Original Article

Potential neural mechanisms of acupuncture therapy on migraine: a systematic review and activation likelihood estimation meta-analysis update

Meng Qi[1,2]^, Yinzhong Wang[3], Yue Zhang[2]^, Yuchao Feng[4], Bo Liu[1,2]^

[1]The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China; [2]Department of Radiology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; [3]Evidence-Based Medicine Center School of Basic Medical Sciences, Lanzhou University, Lanzhou, China; [4]Department of Emergency, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China

Contributions: (I) Conception and design: M Qi; (II) Administrative support: B Liu; (III) Provision of study materials or patients: M Qi; (IV) Collection and assembly of data: M Qi, Y Wang; (V) Data analysis and interpretation: M Qi, Y Zhang, Y Feng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Bo Liu, PhD. The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China; Department of Radiology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, No. 111 Dade Road, Guangzhou 510120, China. Email: liubogzcm@163.com.

Background: Migraine is a common, disabling, chronic headache disorder. Acupuncture is one of the effective complementary therapies for migraine. However, the neural mechanisms of acupuncture on migraine remain unclear. With the increased number of neuroimaging studies of acupuncture for migraine in recent years, there is an urgent need to update the data for pooled analyses. This study aimed to comprehensively summarize the relevant literature, identify brain regions with significant changes in brain activity after acupuncture, and explore the potential neural mechanisms of acupuncture on migraine.

Methods: A search was conducted by two independent researchers for neuroimaging studies using resting-state functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) on the effects of acupuncture on migraine up to October 2023 in the databases of PubMed, MEDLINE, Embase, China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Science and Technology Journal Database (VIP), and Chinese Biomedical Literature Database (SinoMed). Observational studies and clinical trials in Chinese or English were included; abstracts and studies without peer review were excluded. Brain regions with increased or decreased activity in the true acupuncture (TA) and sham acupuncture (SA) groups were pooled. A meta-analysis was performed using the activation likelihood estimation (ALE) algorithm. Fail-safe N (FSN) analysis was performed for publication bias and jackknife analysis was implemented for sensitivity analysis.

Results: The ALE meta-analysis included 15 peer-reviewed functional brain imaging studies with 514 migraine patients (401 female; mean age 32.38 years) and 163 healthy controls (130 female; mean age 27.28 years). A total of 12 studies scored 18 and above on the quality assessment (out of a total of 20). The results showed two increased activity clusters (the left pons and posterior insula) and four decreased activity clusters [the left cerebellum, temporal lobe, and right precuneus (two clusters)] after TA relative to baseline ($P<0.001$ uncorrected, volume $>100\ mm^3$). We also identified five clusters of increased and seven clusters of decreased activity of SA relative to the baseline, and no overlap regions were found between the TA and SA groups ($P<0.001$ uncorrected, volume $>100\ mm^3$). The results showed high replicability and reliability.

^ ORCID: Meng Qi, 0000-0003-1617-7903; Yue Zhang, 0000-0002-8439-1488; Bo Liu, 0000-0002-9159-1226.

Conclusions: Acupuncture for migraine is a complex but targeted neuromodulation process, different from the random, nonspecific effects of SA. Emotional processing and sensitization reduction may be critical neurofunctional mechanisms of acupuncture. More high-quality randomized controlled studies are needed to validate the results.

Keywords: Acupuncture; migraine; magnetic resonance imaging (MRI); positron emission tomography (PET); activation likelihood estimation (ALE)

Submitted May 06, 2024. Accepted for publication Dec 13, 2024. Published online Jan 22, 2025.
doi: 10.21037/qims-24-916
View this article at: https://dx.doi.org/10.21037/qims-24-916

Introduction

Migraine is a common disorder affecting more than one billion people worldwide, resulting in 45.1 million years lived with disability and accounting for 5.6% of the global disease burden, more than all other neurological disorders combined (1). Presently, it seems that a number of migraine patients' demands are met by medication. However, nearly one in four patients assessed the effectiveness of medication as poor or very poor on the Migraine Treatment Optimization Questionnaire (2). As a result, more and more non-pharmacological alternative therapies are gaining attention, providing an important complement to pharmacological treatments (3,4).

Acupuncture has fewer adverse effects and can be used as an alternative treatment for patients for whom prophylactic medications are ineffective or contraindicated (3). The available evidence suggests that in preventing migraine, acupuncture may be at least similar to, and much safer than medications (5,6), and may be sustainable (7,8). Furthermore, acupuncture can reduce the risk of depression and anxiety during long-term follow-up (7). However, the underlying neural mechanisms of acupuncture for analgesia and prevention of migraine remain uncertain and warrant further investigation.

As the most commonly used functional imaging methods, positron emission tomography (PET) and resting-state functional magnetic resonance imaging (fMRI) have been used to study the neural mechanisms of migraine generation and intervention (8). Neuroimaging using fMRI and PET is similarly based on hemodynamic changes induced by vasodilatory mediators released from cortical and subcortical gray matter (GM) in response to increased computational and metabolic demand (9-11). These functional imaging studies have used various neuroimaging techniques to investigate multiple acupuncture therapies for migraine (12). Among these, the amplitude of low-frequency fluctuation (ALFF)/fractional ALFF (fALFF) and regional homogeneity (ReHo) are the main methods used to characterize voxel-level signals from different perspectives, providing complementary information on regional spontaneous brain activity (12-14). As a central nervous system disorder, prolonged and frequent migraine attacks may damage pain-related resting brain networks (15,16). Acupuncture may modulate the activity of brain regions and neural networks in different patterns during the pathogenic period (17,18).

Several articles have conducted systematic reviews (18-20) and coordinate-based meta-analyses on neural mechanisms of acupuncture treatment on migraine (21,22). Systematic reviews have limitations in the integration of objective data. The activation likelihood estimation (ALE) is the most commonly used algorithm for coordinate-based meta-analysis and quantitatively obtaining a more uniform investigation of neurobiological changes in neuropsychiatric disorders. The overlap between foci is assessed by modeling them as probability distributions centered on their respective coordinates (23-25). Due to the ability to reduce the subjectivity of descriptive systematic evaluation, ALE has been widely used in psychological, psychiatric, and neurological research (26-28). However, previous ALE analyses have been flawed regarding the selection and number of included literature. Although several high-quality clinical studies of acupuncture for migraine have been published recently, they have not yet been included in any prior analysis (29-31).

This study aimed to conduct an ALE analysis to include the latest functional imaging literature on acupuncture for migraine, integrate data from multiple studies, and objectively elucidate acupuncture's consistent response to migraine across studies. We present this article in accordance with the PRISMA-A reporting checklist (32) (available at https://qims.amegroups.com/article/view/10.21037/qims-24-916/rc).

Methods

Study registration

We used the meta-analysis definitions adopted by the Cochrane Collaboration. This study was registered with the PROSPERO registry (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42022334871). We used the PRISMA for Acupuncture checklist when writing our report (32). We performed a systematic search strategy to identify all relevant published observational studies and clinical trials. The databases of PubMed, MEDLINE, Embase, China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Science and Technology Journal Database (VIP), and Chinese Biomedical Literature Database (SinoMed) were searched up to October 2023. The key search terms included "migraine" AND "acupuncture OR needle OR electroacupuncture OR transcutaneous auricular vagus nerve stimulation (taVNS) OR taVNS" AND "functional magnetic resonance imaging OR fMRI OR positron emission tomography OR PET". The full search strategies are shown in Appendix 1. The database search was limited to published and peer-reviewed articles (excluding theses and conference abstracts) written in English or Chinese. A secondary search was performed by checking the reference lists of several reviews and related articles (8,17,18,20).

PET and fMRI are neuroimaging techniques commonly used to study migraine (33). Both represent hemodynamic changes due to metabolic demands and visualize activation in specific brain regions by measuring regional cerebral blood flow or blood oxygen levels (23,34). Based on the similarity and close correlation between the two neuroimaging techniques, we included literature using both techniques with reference to previous studies (23,34-37).

Inclusion criteria

The criteria for study selection were as follows: (I) whole-brain analysis using fMRI [including the fALFF, ALFF, ReHo, degree center, and functional connectivity (FC) density] or PET; (II) coordinates of activation lesions were provided in the Montreal Neurological Institute (MNI) or Talairach reference space; (III) all participants in the study were diagnosed with migraine; (IV) migraine was diagnosed according to the International Classification of Headache Disorders, 2nd or 3rd edition, in order to cover studies published before and after 2018 (38,39); (V) controlled studies, including sham acupuncture (SA), waiting groups, and blank or healthy controls. Clarifying note: patients were not restricted in terms of sex, age, acupuncture mode (manual or electroacupuncture), points (single or group), or sessions.

Exclusion criteria

The study exclusion criteria were as follows: (I) studies related to FC, structure, and brain-behavior were excluded because our study focused on changes in brain activity; (II) the study results were based on the area of interest rather than whole-brain analysis; (III) studies that were not peer-reviewed, such as dissertations and theses, were excluded to ensure the reliability of the results of the included studies; (IV) coordinate loci were not reported in the article or available through various approaches.

Data extraction

Independently, two authors (M.Q. and Y.W.) reviewed and identified studies that met the above criteria and collected data from reports, with a third investigator (B.L.) deciding the final inclusion in case of a dispute. Data extracted from each study included the following: (I) published data (author, year); (II) study design (subject cohort, control group, sample size, analytical method of fMRI); (III) acupuncture duration per session, frequency, total sessions, and duration; and (IV) standardized coordinate space (MNI or Talairach coordinates). *Table 1* summarizes the results of each study. PET or fMRI examinations were performed before and after treatment (the single post-treatment scan times are labeled in *Table 1*), and long-term treatment scans were performed after total sessions were completed.

Study quality assessment

We assessed the quality of each functional neuroimaging study using a checklist referencing Zhao *et al.* (21), which is a modified version of two previous articles (52,53) (Table S1). The list consists of sample characteristics (5 items, 10 points), methodology, and reporting (8 items, 10 points). The higher the score, the better the quality of the study. Acquisition of the highest score for each

Table 1 Information of included neuroimaging studies

Study	Year	Study design	Sample size (female/male)				Age (years)		Type of treatment and acupoints	Time/frequency	Total sessions/duration	Analytical method	Coordinate space	Foci	
			TA	SA	BL	HC	Patients	HC						+	–
Li C (29)	2023	RCT	12 (9/3)	13 (8/5)	13 (5/8)	10 (7/3)	TA: 36.1 (10.5); SA: 38.0 (10.4); BL: 38.5 (8.6)	30.4 (7.2)	Hand needle: GB20, LR3, EX-HN5, GV20, EX-HN1	30 min/5 sessions per course	10 sessions/2 courses	ALFF	MNI	2	2
												ReHo		0	1
Feng M (30)	2022	CCS	60 (47/13)	0	0	60 (45/15)	31.72 (6.65)	29.25 (7.26)	TaVNS: left concha	30 min/–	12 sessions/4 weeks	fALFF	MNI	0	8
Zhang Y (40)	2021	RCT	24 (24/0)	20 (20/0)	0	0	TA: 33.04 (6.43); SA: 35.30 (9.43)	–	Hand needle: GB20, GB8, PC6, SP6, and LR3	30 min/2–3 sessions per week	27 or 27±6 sessions/3 menstrual cycles	ALFF	Talairach	1	2
												ReHo		3	1
Liu S (41)	2021	CCS	40 (31/6)[†]	0	0	15 (13/2)	37.97 (9.82)	34.88 (6.66)	Hand needle: GV20, EX-HN5, bilateral GB20, GB8, GB5, GB15, LI4, and LR3	20 min/–	1 session/immediately	ReHo	MNI	1	0
										20 min/2 sessions per week	12 sessions/6 weeks	ReHo		1	0
Jia JN (42)	2021	N-RCT	15 (10/5)	0	0	0	39.3 (12.1)	–	Hand needle: headache location	–/3 sessions per week	12 sessions/4 weeks	ReHo	MNI	0	1
Wang ZW (31)	2021	CCS	18 (18/0)	–	–	10 (10/0)	–	–	Hand needle: GB20, GB8, and LR3/PC6	–/2–3 sessions per week	27 or 27±6 sessions/3 menstrual cycles	ReHo	Talairach	4	6
Wang YH (43)	2019	Crossover-RCT	27 (22/5)	27 (22/5)	0	0	32.5 (7.57)	–	TaVNS: left concha	8 min/–	1 session/30 min after stimulation	ALFF	MNI	1	0
Luo WT (44)	2019	Crossover-RCT	27 (25/2)	27 (25/2)	0	0	29.85 (8.09)	–	TaVNS: left concha	8 min/–	1 session/30 min after stimulation	fALFF	MNI	6	0
Li Z (45)	2017	RCT	35 (27/8)	11 (9/2)	16 (12/4)	42 (34/9)	21.29 (20.85–21.73)	21.21 (20.93–21.49)	Hand needle: GB34, GB40, SJ5/GB33, GB42, SJ8/ST36, ST42, and LI6	30 min/5 sessions per week	20 sessions/4 weeks	ALFF	MNI	3	1
Ning YZ (46)	2017	CCS	16 (13/3)	0	0	16 (13/3)	28.3 (6.0)	27.1 (4.8)	Hand needle: GB41	9 min/–	1 session/immediately	ALFF	MNI	1	4
Han X (47)	2017	N-RCT	10 (8/2)	0	0	10 (8/2)	31.7	–	Hand needle: GB41	10 min 10 sec/–	1 session/immediately	ReHo	Talairach	0	3
Zhao L (48)	2014	RCT-single bland	20 (14/6)	20 (12/8)	0	0	TA: 32.90 (10.99); SA: 37.25 (9.68)	–	Hand needle: SJ5, GB20, GB34, and GB40	30 min/4 sessions per week	32 sessions/8 weeks	ReHo	Talairach	19	14
Yang M (49)	2014	RCT	10[‡]	10[‡]	10[‡]	0	33.28 (8.03)	–	Electroacupuncture: SJ19, SJ8, and GB33	30 min/–	1 session/10 min after stimulation	PET	Talairach	7	1
Yang J (50)	2012	RCT	10[‡]	10[‡]	10[‡]	0	32.87 (8.71)	–	Electroacupuncture: GB34 and GB20	30 min/–	1 session/10 min after stimulation	PET	Talairach	11	7
Li XZ (51)	2008	N-RCT	6 (4/2)	0	0	[§]	32.5	–	Hand needle: SJ5, GB20, and GB34	30 min/–	1 session/immediately	PET	Talairach	2	3

Age: data are presented as mean (SD), median (range), or mean. Time: acupuncture time per session. Total sessions: data are presented as total number or range of total number. Foci: +, increased activity after TA; –, decreased activity after TA. [†], 37 of the 40 patients were included in clinical characterization. [‡], total female/male: 18/12. [§], data from one set of healthy people, without mentioning the number. –, not mentioned in the article. GB20 (Fengchi), LR3 (Taichong), EX-HN5 (Taiyang), GV20 (Baihui), EX-HN1 (Sishengcong), GB8 (Shuaigu), PC6 (Neiguan), SP6 (Sanyinjiao), GB5 (Xuanlu), GB15 (Toulinqi), LI4 (Hegu), GB34 (Yanglingquan), GB40 (Qiuxu), SJ5 (Waiguan), GB33 (Xiyangguan), GB42 (Diwuhui), SJ8 (Sanyangluo), ST36 (Zusanli), ST42 (Chongyang), LI6 (Pianli), GB41 (Zulinqi), and SJ19 (Luxi). TA, true acupuncture; SA, sham acupuncture; BL, blank control; HC, healthy control; RCT, randomized controlled trial; ALFF, amplitude low-frequency fluctuation; ReHo, regional homogeneity; MNI, Montreal Neurological Institute; CCS, case-control study; taVNS, transcutaneous auricular vagus nerve electrical stimulation; fALFF, fractional ALFF; N-RCT, non-RCT; PET, positron emission tomography.

item was considered adequate reporting. Two reviewers discussed the checklist thoroughly to reach a consensus before the formal assessment, and then the same reviewers independently assessed and cross-checked all included studies. Disagreements were resolved through negotiation.

ALE meta-analysis procedure

ALE values were calculated for each brain voxel according to Eickhoff *et al.*'s modified procedure and tested to determine the null distribution of the ALE statistic for each voxel (23). Each coordinate was modeled by a three-dimensional (3D) Gaussian function with a 12 mm full-width half-maximum but not as a single point. The lesions reported in any study were combined into model activation maps. Cluster analysis was performed on the threshold maps.

Meta-analysis was performed using GingerALE software version 3.0.2. (http://brainmap.org/ale/). The foci reported in the original study in Talairach space were converted to MNI space. The statistical significance of our analysis was corrected by using family-wise errors (FWEs) and a more liberal uncorrected P value with a P threshold (25). Results were multiply compared at P<0.05 and corrected for 1,000 replacement FWEs, whereas uncorrected P<0.001 was set to a minimum clustering volume of 100 mm^3. Each threshold ALE map was generated in MNI space and overlaid on the MNI template using MRIcroGL software 1.2.20220720 (https://www.nitrc.org/frs/?group_id=889). GM and white matter (WM) are shown simultaneously.

ALE map statistics comparison

ALE meta-analysis compared changes in brain activity produced by true acupuncture (TA) and SA relative to baseline and direct comparisons of TA and SA. TA means that the needles act on the TA points and produce a De-qi sensation at the site of the needles, which is a complex sensation of acidity, numbness, heaviness, distension, or dull pain (54). SA comprises two forms: (I) not acting on an acupuncture point, which does not produce a De-qi sensation, and (II) acting on a non-therapeutic acupuncture point, which produces a De-qi sensation. In auricular electroacupuncture studies, TA means that the electrode is located within the auricular vagal distribution area, and SA is in the auricular non-vagal distribution area.

Studies with TA group: (1a) increased brain activity (including fMRI and PET) after TA compared to baseline (TA > baseline); (1b) decreased activity after acupuncture compared to baseline (TA < baseline).

Studies with both TA and SA groups: (2a) increased activity after SA (SA > baseline); (2b) decreased activity after SA (SA < baseline); (2c) increased activity after TA relative to SA ("TA > baseline" *vs.* "SA > baseline"); (2d) decreased activity of TA relative to SA ("TA < baseline" *vs.* "SA < baseline"). The 2c and 2d analyses were run with 'Contrast Datasets' in GingerALE, and the positive results represent areas of overlap in the brain regions that changed after TA and SA treatments.

Studies providing a direct comparison between TA and SA: (3a) increased activity of TA relative to SA (TA > SA); (3b) decreased activity of TA relative to SA (TA < SA).

Publication bias

Fail-safe N (FSN) analysis proposed by Acar *et al.* was used to assess robustness against potential publication bias. This method involves adding random noise to the data and then performing the meta-analysis iteratively until a cluster is no longer significant. Noisy data were generated on R using the code provided by Acar *et al.* (55). The ALE analysis was iterated using both raw and noisy data until the actual FSN was determined.

Sensitivity analyses

The jackknife analysis was employed to perform sensitivity analyses, namely, performing the meta-analysis repeatedly while removing one experiment from each iteration (21,56). It is possible to assess whether effects are driven by a single experiment by examining the stability of the results after removing the experiment involved in each iteration.

Results

Study selection

A total of 15 studies were included in this study: nine articles in English and six in Chinese. Of the included studies, 12 used fMRI and three used PET (*Figure 1*, *Table 1*). Details of the method of acupuncture, acupoints, frequency and duration of treatment, and dropout state and reasons are shown in Table S2. PubMed, MEDLINE, Embase, CNKI, Wanfang Data, VIP, and SinoMed searches were conducted on 24 October 2023. The 15 peer-reviewed studies included 514 migraine patients (401 female; mean

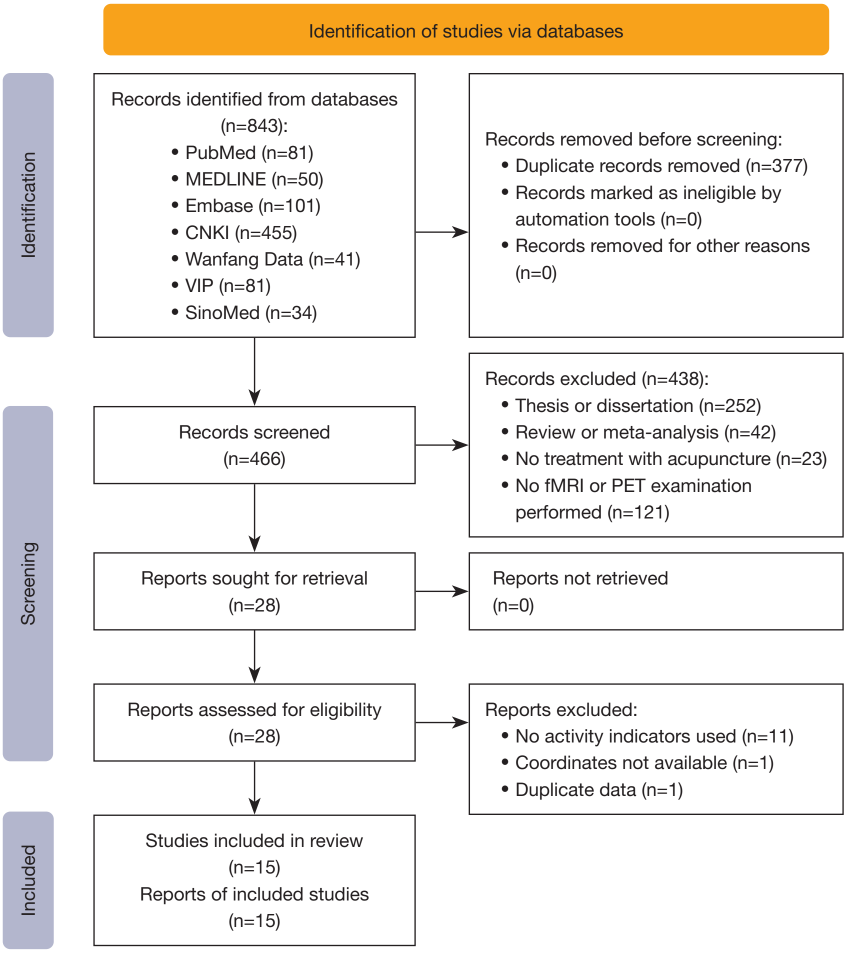

Figure 1 PRISMA flow diagram showing the ALE meta-analysis selection process procedure. CNKI, China National Knowledge Infrastructure; VIP, Chinese Science and Technology Journal Database; SionMed, Chinese Biomedical Literature Database; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; ALE, activation likelihood estimation.

age 32.38 years) and 163 healthy controls (130 female; mean age 27.28 years).

Eight studies used SA controls, of which four used SA point controls (without De-qi sensation), two used inactive TA points (with De-qi sensation), and two used an auricular scapha (non-vagal distribution area) as a control.

Quality assessment

Of the 15 included studies, four scored 20, seven scored 19, one scored 18, one scored 14, and two scored 12. All items were adequately reported in category 2 (methodology and reporting) in all studies except in the study by Han *et al.* (47). The results of the quality assessment are shown in *Table 2*.

ALE meta-analysis of TA studies

All 15 studies provided areas of altered brain activity after TA (364 participants), extracting 13 groups (293 participants, 62 foci) with increased activity and 14 groups (272 participants, 54 foci) with decreased activity coordinate data.

- ❖ (1a) Brain regions with increased activity after acupuncture (TA > baseline).

  The results of the ALE analysis showed two clusters (three peaks) of increased brain activity after TA, including the left pons (dorsomedial) and left insula (posterior) (*Table 3*, *Figure 2*).
- ❖ (1b) Brain regions with decreased activity after acupuncture (TA < baseline).

Table 2 Results of the quality assessment of the included studies

Study (first author, year)	Category 1: sample characteristics, item [score]					Category 2: methodology and reporting, item [score]								Total score
	1 [1]	2 [2]	3 [1]	4 [4]	5 [2]	1 [3]	2 [1]	3 [1]	4 [1]	5 [1]	6 [1]	7 [1]	8 [1]	
Li, 2023 (29)	1	2	1	4	2	3	1	1	1	1	1	1	1	20
Feng, 2022 (30)	1	2	1	4	2	3	1	1	1	1	1	1	1	20
Zhang, 2021 (40)	1	2	0	4	2	3	1	1	1	1	1	1	1	19
Liu, 2021 (41)	1	2	1	4	2	3	1	1	1	1	1	1	1	20
Jia, 2021 (42)	1	2	0	4	2	3	1	1	1	1	1	1	1	19
Wang, 2021 (31)	1	0	1	4	2	3	1	1	1	1	1	1	1	18
Wang, 2019 (43)	1	2	0	4	2	3	1	1	1	1	1	1	1	19
Luo, 2019 (44)	1	2	0	4	2	3	1	1	1	1	1	1	1	19
Li, 2017 (45)	1	2	1	4	2	3	1	1	1	1	1	1	1	20
Ning, 2017 (46)	1	0	1	0	2	3	1	1	1	1	1	1	1	14
Han, 2017 (47)	1	0	1	0	2	3	1	0	1	1	1	0	1	12
Zhao, 2014 (48)	1	2	0	4	2	3	1	1	1	1	1	1	1	19
Yang, 2014 (49)	1	2	0	4	2	3	1	1	1	1	1	1	1	19
Yang, 2012 (50)	1	2	0	4	2	3	1	1	1	1	1	1	1	19
Li, 2008 (51)	1	0	1	0	0	3	1	1	1	1	1	1	1	12

The results of the ALE analysis showed four clusters (four peaks) of decreased brain activity after TA, including the left cerebellum, temporal lobe, and right precuneus (two clusters) (*Table 3*, *Figure 2*).

ALE meta-analysis of SA studies

A total of six studies provided areas of altered brain activity after SA, extracting six groups (107 participants, 34 foci) with increased activity and three groups (40 participants, 9 foci) with decreased activity coordinate data.

❖ (2a) Brain regions with increased activity after SA (SA > baseline).

Meta-analysis revealed five clusters (eight peaks) of brain activity increased after SA, including the right insula (WM) and transverse temporal gyrus (TTG), left lingual gyrus (LG), middle frontal gyrus (MFG-GM and WM), insula (WM), and inferior frontal gyrus (IFG) (*Table 3*, *Figure 3*).

❖ (2b) Brain regions with decreased activity after SA (SA < baseline).

Meta-analysis revealed seven clusters (seven peaks) of reduced brain activity after SA, including the right parahippocampal gyrus (PG-WM), MFG, LG, cerebellum (two clusters), left inferior occipital gyrus (IOG), and posterior limb of the internal capsule (PLIC) (*Table 3*, *Figure 3*).

ALE meta-analysis of TA vs. SA studies

❖ (2c) Increased activity of TA compared to SA (“TA > baseline” *vs.* “SA > baseline”).

No clusters were found.

❖ (2d) Decreased activity of TA compared to SA (“TA < baseline” *vs.* “SA < baseline”).

No clusters were found.

❖ (3a, 3b) Only one article directly compared TA and SA, and no ALE analysis could be performed.

FSN analysis results

The number of additional noise clusters that must be added to cause the failure of the identification of brain clusters to converge is listed in *Table 3*. Based on the literature by Acar *et al.*, we used two times the number of included studies as a lower bound and 10 times as an upper bound (55). That

Table 3 Clusters and brain regions derived from ALE meta-analyses

Cluster number	ALE value	MNI			Label			Matter	Brodmann area	Cluster size (mm^3)	FSN	Jackknife analysis
		X	Y	Z	Left/right brain divisions	Lobes	Gyrus					
1a												
1	0.010479	–12	–34	–34	Left brainstem	Pons	DMP	Gray	–	360	32	11/13
	0.010404	–12	–38	–38	Left brainstem	Pons	DMP	Gray	–	–	32	11/13
2	0.009311	–44	–10	4	Left cerebrum	Sub-lobar	Insula	Gray	13	176	27	11/13
1b												
1	0.012874	–18	–74	–20	Left cerebellum	Posterior lobe	Declive	Gray	–	432	50	13/14
2	0.010656	2	–54	42	Right cerebrum	Parietal lobe	Precuneus	Gray	7	320	69	12/14
3	0.010745	–48	–46	–6	Left cerebrum	Temporal lobe	Sub-gyral	White	37	312	32	12/14
4	0.010084	6	–60	66	Right cerebrum	Parietal lobe	Precuneus	Gray	7	152	69	13/14
2a												
1	0.010884	42	–18	4	Right cerebrum	Sub-lobar	Insula	White	13	824	50	5/6
	0.009665	42	–24	12	Right cerebrum	Temporal lobe	TTG	Gray	41	–	13	5/6
2	0.008414	4	–70	0	Inter-hemispheric	Occipital lobe	LG	Gray	–	304	54	4/6
	0.008407	–2	–70	0	Left cerebrum	Occipital lobe	LG	Gray	–	–	54	5/6
3	0.008116	–6	50	–16	Left cerebrum	Frontal lobe	MFG	White	32	232	<10	5/6
	0.008015	–6	54	–16	Left cerebrum	Frontal lobe	MFG	Gray	10	–	<10	5/6
4	0.008241	–40	–12	16	Left cerebrum	Sub-lobar	Insula	White	13	160	50	5/6
5	0.007959	–30	10	–22	Left cerebrum	Frontal lobe	IFG	Gray	47	120	51	5/6
2b												
1	0.006526	32	–28	–16	Right cerebrum	Limbic lobe	PG	White	–	328	42	2/3
2	0.00811	50	8	44	Right cerebrum	Frontal lobe	MFG	Gray	6	328	42	2/3
3	0.006331	36	–54	–40	Right cerebellum	Posterior lobe	Cerebellar Tonsil	Gray	–	240	<10	2/3
4	0.006405	–32	–88	–14	Left cerebrum	Occipital lobe	IOG	Gray	–	240	<10	2/3
5	0.0065	6	–72	–6	Right cerebrum	Occipital lobe	LG	Gray	–	232	<10	2/3
6	0.006462	44	–60	–54	Right cerebellum	*	*	*	–	224	49	2/3
7	0.006596	22	–10	12	Right cerebrum	Sub-lobar	PLIC	White	–	224	<10	2/3
2c	None											
2d	None											
3a	None											
3b	None											

*, clusters outside the brain atlas. Clusters above the threshold, the maximum ALE value of that cluster, and the MNI coordinates (X, Y, and Z) of the maximum ALE value. The threshold was set at P<0.001 with volume >100 mm^3. (1a) Brain regions with increased brain activity after TA compared to baseline (TA > baseline); (1b) decreased activity after acupuncture compared to baseline (TA < baseline); (2a) increased activity after SA (SA > baseline); (2b) decreased activity after SA (SA < baseline); (2c) increased activity after TA relative to SA ("TA > baseline" *vs*. "SA > baseline"); (2d) decreased activity of TA relative to SA ("TA < baseline" *vs*. "SA < baseline"); (3a) increased activity of TA relative to SA (TA > SA); (3b) decreased activity of TA relative to SA (TA < SA). Label: describe the location of each cluster, with three columns representing left/right cerebrum/cerebellum, lobes, and gyrus respectively; the number of additional noise clusters that must be added to cause the failure of the identification of brain clusters to converge. ALE, activation likelihood estimation; MNI, Montreal Neurologic Institute; FSN, fail-safe N; DMP, dorsomedial pons; TTG, transverse temporal gyrus; LG, lingual gyrus; MFG, medial frontal gyrus; IFG, inferior frontal gyrus; PG, parahippocampal gyrus; IOG, inferior occipital gyrus; PLIC, posterior limb of the internal capsule; TA, true acupuncture; SA, sham acupuncture.

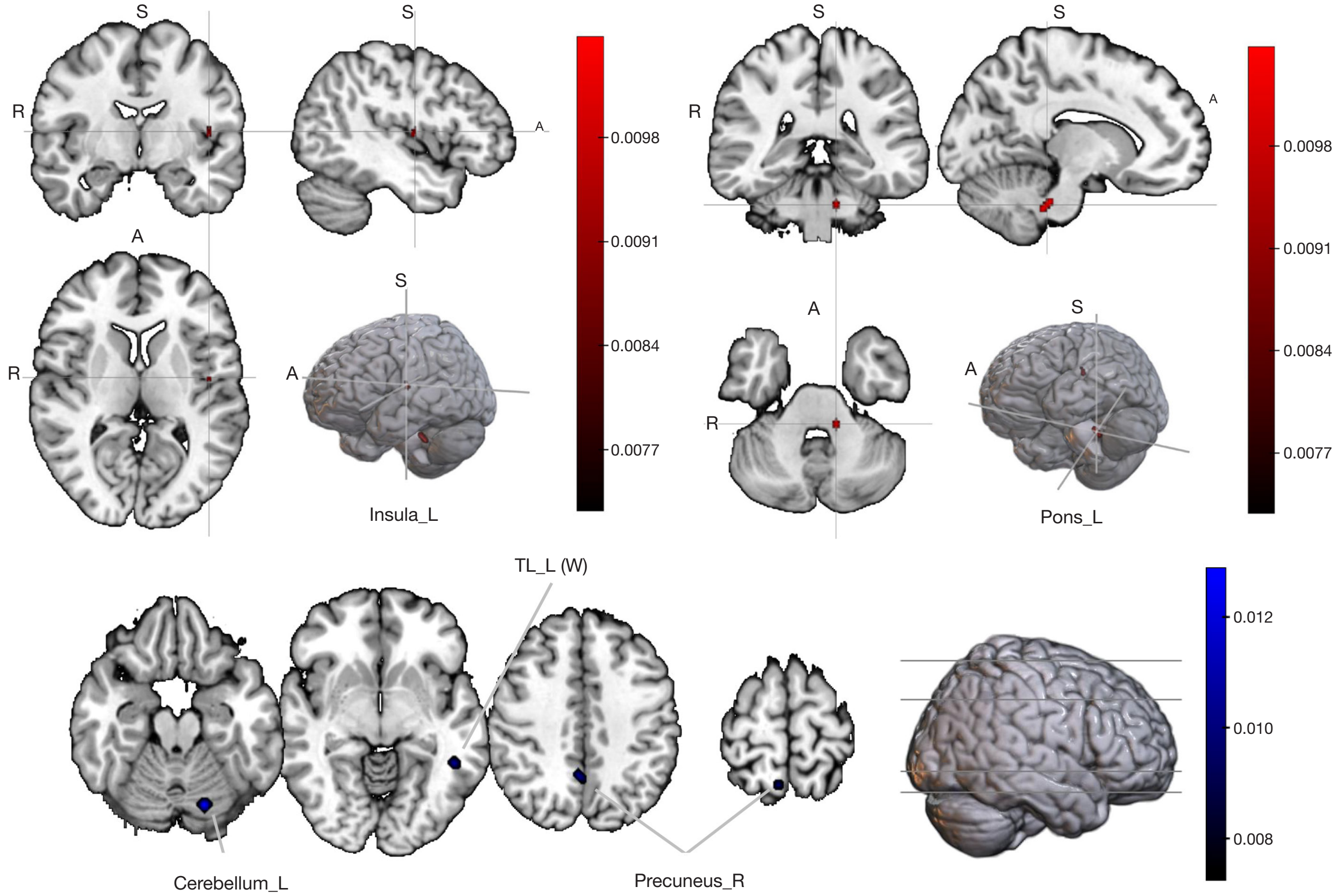

Figure 2 Brain regions with altered functional brain activity after TA. The results are superimposed on a template brain (in MNI coordinate space) using MRIcroGL. Red colors indicate regions with increased activity; blue indicates decreased activity. Color bars show ALE scores. S, superior; R, right; A, anterior; L, left; TL, temporal lobe; W, white matter; TA, true acupuncture; MNI, Montreal Neurological Institute; ALE, activation likelihood estimation.

is, an FSN between 30 and 150 was considered robustly adequate, and within this bound, the higher the amount of noise clusters, the better robustness of the results. In our results, except for the left insula in 1a (FSN =27), the robustness in the TA group was adequate, the right precuneus in 1b showed the best robustness (FSN =69). In the SA group, six out of eight peaks in 2a and three out of seven peaks in 2b showed adequate robustness. The left MFG in 2a, the right cerebellum, left IOG, and right LG in 2b showed poor robustness (FSN <10), whereas the left LG in 2a showed the best robustness (FSN =54).

Jackknife analysis results

We performed jackknife analysis of increased and decreased activity after TA and SA (ALE meta-analysis 1a, 1b, 2a, 2b). The results showed that in ALE 1a, the reproducibility of all clusters was up to 11/13, representing that the corresponding clusters survived 11 out of 13 repeated operations. In ALE 1b, the reproducibility of clusters 1 and 4 was 13/14, and that of clusters 2 and 3 was 12/14. The results of the sensitivity analysis suggested that the results of the meta-analysis were of high replicability and reliability. The results are shown in *Table 3* and appendix available at https://cdn.amegroups.cn/static/public/10.21037qims-24-916-1.xlsx.

Discussion

The results of ALE analysis showed increased brain activity in the left pons and insula, specifically in the left dorsomedial pons (DMP) and posterior insula (PI) after TA. The decreased activity regions were located in the left cerebellum,

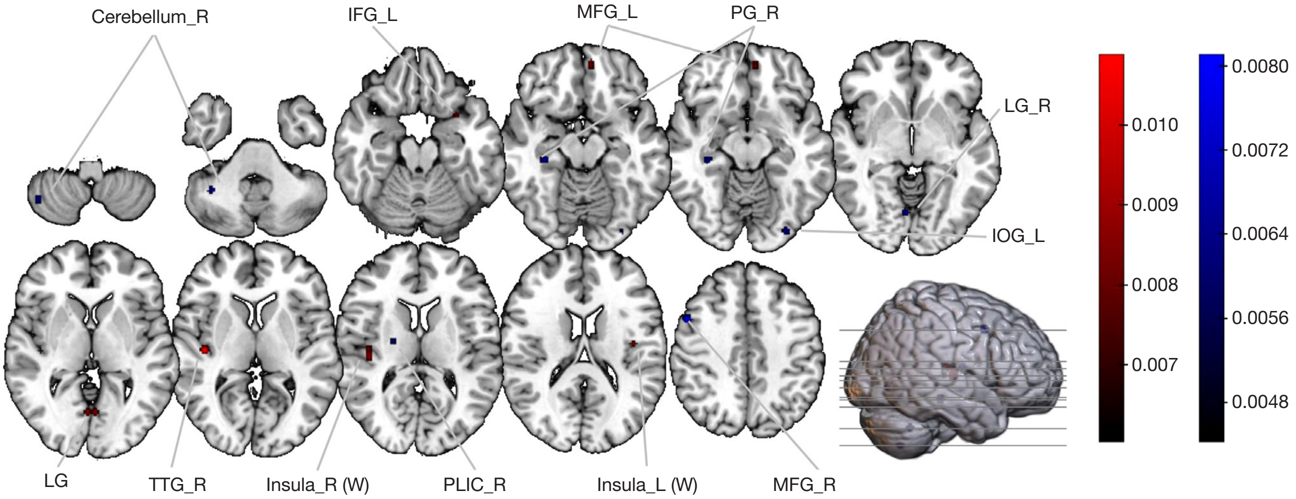

Figure 3 Brain regions with altered functional brain activity after SA. Red colors indicate regions with increased activity; blue indicates decreased activity. Color bars show ALE scores. R, right; IFG, inferior frontal gyrus; L, left; MFG, medial frontal gyrus; PG, parahippocampal gyrus; LG, lingual gyrus; IOG, inferior occipital gyrus; TTG, transverse temporal gyrus; W, white matter; PLIC, posterior limb of the internal capsule; SA, sham acupuncture; ALE, activation likelihood estimation.

temporal lobe (WM), and the right precuneus. SA increased activity in brain regions of the bilateral insula (WM), right TTG, left LG, MFG, and IFG, and decreased activity in brain regions of the right PG (GM), MFG, cerebellum, LG, PLIC, and left IOG. There was no overlap between the brain areas with activity changes after TA and SA.

Increased brain activity

The results showed that the brain regions with increased activity after acupuncture had the largest cluster size located in the DMP. The DMP contains 5-hydroxytryptamine (5-HT) neurons, essential in emotional regulation (57). Migraine attacks increase 5-HT receptor availability in this region. Conversely, a weakening of the 5-HT system may lead to chronicity of the migraine course, consistent with a significant reduction in DMP volume in migraine patients (58). Acupuncture can promote the release of 5-HT. For example, electroacupuncture stimulation at the Jianshi to Neiguan (PC5–PC6) acupoints on the median nerve of the forelimbs activates 5-HT-containing neurons and attenuates sympathetic excitatory cardiovascular reflexes (59). In addition, increased release of 5-HT from the volar nucleus was observed after 20 minutes of acupuncture at bilateral Shenshu points (BL23) (60). The present study showed the most significant increase in DMP activity after acupuncture, which, given the close relationship between DMP and emotion, would suggest that the procedure of acupuncture treatment on migraine may involve emotional processing.

The left PI is another brain region with increased activity after acupuncture and the most pain-related area among the three subregions of the insula (61). The PI may play a fundamental role in human pain by acting as a nonspecific central station for perception (62,63). In contrast to SA without somatosensory contact, the PI of TA showed greater activation relative to the anterior insula, demonstrating the critical role of the PI in pain perception during acupuncture (64). The PI is also a vital pain integration center strongly associated with the thalamus, the primary and secondary somatosensory cortex (65). In female migraine patients, the PI has decreased nodal centrality and exhibits reduced connectivity to many other brain regions (66). Shuaigu (GB8) electroacupuncture treatment triggers immediate pain relief by partially reversing the FC between the PI, which can be stabilized by repeated stimulation (67). The increased activity of the PI after acupuncture may provide some indirect evidence supporting the important role of PI in pain perception and integration, and perhaps provide some additional objective evidence for pain reduction after acupuncture in migraine patients.

Notably, although the thalamus is closely related to migraine, and some previous systematic evaluations and meta-analyses have found increased activity of the thalamus after acupuncture in migraine patients (21,68), no effect of acupuncture on thalamic activity was found in our results. The reason may be the different literatures included and the thresholds analyzed. Since we used a more stringent threshold, the thalamus was not involved in the results.

It is important to note that the current findings, in addition to suggesting specific changes resulting from acupuncture intervention for migraine, may also include general changes from the acupuncture intervention itself that are not limited to migraine (69). For example, insula activity changes also occur after acupuncture treatment for conditions such as shoulder and neck pain, primary insomnia, and mild cognitive impairment (70-72). However, a significant portion of current acupuncture research involving pons and insula still focuses on pain-related disorders (73,74). More cross-sectional statistical studies are needed to provide sufficient evidence.

Decreased brain activity

We found that acupuncture decreased brain activity in the cerebellum in migraine patients. The cerebellum possesses the largest number of neuropeptide calcitonin gene-related peptide (CGRP)-binding sites in the central nervous system, and CGRP plays an important role in the pathophysiology of migraine (75,76). Migraine-like symptoms were induced in mice when CGRP was injected into the intracerebral ventricles or the cerebellar nucleus (77). Migraine patients show alterations in the structure and function of the posterior cerebellum (78). Long-term follow-up studies have shown that migraine patients with poor prognosis had increased cerebellar GM volume. Moreover, cerebellar GM volume and structural connectivity between the cerebellum and cerebral cortex correlate with headache frequency. In other words, the increased structural volume and FC of the cerebellum may account for the persistence of headache symptoms with high-frequency migraine (79). The decrease in cerebellar activity after acupuncture may be associated with a reduced sensitivity of the CGPR to migraine-inducing symptoms, thereby reducing the incidence of migraine attacks. However, more direct evidence should be presented and validated in the future.

Another cluster of reduced activity after acupuncture was centered in the precuneus. The precuneus is closely associated with pain sensitivity and is thought to be the center of an integrated task involved in nociception and transmission (80,81). Individuals with the greatest increase in precuneus neural responses also experience pain most rapidly (82). Stronger transient dynamic functional network connections between the precuneus and posterior thalamus imply more frequent headache attacks (83). After 4 weeks of taVNS therapy on migraine, a significant decrease in fALFF values was observed in the bilateral precuneus and was positively correlated with a decrease in attacks, which can be used as a reliable biomarker to predict the response (30). Based on the relationship between precuneus and pain sensitivity, our study, combined with previous studies, suggests that acupuncture may modulate the precuneus to reduce sensitivity and decrease the frequency of attacks.

SA effects on brain activity

The activity-changing brain regions involved in SA were more dispersed than those involved in TA, consistent with previous PET studies' results. As Yang *et al.* presumed, SA may induce brain responses generally without a specific target, presenting a random, nonspecific brain response (49). In addition, the literature we included used different SA modalities, such as stimulation of sham acupoints, real acupoints that are not specific to migraine, or areas in the ear without vagus nerve distribution. This heterogeneity may also account for the dispersion of brain region responses to SA.

Although SA can cause widespread activity changes throughout the brain, none of these regions overlap with TA. We did not find overlapping brain regions in our analysis of both direct and indirect comparisons of TA and SA, even some brain regions are very close to each other. For example, our study showed increased activity in the insula with differences in GM (TA) and WM (SA). The results of the 2c and 2d subgroup analyses showed negative results, representing that no overlapping of brain regions that changed after TA and SA treatments were identified, after the ALE algorithm calculation. This finding is of great importance because only on this basis does the specific effect of TA on migraine patients make sense. TA and SA affect neural activity through different pathways, which may explain the differences in attack frequency (45).

From the currently available results of our study, there is insufficient evidence that TA may act through a placebo effect (that is, the overlap between TA and SA exists), but given the insufficient amount and heterogeneity of the included studies, further research is needed.

Advantages and significance

This study used the ALE method to avoid the subjective component of descriptive analysis (17,18,20). Compared with previous pooled neuroimaging analyses of acupuncture for migraine, our study has the following advances and strengths. First, to the best of our knowledge, our study included the largest number and highest quality of literature. On the one hand, the publication of high-quality papers in recent years has dramatically improved the quality level of the literature included in this paper (29,30,45,46). On the other hand, our study only includes peer-reviewed literature, and the quality of the literature and reliability of the data is further guaranteed to a certain extent. Second, we included fMRI and PET to ensure the comprehensiveness of the data. Third, we grouped loci according to increased and decreased activity after acupuncture, and set effective cluster thresholds to exclude loci with smaller ranges. Consequently, our results are likely to focus on brain regions with greater impact. As a result, the results of the present study are more comprehensive, accurate, and well-focused than those of previous studies.

Limitations and future research directions

First, although we included the largest number of articles to date, differences in imaging data analysis techniques reduced the number of studies that could be combined, resulting in findings that are shown at an uncorrected $P<0.001$. The next step is to increase the included literature and validate our results with more stringent corrections and thresholds.

In addition, the heterogeneity of the included studies should also be noted. First, although we excluded FC-related literature and focused on brain activity, we still included PET, ALFF, and ReHo, potential sources of heterogeneity. Second, we also included studies of hand acupuncture and auricular acupuncture, both of which have been shown to perform well in treating migraine (30,50), and both have been included in previous systematic analyses (18,84,85), yet the possibility of heterogeneity remains. Third, there may be potential differences in the immediate and long-term effects of acupuncture. The literature on different functional indicators, acupuncture techniques, and treatment duration is insufficient for subgroup analysis, which is another direction for future research.

Lastly, more evidence is needed to interpret neuroimaging results. It is important to point out that, unlike PET metabolic changes that can be directly correlated with the intensity of local neuronal activity, the blood oxygen level-dependent (BOLD) signal of fMRI can only be interpreted relatively, for example, compared with another experimental condition or with other time series of the same voxel. Resting-state fMRI data must be represented by a variety of metrics that only indirectly reflect the intensity of neuronal activity, such as ALFF for voxel fluctuations within a certain frequency range and ReHo for consistency of local activity (12-14). Although functional imaging is one of the best tools available to study spontaneous brain activity, it remains an indirect response to neural activity. However, despite the differences in actual possible brain activity represented by PET and fMRI, they have in common the ability to respond to the coordinates of abnormal or changed brain regions, which is the basis on which coordinate-based meta-analyses, including ALE analyses, are able to combine these studies (29-31).

More evidence is still needed on the relationship between functional imaging changes and the pathophysiology of migraine patients, as well as other techniques and indicators. Future studies should also focus on the neurological differences between subregions. More studies are needed to validate the differences in therapeutic effects and mechanisms between TA and SA, or combine functional imaging with clinical outcome between groups to be more compelling.

Conclusions

This ALE analysis identifies the effects of acupuncture on brain activity in migraine, including increased pain processing and integration, positive emotional activity, and decreased nociceptive sensitivity. Emotional processing and sensitization reduction may be critical neurofunctional mechanisms of acupuncture. Further functional imaging and longitudinal studies are needed to validate these findings and elucidate the causal mechanisms.

Acknowledgments

The authors acknowledge the published data available in the public domain for meta-analyses.

Footnote

Reporting Checklist: The authors have completed the PRISMA-A reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-916/rc

Funding: This work was supported by the Traditional Chinese Medicine Science and Technology Project of Guangdong Hospital of Traditional Chinese Medicine (No. YN2020MS09) (to B.L.), and the Science and Technology

Program of Guangzhou (No. 202102010260) (to B.L.).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-916/coif). B.L. reports that this study was supported by the Traditional Chinese Medicine Science and Technology Project of Guangdong Hospital of Traditional Chinese Medicine (No. YN2020MS09), and the Science and Technology Program of Guangzhou (No. 202102010260). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:459-80.
2. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology 2015;84:688-95.
3. Ashina M, Buse DC, Ashina H, Pozo-Rosich P, Peres MFP, Lee MJ, Terwindt GM, Halker Singh R, Tassorelli C, Do TP, Mitsikostas DD, Dodick DW. Migraine: integrated approaches to clinical management and emerging treatments. Lancet 2021;397:1505-18.
4. Puledda F, Shields K. Non-Pharmacological Approaches for Migraine. Neurotherapeutics 2018;15:336-45.
5. Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Vertosick EA, Vickers A, White AR. Acupuncture for the prevention of episodic migraine. Cochrane Database Syst Rev 2016;2016:CD001218.
6. Giovanardi CM, Cinquini M, Aguggia M, Allais G, Campesato M, Cevoli S, Gentili F, Matrà A, Minozzi S. Acupuncture vs. Pharmacological Prophylaxis of Migraine: A Systematic Review of Randomized Controlled Trials. Front Neurol 2020;11:576272.
7. Liao CC, Liao KR, Lin CL, Li JM. Long-Term Effect of Acupuncture on the Medical Expenditure and Risk of Depression and Anxiety in Migraine Patients: A Retrospective Cohort Study. Front Neurol 2020;11:321.
8. Schwedt TJ, Chiang CC, Chong CD, Dodick DW. Functional MRI of migraine. Lancet Neurol 2015;14:81-91.
9. Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc Natl Acad Sci U S A 1986;83:1140-4.
10. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995;34:537-41.
11. Logothetis NK. The underpinnings of the BOLD functional magnetic resonance imaging signal. J Neurosci 2003;23:3963-71.
12. Zou QH, Zhu CZ, Yang Y, Zuo XN, Long XY, Cao QJ, Wang YF, Zang YF. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. J Neurosci Methods 2008;172:137-41.
13. Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. Neuroimage 2004;22:394-400.
14. Wen JJ, Gao YY, Li MT, Hu S, Zhao MQ, Su C, Wang Q, Xi HY, Zhan LL, Lv YT, Antwi CO, Ren J, Jia XZ. Regional abnormalities of spontaneous brain activity in migraine: A coordinate-based meta-analysis. J Neurosci Res 2023;101:1205-23.
15. Ferrari MD, Goadsby PJ, Burstein R, Kurth T, Ayata C, Charles A, Ashina M, van den Maagdenberg AMJM, Dodick DW. Migraine. Nat Rev Dis Primers 2022;8:2.
16. Schwedt TJ, Chong CD. Functional imaging and migraine: new connections? Curr Opin Neurol 2015;28:265-70.
17. Chang CM, Yang CP, Yang CC, Shih PH, Wang SJ. Evidence of Potential Mechanisms of Acupuncture from Functional MRI Data for Migraine Prophylaxis. Curr Pain Headache Rep 2021;25:49.
18. Liu L, Tian T, Li X, Wang Y, Xu T, Ni X, Li X, He Z, Gao S, Sun M, Liang F, Zhao L. Revealing the Neural Mechanism Underlying the Effects of Acupuncture on Migraine: A Systematic Review. Front Neurosci

2021;15:674852.
19. Chen Y, Liu Y, Song Y, Zhao S, Li B, Sun J, Liu L. Therapeutic applications and potential mechanisms of acupuncture in migraine: A literature review and perspectives. Front Neurosci 2022;16:1022455.
20. Ma P, Dong X, Qu Y, He Z, Yin T, Cheng S, Tian Z, Teng Y, Xie K, Sun R, Yu S, Zeng F. A Narrative Review of Neuroimaging Studies in Acupuncture for Migraine. Pain Res Manag 2021;2021:9460695.
21. Zhao J, Guo LX, Li HR, Gou XY, Liu XB, Zhang Y, Zhong DL, Li YX, Zheng Z, Li J, Feng Y, Jin RJ. The effects of acupuncture therapy in migraine: An activation likelihood estimation meta-analysis. Front Neurosci 2022;16:1097450.
22. Li M, Huang H, Yao L, Yang H, Ma S, Zheng H, Zhong Z, Yu S, Yu B, Wang H. Effect of acupuncture on the modulation of functional brain regions in migraine: A meta-analysis of fMRI studies. Front Neurol 2023;14:1036413.
23. Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. 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.
24. Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P. Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. Hum Brain Mapp 2012;33:1-13.
25. Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT. Activation likelihood estimation meta-analysis revisited. Neuroimage 2012;59:2349-61.
26. Qiu Y, Fan Z, Zhong M, Yang J, Wu K, Huiqing H, Zhang R, Guo Y, Lee TMC, Huang R. Brain activation elicited by acute stress: An ALE meta-analysis. Neurosci Biobehav Rev 2022;132:706-24.
27. Fuelscher I, Caeyenberghs K, Enticott PG, Williams J, Lum J, Hyde C. Differential activation of brain areas in children with developmental coordination disorder during tasks of manual dexterity: An ALE meta-analysis. Neurosci Biobehav Rev 2018;86:77-84.
28. Cogdell-Brooke LS, Sowden PT, Violante IR, Thompson HE. A meta-analysis of functional magnetic resonance imaging studies of divergent thinking using activation likelihood estimation. Hum Brain Mapp 2020;41:5057-77.
29. Li C, Li X, He K, Wu Y, Xie X, Yang J, Zhang F, Yue Y, Hao H, Zhao S, Li X, Tian G. Discovery of the mechanisms of acupuncture in the treatment of migraine based on functional magnetic resonance imaging and omics. Front Med 2023;17:993-1005.
30. Feng M, Zhang Y, Wen Z, Hou X, Ye Y, Fu C, Luo W, Liu B. Early Fractional Amplitude of Low Frequency Fluctuation Can Predict the Efficacy of Transcutaneous Auricular Vagus Nerve Stimulation Treatment for Migraine Without Aura. Front Mol Neurosci 2022;15:778139.
31. Wang ZW, Zhang YT, Xu T, Du JR, Gao Q, Zhao L. Analysis of cerebral functional regional homogeneity of treating menstrual migraine with different distal-proximal points combination. Lishizhen Medicine and Materia Medica Research 2021;32:2455-8.
32. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. J Clin Epidemiol 2021;134:178-89.
33. Schwedt TJ, Dodick DW. Advanced neuroimaging of migraine. Lancet Neurol 2009;8:560-8.
34. Disner SG, Marquardt CA, Mueller BA, Burton PC, Sponheim SR. Spontaneous neural activity differences in posttraumatic stress disorder: A quantitative resting-state meta-analysis and fMRI validation. Hum Brain Mapp 2018;39:837-50.
35. Althubeati S, Avery A, Tench CR, Lobo DN, Salter A, Eldeghaidy S. Mapping brain activity of gut-brain signaling to appetite and satiety in healthy adults: A systematic review and functional neuroimaging meta-analysis. Neurosci Biobehav Rev 2022;136:104603.
36. Müller VI, Cieslik EC, Serbanescu I, Laird AR, Fox PT, Eickhoff SB. Altered Brain Activity in Unipolar Depression Revisited: Meta-analyses of Neuroimaging Studies. JAMA Psychiatry 2017;74:47-55.
37. Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage 2002;16:765-80.
38. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1-211.
39. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160.
40. Zhang Y, Wang Z, Du J, Liu J, Xu T, Wang X, Sun M, Wen Y, Li D, Liao H, Zhao Y, Zhao L. Regulatory Effects of Acupuncture on Emotional Disorders in Patients With Menstrual Migraine Without Aura: A Resting-State fMRI Study. Front Neurosci 2021;15:726505.
41. Liu S, Luo S, Yan T, Ma W, Wei X, Chen Y, Zhan S, Wang B. Differential Modulating Effect of Acupuncture

in Patients With Migraine Without Aura: A Resting Functional Magnetic Resonance Study. Front Neurol 2021;12:680896.
42. Jia JN, Yan CQ, Zheng XC, Shi AQ, Xu LF, Qi XH, Wang J. Clinical Efficacy and Regulation of Brain Region of Differentiation of Meridians Acupuncture Based on the Theory of "Gen-Jie" in Migraine Patients without Aura. Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease 2021;29:98-102.
43. Wang YH, Zhang Y, Luo WT, Yan ZX, Zhang Y, Liu B. Effect of Transcutaneous Auricular Vagus Nerve Stimulation on Fractional Amplitude of Low-Frequency Fluctuation in Migraine Without Aura. Journal of Clinical Radiology 2019;38:2010-4.
44. Luo WT, Zhang Y, Zhang Y, Zhou SF, Yan ZX, Liu B. Effect of auricular acupoint continuous stimulation on brain fraction amplitude of low-frequency fluctuation in patients with migraine without aura. Chinese Imaging Journal of Integrated Traditional and Western Medicine 2019;17:441-4.
45. Li Z, Zeng F, Yin T, Lan L, Makris N, Jorgenson K, Guo T, Wu F, Gao Y, Dong M, Liu M, Yang J, Li Y, Gong Q, Liang F, Kong J. Acupuncture modulates the abnormal brainstem activity in migraine without aura patients. Neuroimage Clin 2017;15:367-75.
46. Ning YZ, Li KS, Zhang Y, Liu HW, Fu CH, Han X, Ren Y, Zou YH. Effect of acupuncture at Zulinqi (GB41) on the amplitude of low frequency fluctuations in migraine without aura patients: a resting-state functional magnetic resonance imaging study. Int J Clin Exp Med 2017;10:3038-48.
47. Han X, Zou YH, Li KS, Liu HW, Ning YZ, Tan ZJ, Ren Y. Study on the effect of Zulinqi(GB41) acupuncture on the regional homogeneity on migraine. Modern Chinese Clinical Medicine 2017;24:31-5, 65.
48. Zhao L, Liu J, Zhang F, Dong X, Peng Y, Qin W, Wu F, Li Y, Yuan K, von Deneen KM, Gong Q, Tang Z, Liang F. Effects of long-term acupuncture treatment on resting-state brain activity in migraine patients: a randomized controlled trial on active acupoints and inactive acupoints. PLoS One 2014;9:e99538.
49. Yang M, Yang J, Zeng F, Liu P, Lai Z, Deng S, Fang L, Song W, Xie H, Liang F. Electroacupuncture stimulation at sub-specific acupoint and non-acupoint induced distinct brain glucose metabolism change in migraineurs: a PET-CT study. J Transl Med 2014;12:351.
50. Yang J, Zeng F, Feng Y, Fang L, Qin W, Liu X, Song W, Xie H, Chen J, Liang F. A PET-CT study on the specificity of acupoints through acupuncture treatment in migraine patients. BMC Complement Altern Med 2012;12:123.
51. Li XZ, Liu XG, Song WZ, Tang Y, Zeng F, Liang FR. Effect of acupuncture at acupoints of the Shaoyang Meridian on cerebral glucose metabolism in the patient of chronic migraine. Zhongguo Zhen Jiu 2008;28:854-9.
52. Pan P, Zhan H, Xia M, Zhang Y, Guan D, Xu Y. Aberrant regional homogeneity in Parkinson's disease: A voxel-wise meta-analysis of resting-state functional magnetic resonance imaging studies. Neurosci Biobehav Rev 2017;72:223-31.
53. Iwabuchi SJ, Krishnadas R, Li C, Auer DP, Radua J, Palaniyappan L. Localized connectivity in depression: a meta-analysis of resting state functional imaging studies. Neurosci Biobehav Rev 2015;51:77-86.
54. Kong J, Gollub R, Huang T, Polich G, Napadow V, Hui K, Vangel M, Rosen B, Kaptchuk TJ. Acupuncture de qi, from qualitative history to quantitative measurement. J Altern Complement Med 2007;13:1059-70.
55. Acar F, Seurinck R, Eickhoff SB, Moerkerke B. Assessing robustness against potential publication bias in Activation Likelihood Estimation (ALE) meta-analyses for fMRI. PLoS One 2018;13:e0208177.
56. Cai M, Liu J, Wang X, Ma J, Ma L, Liu M, Zhao Y, Wang H, Fu D, Wang W, Xu Q, Guo L, Liu F. Spontaneous brain activity abnormalities in migraine: A meta-analysis of functional neuroimaging. Hum Brain Mapp 2023;44:571-84.
57. Hornung JP. The human raphe nuclei and the serotonergic system. J Chem Neuroanat 2003;26:331-43.
58. Marciszewski KK, Meylakh N, Di Pietro F, Macefield VG, Macey PM, Henderson LA. Altered brainstem anatomy in migraine. Cephalalgia 2018;38:476-86.
59. Moazzami A, Tjen-A-Looi SC, Guo ZL, Longhurst JC. Serotonergic projection from nucleus raphe pallidus to rostral ventrolateral medulla modulates cardiovascular reflex responses during acupuncture. J Appl Physiol (1985) 2010;108:1336-46.
60. Yoshimoto K, Fukuda F, Hori M, Kato B, Kato H, Hattori H, Tokuda N, Kuriyama K, Yano T, Yasuhara M. Acupuncture stimulates the release of serotonin, but not dopamine, in the rat nucleus accumbens. Tohoku J Exp Med 2006;208:321-6.
61. Chang LJ, Yarkoni T, Khaw MW, Sanfey AG. Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. Cereb Cortex 2013;23:739-49.
62. Segerdahl AR, Mezue M, Okell TW, Farrar JT, Tracey I. The dorsal posterior insula subserves a fundamental role in

human pain. Nat Neurosci 2015;18:499-500.
63. Davis KD, Bushnell MC, Iannetti GD, St Lawrence K, Coghill R. Evidence against pain specificity in the dorsal posterior insula. F1000Res 2015;4:362.
64. Jung WM, Lee IS, Wallraven C, Ryu YH, Park HJ, Chae Y. Cortical Activation Patterns of Bodily Attention triggered by Acupuncture Stimulation. Sci Rep 2015;5:12455.
65. Wiech K, Jbabdi S, Lin CS, Andersson J, Tracey I. Differential structural and resting state connectivity between insular subdivisions and other pain-related brain regions. Pain 2014;155:2047-55.
66. Zhang J, Su J, Wang M, Zhao Y, Zhang QT, Yao Q, Lu H, Zhang H, Li GF, Wu YL, Liu YS, Liu FD, Zhuang MT, Shi YH, Hou TY, Zhao R, Qiao Y, Li J, Liu JR, Du X. The Posterior Insula Shows Disrupted Brain Functional Connectivity in Female Migraineurs Without Aura Based on Brainnetome Atlas. Sci Rep 2017;7:16868.
67. Wei XY, Luo SL, Chen H, Liu SS, Gong ZG, Zhan SH. Functional connectivity changes during migraine treatment with electroacupuncture at Shuaigu (GB8). J Integr Med 2022;20:237-43.
68. Younis S, Hougaard A, Noseda R, Ashina M. Current understanding of thalamic structure and function in migraine. Cephalalgia 2019;39:1675-82.
69. Li X, Cai L, Jiang X, Liu X, Wang J, Yang T, Wang F. Resting-State fMRI in Studies of Acupuncture. Evid Based Complement Alternat Med 2021;2021:6616060.
70. Xu H, Chen Y, Tao Y, Zhang Y, Zhao T, Wang M, Fan L, Zheng Y, Guo C. Modulation effect of acupuncture treatment on chronic neck and shoulder pain in female patients: Evidence from periaqueductal gray-based functional connectivity. CNS Neurosci Ther 2022;28:714-23.
71. Yu S, Guo B, Shen Z, Wang Z, Kui Y, Hu Y, Feng F. The imbalanced anterior and posterior default mode network in the primary insomnia. J Psychiatr Res 2018;103:97-103.
72. Liu Z, Wei W, Bai L, Dai R, You Y, Chen S, Tian J. Exploring the patterns of acupuncture on mild cognitive impairment patients using regional homogeneity. PLoS One 2014;9:e99335.
73. Ishiyama S, Shibata Y, Ayuzawa S, Matsushita A, Matsumura A, Ishikawa E. The Modifying of Functional Connectivity Induced by Peripheral Nerve Field Stimulation using Electroacupuncture for Migraine: A Prospective Clinical Study. Pain Med 2022;23:1560-9.
74. Cho SY, Jahng GH, Park SU, Jung WS, Moon SK, Park JM. fMRI study of effect on brain activity according to stimulation method at LI11, ST36: painful pressure and acupuncture stimulation of same acupoints. J Altern Complement Med 2010;16:489-95.
75. Russo AF. CGRP-based Migraine Therapeutics: How Might They Work, Why So Safe, and What Next? ACS Pharmacol Transl Sci 2019;2:2-8.
76. Ashina H, Schytz HW, Ashina M. CGRP in Human Models of Migraine. Handb Exp Pharmacol 2019;255:109-20.
77. Wang M, Duong TL, Rea BJ, Waite JS, Huebner MW, Flinn HC, Russo AF, Sowers LP. CGRP Administration Into the Cerebellum Evokes Light Aversion, Tactile Hypersensitivity, and Nociceptive Squint in Mice. Front Pain Res (Lausanne) 2022;3:861598.
78. Mehnert J, May A. Functional and structural alterations in the migraine cerebellum. J Cereb Blood Flow Metab 2019;39:730-9.
79. Liu HY, Lee PL, Chou KH, Lai KL, Wang YF, Chen SP, Chen WT, Wang SJ. The cerebellum is associated with 2-year prognosis in patients with high-frequency migraine. J Headache Pain 2020;21:29.
80. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006;129:564-83.
81. Zhe X, Zhang X, Chen L, Zhang L, Tang M, Zhang D, Li L, Lei X, Jin C. Altered Gray Matter Volume and Functional Connectivity in Patients With Vestibular Migraine. Front Neurosci 2021;15:683802.
82. Goffaux P, Girard-Tremblay L, Marchand S, Daigle K, Whittingstall K. Individual differences in pain sensitivity vary as a function of precuneus reactivity. Brain Topogr 2014;27:366-74.
83. Tu Y, Fu Z, Zeng F, Maleki N, Lan L, Li Z, Park J, Wilson G, Gao Y, Liu M, Calhoun V, Liang F, Kong J. Abnormal thalamocortical network dynamics in migraine. Neurology 2019;92:e2706-16.
84. Seo SY, Lee KB, Shin JS, Lee J, Kim MR, Ha IH, Ko Y, Lee YJ. Effectiveness of Acupuncture and Electroacupuncture for Chronic Neck Pain: A Systematic Review and Meta-Analysis. Am J Chin Med 2017;45:1573-95.
85. Li X, Dai Q, Shi Z, Chen H, Hu Y, Wang X, Zhang X, Tian G. Clinical Efficacy and Safety of Electroacupuncture in Migraine Treatment: A Systematic Review and Network Meta-Analysis. Am J Chin Med 2019;47:1755-80.

Cite this article as: Qi M, Wang Y, Zhang Y, Feng Y, Liu B. Potential neural mechanisms of acupuncture therapy on migraine: a systematic review and activation likelihood estimation meta-analysis update. Quant Imaging Med Surg 2025;15(2):1653-1668. doi: 10.21037/qims-24-916

