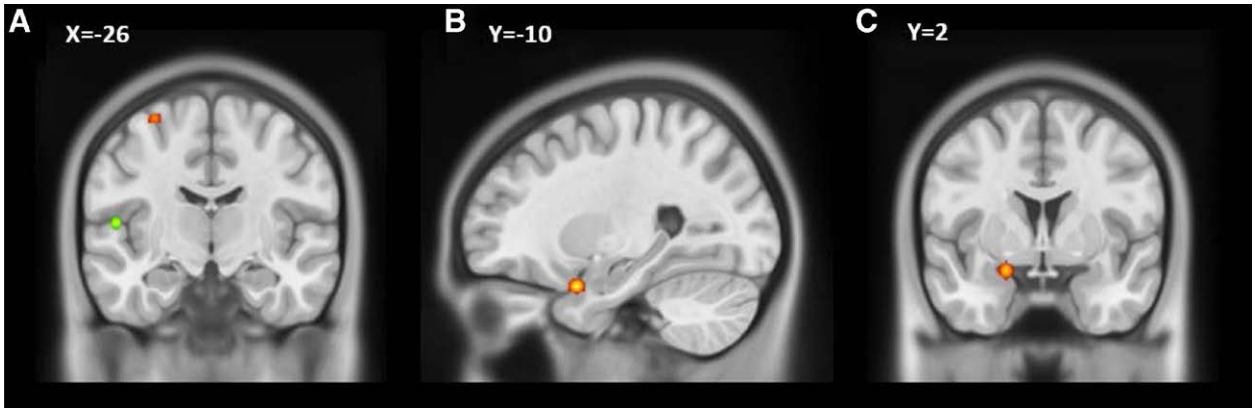

Figure 5. ALE maps of subgroup analysis of GMV reduction between CM (red) and EM (green). (A) Left uncus and precentral gyrus, (B) Left precentral gyrus, (C) Parahippocampus. ALE = activation likelihood estimation, CM = chronic migraine, EM = episodic migraine, GMV = gray matter volume.

4. Discussion

4.1. Main findings

4.1.1. Functional abnormalities. The ALE meta-analysis on fMRI studies revealed clusters of activation and deactivation in the subcortical regions including the substantia nigra, subthalamic and red nuclei of the midbrain. These regions show an important involvement in pain integration and processing.[31] Several studies reported atypical activation of the basal ganglia in pain induction and demonstrated the role of subthalamic and caudate nuclei in the integration of multisensory signals, which may be associated with the pathophysiology of migraine. In addition to its function in pain sensation, the subthalamic nucleus also participates in thermal sensation, playing a role in the decreased sensitivity to thermal and mechanical pain during heat or pain stimulation. Although several MRI studies reported different patterns of activation in frontal,[32–34] and cerebellar regions,[34,35] our results, did not reveal any clusters of increased or decreased activation in the prefrontal cortex or cerebellar regions. However, when we applied a more lenient threshold, clusters of increased activation were observed in the middle frontal gyrus in addition to the substantia nigra. On the other hand, clusters of decreased activation were observed in the bilateral anterior lobes of the cerebellum. These functional abnormalities correspond to the structural changes in GMV in migraineurs as observed in our study.

Surprisingly, an fMRI study by Stankewitz et al,[37] revealed stronger activation in HC than interictal migraineurs at the level of the trigeminal nuclei but did not show any difference in the thalamic nuclei or the somatosensory regions. However, this might be attributed to the biological differences between migraineurs and HC in the transmission of nociceptive stimulation signals, or that these findings are specific to and driven by trigeminal stimulation.[36]

4.1.2. GMV alterations. Several studies have reported consistent results of structural abnormalities in migraineurs using VBM analysis as an increase or decrease in GMV. In our study, we found clusters of increased GMV in limbic regions including the parahippocampus extending to the amygdala, subcortical regions such as the putamen of the lentiform nucleus, temporal cortex such as the superior temporal gyrus, the visual cortex including the cuneus of the occipital lobe, and cerebellar regions such as the cerebellar tonsils in the posterior lobe. On the other hand, we also found clusters of decreased GMV in migraineurs when compared to HC. These clusters were primarily located in the prefrontal cortex including the bilateral inferior frontal gyri, superior, and middle frontal gyri.

The prefrontal cortex is known to modulate executive functions and attention networks. However, several studies have reported an association of the prefrontal cortex activation in pain stimulation tasks. Its role can be thought of as directing the cognitive aspects to process and respond to pain stimuli.[38] Several studies have also

shown activation of the cerebellum in association with trigeminal nociception. The role of the cerebellum is underlined by pain perception rather than specifically on pain processing. Apart from its role in nociception, the cerebellum has also shown activation in migraine episodes.[30] The limbic network has also demonstrated a role in pain processing in migraineurs through the amygdala. While emotional processing is the major role served by the amygdala, in addition to the sensory perception of fear and anxiety, it also contributes to pain cognition such as memories and pain prediction, through its connection with cortical structures. It also receives nociceptive signals from the trigeminal system as well as subcortical regions and the spinal cord. When compared to MwoA, MwA patients showed GMV reduction in frontal and visual cortex regions, such as the cerebellum. This finding could be associated with the visual aura phenomena observed in these patients. A study by Rocca et al,[39] did not reveal any difference between MwA and MwoA, however, this may be due to the small sample size in each group. A case report and a cohort study found an association between the brainstem in the pathogenesis of migraine with aura.[40,41] In contrast to our results, a study by Neeb et al,[42] showed GMV increase in CM patients compared to HC, while showing GMV reduction in the prefrontal cortex for EM patients as observed in our study. As GMV reduction can be attributed to older age, we performed a sensitivity analysis excluding the study on elderly patients, however, we did not find any different clusters than the pooled analysis. This may be attributed to only one study had older patients.

4.2. Applicability of the evidence

Functional MRI studies on migraine patients have shown abnormal brain activation compared to HC, these patterns of hyperactivation or hypoactivation might be associated with an abnormal pattern of GMV increase or decrease as observed by VBM studies. In a study by Hubbard et al,[43] the resting-state functional connectivity in migraine patients showed disrupted connectivity in the default mode network and sensory network, including the posterior cingulate cortex, inferior frontal and temporal gyri, and the prefrontal cortex. These patterns were associated with increased attention and sensitivity to visual stimuli, or hypervigilance to ongoing pain.

To validate and increase the evidence of the applicability of fMRI or VBM studies on migraine, we collected all the results and quantitively synthesize them to present a putative biomarker in the diagnosis and management of migraine and migraine subtypes. The applicability of our findings relies on the methodology used to synthesize them and the number of evidence that contributed to the analysis.

4.3. Quality of the evidence

All Recruited studies allowed studying the functional and structural abnormalities associated with pain processing in migraine patients. As only 5 studies studied migraine patients with a follow-up after different time points, the long-term effect or the effect of medication from baseline could not be studied. All VBM studies used strong thresholds with correction for multiple comparisons such as false-discovery rate (FDR) or family-wise error (FWE), which provide more reliable results except for two studies.[44,45] Eight out of 16 fMRI studies did not use corrected *P* values.[32,35,37,38,46–49] And to avoid the bias of ROI-based analysis in fMRI studies, we constricted our inclusion to whole-brain analysis only.

4.4. Potential biases in the review process

The meta-analyses conducted in this study have several strengths. First, studies that used ROI-based analysis were excluded as this approach can present biased results and does not represent changes across the whole brain. Thus, to avoid the risk of biased results in our study, we limited our inclusion criteria to whole-brain neuroimaging studies only. Second, subgroup analyses were performed on the GMV changes in migraine groups according to the presence or absence of visual aura, and the duration of migraine into chronic or episodic. Third, the fMRI studies included in our meta-analysis are all consistent in terms of the studied behavioral domain, which was pain processing and management, this in turn adds homogeneity to the included studies. Fourth, we investigated the association of functional and structural abnormalities observed in migraine patients and concluded that GMV changes were concordant with the affected functional domains. Lastly, our study presents with high power due to a large number of studies included.

However, our findings should be interpreted with caution in the context of several limitations, some of which were out of our control. First, we could not apply the most stringent threshold settings of FWE-corrected for multiple comparisons as this approach needs a large number of foci and some clusters may be eliminated, so we applied a conservative threshold of uncorrected P value < .001. Second, our analysis was not constricted to a specific paradigm class, due to the heterogeneity across studies in experimental designs, and the results can be affected by the stimuli type or the induced regions. Regarding the VBM analysis, as it is based on linear statistics, and the distribution in reality is based on a Gaussian distribution, a non-linear hyperplane is a better representation for between group comparisons, thus, the VBM analysis can result in systemic differences between groups.[50–52] Third, some fMRI studies did not use correction methods for P values, which may affect the reliability of their results. Finally, we could not perform a subgroup analysis between different magnetic field strengths, as most studies used high strength, however, low field strength could affect the neuroimaging results, as the 3.0 T magnetic strength demonstrates a high-signal-noise ratio and can detect subtle changes in GMV and therefore more reliable than the 1.0 T strength.[25,26]

4.5. Future recommendations

There are several important recommendations for the advanced understanding of pain processing in migraineurs that should be addressed. First, future studies should report coordinate data of fMRI and VBM experiments using corrected thresholds, as our meta-analysis has included some uncorrected P value. Second, further longitudinal studies are also needed to evaluate the structural and functional differences between MwA in comparison with MwoA, and the potential changes occurring between its phases: preictal, ictal, postictal, and interictal phases. In addition, future exploration of the effects of medications on pain processing in migraineurs, and the comparison between medicated migraineurs and non-medicated is necessary. Finally, additional investigations of the potential effects of comorbidities on pain processing in migraineurs are needed.

5. Conclusions

In this study, we aimed to investigate the converged regions of abnormal activation and GMV patterns associated with migraine. Our results represent a potential biomarker for the diagnosis and management of migraine. Our findings suggest that the observed patterns of different brain activation and deactivation in frontal and cerebellar regions between migraineurs and HC might be associated with decreased pain sensitivity and increased attention to painful stimuli in migraineurs. These functional changes are parallel to the structural changes in the GMV of frontal and limbic regions in migraineurs, which represent an association between the structural and functional integrities of migraineurs' brain. Our sub-group analysis revealed

different clusters of GMV changes between MwA and MwoA, as MwA showed cerebellar changes which may indicate an association with the visual aura phenomenon in these patients. Thus, our study represents a potential biomarker for the diagnosis and management of migraine and the differentiation between migraine subtypes. Further studies are required to establish how these functional and structural changes can be used to observe disease progression or utilized in therapeutic interventions.

Author contributions

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References

[1] Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163–96.
[2] Olesen J, Bes A, Kunkel R, et al. The International classification of headache disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629–808.
[3] Gallagher RM, Cutrer FM. Migraine: diagnosis, management, and new treatment options – PubMed. Am J Manag Care. 2002:S58–73. Available at: https://pubmed.ncbi.nlm.nih.gov/11859906/ [access date May 31, 2022].
[4] Coppola G, Di Lorenzo C, Parisi V, et al. Clinical neurophysiology of migraine with aura. J Headache Pain. 2019;20:42.
[5] Russel MB, Olesen J. A nosographic analysis of the migraine aura in a general population. Brain. 1996;119:355–61.
[6] Eriksen MK, Thomsen LL, Andersen I, et al. Clinical characteristics of 362 patients with familial migraine with aura. Cephalalgia. 2004;24:564–75.
[7] Aurora SK, Brin MF. Chronic migraine: an update on physiology, imaging, and the mechanism of action of two available pharmacologic therapies. Headache. 2017;57:109–25.
[8] Peng KP, May A. Redefining migraine phases – a suggestion based on clinical, physiological, and functional imaging evidence. Cephalalgia. 2020;40:866–70.
[9] Schwedt TJ, Krauss MJ, Frey K, et al. Episodic and chronic migraineurs are hypersensitive to thermal stimuli between migraine attacks. Cephalalgia 2011;31:6–12.
[10] Kelman L. The triggers or precipitants of the acute migraine attack. Cephalalgia. 2007;27:394–402.
[11] Evans RW, Gladstein J. Postictal headache and migraine. Headache. 2006;46:810–2.
[12] Filippi V, Steiger R, Beliveau V, et al. Investigating the migraine cycle over 21 consecutive days using proton magnetic resonance spectroscopy and resting-state fMRI: a pilot study. Brain Sci. 2022;12:646.
[13] Vincent M, Pedra E, Mourão-Miranda J, et al. Enhanced interictal responsiveness of the migraineous visual cortex to incongruent bar stimulation: a functional MRI visual activation study. Cephalalgia. 2003;23:860–8.
[14] Ashina S, Bentivegna E, Martelletti P, et al. Structural and functional brain changes in migraine. Pain Ther. 2021;10:211–23.
[15] Erdener SE, Kaya Z, Dalkara T. Parenchymal neuroinflammatory signaling and dural neurogenic inflammation in migraine. J Headache Pain. 2021;22:138.
[16] Terrin A, Bello L, Valentino ML, et al. The relevance of migraine in the clinical spectrum of mitochondrial disorders. Sci Rep. 2022;12:4222.
[17] Schwedt TJ, Chiang CC, Chong CD, et al. Functional MRI of migraine. Lancet Neurol. 2015;14:81–91.
[18] Ashburner J, Friston KJ. Voxel-based morphometry – the methods. Neuroimage. 2000;11:805–21.
[19] Ashburner J, Friston KJ. Why voxel-based morphometry should be used. Neuroimage. 2001;14:1238–43.
[20] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2000. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[21] Strakowski SM, Fleck DE, Welge J, et al. fMRI brain activation changes following treatment of a first bipolar manic episode. Bipolar Disord. 2016;18:490–501.
[22] Eickhoff SB, Laird AR, Grefkes C, et al. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp. 2009;30:2907–26.
[23] Eickhoff SB, Bzdok D, Laird AR, et al. Activation likelihood estimation revisited. Neuroimage. 2012;59:2349–61.
[24] Turkeltaub PE, Eickhoff SB, Laird AR, et al. Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. Hum Brain Mapp. 2012;33:1–13.
[25] Lancaster JL, Tordesillas-Gutiérrez D, Martinez M, et al. Bias between MNI and talairach coordinates analyzed using the ICBM-152 brain template. Hum Brain Mapp. 2007;28:1194–205.
[26] Laird AR, Robinson JL, McMillan KM, et al. Comparison of the disparity between Talairach and MNI coordinates in functional neuroimaging data: validation of the Lancaster transform. Neuroimage. 2010;51:677–83.
[27] Fonov V, Evans A, McKinstry R, et al. Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. Neuroimage. 2009;47:S102.
[28] Fonov V, Evans AC, Botteron K, et al. Unbiased average age-appropriate atlases for pediatric studies. Neuroimage. 2011;54:313–27.
[29] Jack L. Lancaster MJM. Multi-image analysis GUI – MANGO. 2020. Available at: http://rii.uthscsa.edu/mango/.
[30] Celle S, Créac'h C, Boutet C, et al. Elderly patients with ongoing migraine show reduced gray matter volume in second somatosensory cortex. J Oral Facial Pain Headache. 2018;32:67–74.
[31] Maleki N, Becerra L, Nutile L, et al. Migraine attacks the Basal Ganglia. Mol Pain. 2011;7:17.
[32] Russo A, Tessitore A, Esposito F, et al. Pain processing in patients with migraine: an event-related fMRI study during trigeminal nociceptive stimulation. J Neurol. 2012;259:1903–12.
[33] Schwedt TJ, Chong CD, Chiang CC, et al. Enhanced pain-induced activity of pain-processing regions in a case-control study of episodic migraine. Cephalalgia. 2014;34:947–58.
[34] Mathur VA, Moayedi M, Keaser ML, et al. High frequency migraine is associated with lower acute pain sensitivity and abnormal insula activity related to migraine pain intensity, attack frequency, and pain catastrophizing. Front Hum Neurosci. 2016;10:1–16.
[35] Chen N, Zhang J, Wang P, et al. Functional alterations of pain processing pathway in migraine patients with Cutaneous Allodynia. Pain Med (United States). 2015;16:1211–20.
[36] Hu X, Du M, Chen L, et al. Meta-analytic investigations of common and distinct grey matter alterations in youths and adults with obsessive-compulsive disorder. Neurosci Biobehav Rev. 2017;78:91–103.
[37] Stankewitz A, Aderjan D, Eippert F, et al. Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. J Neurosci. 2011;31:1937–43.
[38] Russo A, Tessitore A, Silvestro M, et al. Advanced visual network and cerebellar hyperresponsiveness to trigeminal nociception in migraine with aura. J Headache Pain. 2019;20:46.

[39] Rocca MA, Ceccarelli A, Falini A, et al. Brain gray matter changes in migraine patients with T2-visible lesions: a 3-T MRI study. Stroke. 2006;37:1765–70.
[40] Welch KMA, Cao Y, Aurora S, et al. MRI of the occipital cortex, red nucleus, and substantia Nigra during visual aura of migraine. Neurology. 1998;51:1465–9.
[41] Cao Y, Aurora SK, Nagesh V, et al. Functional MRI-BOLD of brainstem structures during visually triggered migraine. Neurology. 2002;59:72–8.
[42] Neeb L, Bastian K, Villringer K, et al. Structural gray matter alterations in chronic migraine: implications for a progressive disease? Headache. 2017;57:400–16.
[43] Hubbard CS, Khan SA, Keaser ML, et al. Altered brain structure and function correlate with disease severity and pain catastrophizing in migraine patients. eNeuro. 2014;1:e20.14.
[44] Coppola G, Di Renzo A, Tinelli E, et al. Evidence for brain morphometric changes during the migraine cycle: a magnetic resonance-based morphometry study. Cephalalgia. 2015;35:783–91.
[45] Yu Y, Zhao H, Dai L, et al. Headache frequency associates with brain microstructure changes in patients with migraine without aura. Brain Imaging Behav. 2021;15:60–7.
[46] Eck J, Richter M, Straube T, et al. Affective brain regions are activated during the processing of pain-related words in migraine patients. Pain. 2011;152:1104–13.
[47] Moulton EA, Burstein R, Tully S, et al. Interictal dysfunction of a brainstem descending modulatory center in migraine patients. PLoS One. 2008;3:1–5.
[48] Russo A, Esposito F, Conte F, et al. Functional interictal changes of pain processing in migraine with ictal cutaneous allodynia. Cephalalgia. 2017;37:305–14.
[49] Russo A, Tessitore A, Esposito F, et al. Functional changes of the perigenual part of the anterior cingulate cortex after external trigeminal neurostimulation in migraine patients. Front Neurol. 2017;8:1–9.
[50] Davatzikos C. Why voxel-based morphometric analysis should be used with great caution when characterizing group differences. Neuroimage. 2004;23:17–20.
[51] Feng Y, Zhang XD, Zheng G, et al. Chemotherapy-induced brain changes in breast cancer survivors: evaluation with multimodality magnetic resonance imaging. Brain Imaging Behav. 2019;13:1799–814.
[52] Fouche JP, Du Plessis S, Hattingh C, et al. Cortical thickness in obsessive-compulsive disorder: multisite mega-analysis of 780 brain scans from six centres. Br J Psychiatry. 2017;210:67–74.