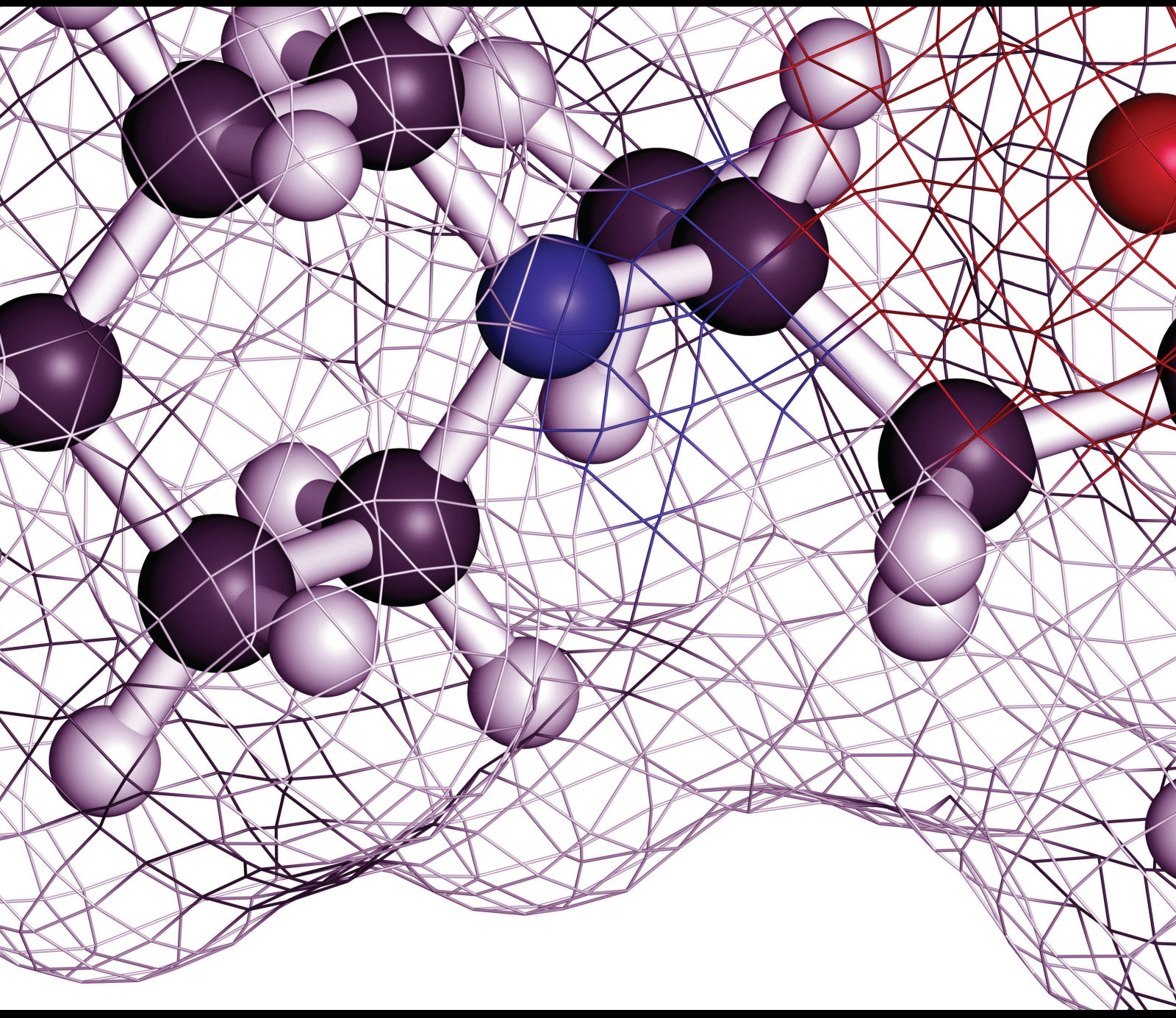
Pain Research and Management

The Application of Neuroimaging in Pain Research and Management

Lead Guest Editor: Fang Zeng
Guest Editors: Mailan Liu and Mingxiao Yang



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Contents

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Review Article

Neuroimaging Studies of Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Evidence shows that chronic prostatitis/chronic pelvic pain syndrome hugely impacts the body and mind. The central mechanisms in patients with CP/CPPS resulted in increased attention as neuroimaging techniques developed. This review investigated the study design and major neuroimaging findings in CP/CPPS patients to provide comprehensive evidence. Seven databases were searched and screened: PubMed, EMBASE/SCOPUS, Cochrane Library Database, China National Knowledge Infrastructure, VIP, Wanfang, and China Biology Medicine disc. Nine studies were eventually included in the analysis. The results demonstrate that the insula, anterior cingulate gyrus, postcentral gyrus, and precuneus are significantly associated with CP/CPPS patients' pain feelings and cause dysregulation of painful emotions, lowering patients' tolerance to stimulus.

1. Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common urological disorder characterized by pelvic pain or discomfort and abnormal urination [1]. Epidemiological studies showed that the global prevalence of CP/CPPS ranges between 9% and 16% [2]. Meanwhile, approximately 60% of CP/CPPS patients suffer from severe depression [3]. More importantly, long-term chronic pain leads to a lower quality of life to levels comparable to cardiovascular diseases, including severe congestive heart failure [4, 5]. The National Institutes of Health (NIH) classified prostatitis into acute bacterial prostatitis (type I), chronic bacterial prostatitis (type II), chronic prostatitis/chronic pelvic pain syndrome (type III), and asymptomatic prostatitis (type IV) based on different causes of prostatitis [1]. Types I and II have a bacterial infection, and type IV has evidence of inflammation. CP/CPPS is the most common type of chronic prostatitis [1], and it lacks objective and specific biological indicators when compared to the other three types.

The advancement of neuroimaging techniques has aided in identifying functional/structural brain alterations in patients with chronic pain disorders, including CP/CPPS and chronic low back pain [6]. The CP/CPPS mechanisms studies have gradually shifted to investigating critical pathological features. A functional magnetic resonance imaging (fMRI) study [7], for example, demonstrated that anterior insula activity increased in CP/CPPS patients compared to healthy individuals and was correlated with clinical pain intensity. Meanwhile, in CP/CPPS patients, the right anterior insula and parietal regions were more specifically active during spontaneous pain. Using structural magnetic resonance imaging (MRI) [8], researchers discovered that CP/CPPS patients had lower gray matter volume in the anterior cingulate cortex in the dominant hemisphere. These neuroimaging studies demonstrate that CP/CPPS is not only a genitourinary disorder but also has abnormal changes in the brain function and structure. This scattered evidence needs further exploration to better understand the critical pathological changes in CP/CPPS. Therefore, this study aimed to review the critical brain

regions involved in pain regulation in CP/CPPS and compare functional brain activity/structural differences between CP/CPPS patients and healthy controls.

2. Materials and Methods

2.1. Eligibility Criteria. Inclusion criteria are as follows: (1) controlled trial; (2) patients with CP/CPPS (type III); (3) pain in the perineum and pelvic area; (4) disease course of at least two weeks; (5) outcome measures including pain in the perineum and pelvic area and fMRI/MRI data.

Exclusion criteria are as follows: (1) Animal experiments, case reports, pharmacological-pharmacokinetic studies, or literature reviews; (2) study subjects had urological disorders other than CP/CPPS, including erectile dysfunction, infertility, and other male diseases; (3) history of using alcohol or any drug that influences the brain function or structure such as psychotropic drugs.

2.2. Information Sources. Computer searches of seven databases (PubMed, EMBASE/SCOPUS, Cochrane Library Database, China National Knowledge Infrastructure, Vipshop, Wanfang, and China Biology Medicine Disc) were conducted for articles published since the database's inception until September 1, 2021, for CP/CPPS neuroimaging studies based on MRI/fMRI technology.

2.3. Search Strategy. The search was performed using a combination of subject headings and free words. The English search terms include the following: ("prostatitis" [MeSH Terms] OR "prostatitis" [All Fields] OR ("chronic" [All Fields] AND "prostatitis" [All Fields] AND "chronic"[All Fields] AND "pelvic" [All Fields] AND "pain" [All Fields] AND "syndrome" [All Fields]) OR "chronic prostatitis chronic pelvic pain syndrome" [All Fields] OR("chronic nonbacterial prostatitis" [All Fields] AND "prostatodynia" [All Fields])) AND ("magnetic resonance imaging" [MeSH Terms] OR ("magnetic" [All Fields] AND "resonance" [All Fields] AND "imaging" [All Fields]) OR "magnetic resonance imaging" [All Fields] OR "MRI" [All Fields]) AND ("brain" [MeSH Terms] OR "brain" [All Fields]). Supplementary Materials include the corresponding search terms used in the Chinese search. Chinese search terms are listed in Supplementary Table 1 in Supplementary Materials.

2.4. Selection Process. Two fully independent evaluators screened the literature based on the inclusion and exclusion criteria, respectively. First, duplicates and those who did not meet the inclusion criteria were eliminated by reading the title and abstract; second, the full text was read again, and the results were cross-checked for potential inclusion. Any disagreement was solved by the two evaluators through discussion and negotiation, and if no agreement was reached, a third evaluator was asked to review the literature further. If the authors have not provided the activation zone coordinates in the text, the evaluator should send emails to the authors to ask about data; if the authors do not respond within two weeks, the study will be excluded from the ALE analysis.

2.5. Data Collection Process. The following data were extracted from the literature based on the inclusion criteria: (1) general information: title, author, journal, country or region of origin, and publication date; (2) study characteristics: study subject sample size, age, handedness, education, duration of illness, type of trial, CP/CPPS diagnostic criteria, baseline and intervention criteria, imaging methods, clinical/behavioral indicators, and emotional indicators; (3) nodal indicators: abnormal brain areas and trends in CP/CPPS, coordinates, and clinical correlation. The current systematic review was performed following the PRISMA checklist. Figure 1 depicts the flowchart of literature screening.

2.6. Data Analysis. The likelihood estimation (ALE) is a coordinate-based functional analysis approach proposed by Turkehaub et al. [9] to localize brain areas by performing three-dimensional Gaussian function smoothing and alignment tests on the relevant coordinates incorporated into the literature. Eickhoff et al. [10] improved the original statistical model by changing the fixed model into a random model, making the analysis results more objective and accurate.

Specifically, (1) the Talairach coordinates were converted to MNI (Montreal Neurological Institute) coordinates using the coordinate conversion function of the Icbm2tal software. The coordinates were grouped and entered into the Ginger-ALE software according to the data entry method in the ALE manual. (2) Data were analyzed, and ALE maps were calculated using Ginger-ALE 2.3 software. Based on the peak maximum activation coordinates, a three-dimensional Gaussian distribution was modeled with the following parameters: the Gaussian filtered full width half maximum (FWHM) value was used as the default setting based on the number of subjects, and the software calculated the whole-brain ALE distribution. Cluster thresholds were p-FWE <0.05, voxel thresholds were p-uncorrected < 0.05, and the number of thresholding permutations was 5000. Brain region image results were presented using the DPABI toolbox (https://rfmri.org/).

3. Results

3.1. Study Information. A total of 247 English and 39 Chinese records were obtained through preliminary retrieval. After checking titles and abstracts, 277 duplicates and those that did not meet the inclusion criteria were eliminated; 0 were excluded by further reading the full text. Finally, nine studies were included (S1–S9); those published between 2011 and 2021 were included in this review (Table 1; Table 2). Five of these studies were conducted in China (S4; S6; S7; S8; S9), two in the United States (S1; S3), and 2 in Switzerland (S2; S5). No risk of bias was found in the included references.

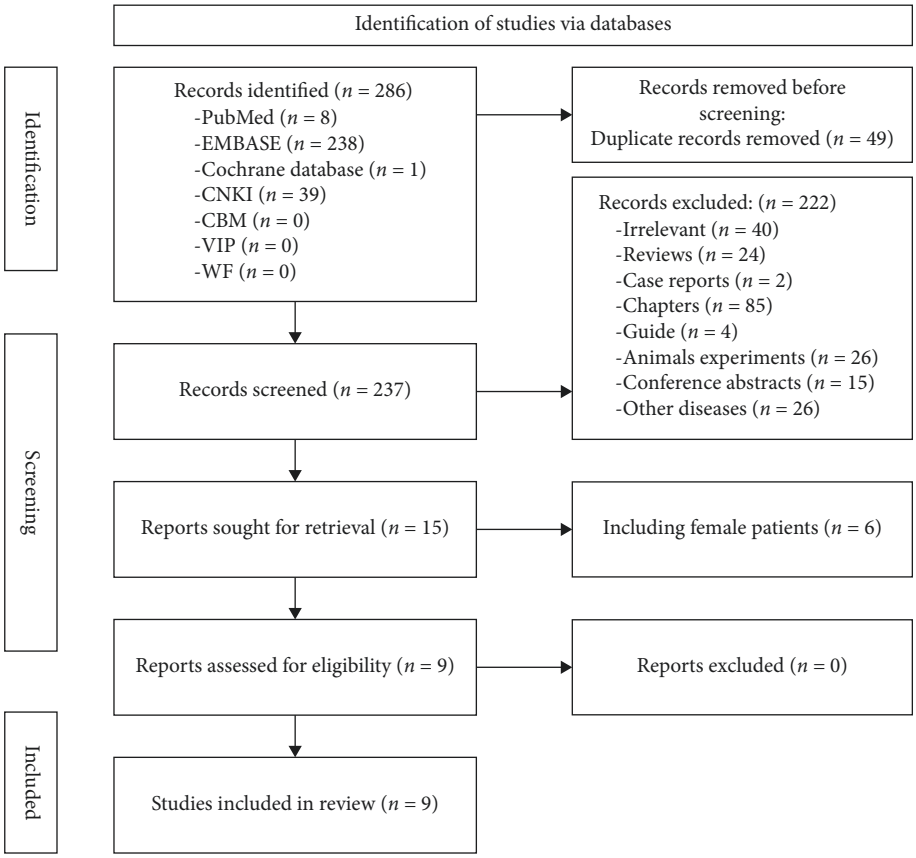

Figure 1: Flowchart of literature screening.

3.2. Participants. The nine studies enrolled 431 study subjects, including 233 patients with CP/CPPS and 198 healthy subjects (HC). Eight of the nine studies (S1–S4; S6–S9) compared CP/CPPS patients with HC, while 1 study (S5) recruited only CP/CPPS patients. The maximum sample size for a single group of patients with CP/CPPS 31 was 19 in nine studies.

3.3. Control Group. One of the nine studies (S5) used acoustic magnetic therapy in the treatment group and sham stimulation in the control group. The other eight studies used healthy subjects as control groups.

3.4. Intervention Details. All studies required patients to be right-handed; two studies (S3; S7) required subjects to empty their bladders before the MRI examination; two studies (S4; S6) required subjects to have a visual analog score of 0 before the MRI examination; six studies (S1; S3–S6; S7) required subjects to be resting with their eyes closed but not asleep; three of these studies (S2; S8; S9) did not specify any patient requirements.

3.5. Magnetic Resonance Imaging Techniques and Analysis Methods. All studies adopted magnetic resonance imaging (MRI) to detect changes in the structural/functional activity of the brain of CP/CPPS patients. Five of the nine studies examined structural changes. Two studies (S8; S9) used diffusion tensor imaging (DTI) techniques to compare the global functional connectivity of brain white matter structures in CP/CPPS patients and healthy subjects. Two studies (S1, S7) compared regional gray matter (location of neuronal vesicles) and white matter (location of axonal tracts) features and functional brain connectivity in patients with CP/CPPS to those in healthy subjects using DTI and high-resolution T1-weighted MRI. Another study (S3) compared the functional connectivity of motor cortex areas directly controlling the pelvic floor in patients with CP/CPPS and healthy subjects using T1- and T2-weighted MRI image analysis. Two studies (S4; S6) used rs-fMRI to assess the mean regional homogeneity (ReHo) values of voxels in standardized brain regions. One study (S5) investigated the possibility of longitudinal cerebral blood flow (CBF) changes in CP/CPPS patients using arterial spin labeling (ASL) techniques. Another study (S2) investigated the role of the anterior cingulate cortex in chronic pelvic pain syndrome using T1-weighted MRI.

3.6. Brain Alterations in Patients. The findings of nine studies revealed that patients with CP/CPPS had changes in 39 brain regions, primarily the left anterior cingulate cortex, right anterior cingulate cortex, right insula, left postcentral gyrus, left precentral gyrus, and left precuneus.

Table 1: Basic information for inclusion in the study.

No.	Author (year) country	Disease	Design	Sample capacity	Age	Intervention/ control	Manipulation modality	Imaging modality	Analytical approaches	Cluster1 contribution degree	Cluster2 contribution degree
S1	Melissa A Farmer (2011) American Farmer et al., 2011	CP/ CPPS	Non-RCT	19/16	36.94	—	Resting state	DTI, T1-weighted MRI, rs-fMRI	Talairach space	1	0
S2	Livio Mordasini (2012) Switzerland Mordasini et al., 2012	CP/ CPPS	Non-RCT	20/20	40 ± 14	—	—	T1-weighted MRI	Talairach space	0	1
S3	Jason J kutch (2015) American Kutch et al., 2015	CP/ CPPS	Non-RCT	28/27	32.7 ± 1.5	—	Resting state; participants need to empty their bladders	rs-fMRI, T2-weighted MRI, T1-weighted MRI	MNI	6	0
S4	Yusong Lin (2017) China Lin et al., 2017	CP/ CPPS	Non-RCT	31/31	34.1 ± 10.3	—	Resting state, no spontaneous pelvic pain; the visual analog scale test must score 0 within 10 minutes before and after the MRI scan, respectively	rs-fMRI, T1-weighted MRI	MNI	1	2
S5	Christian Weisstanner (2017) Switzerland Weisstanner et al., 2017	CP/ CPPS	RCT	30 (therapy)/30 (sham therapy)	46 ± 14	Sono-electromagnetic/ sham therapy 12 weeks of treatment	Resting state	T1-weighted MRI, ASL, BOLD-MRI	MNI	0	1
S6	Yan Bai (2017) China Bai et al., 2017	CP/ CPPS	Non-RCT	19/19	34.8 ± 9.6	—	Resting state; the visual analog scale test must score 0 within 10 minutes before and after the MRI scan, respectively	Rs-fMRI	MNI	0	2
S7	Shengyang Ge (2021) China Ge et al., 2021	CP/ CPPS	Non-RCT	18/21	30.92 ± 7.69	—	Resting state; participants need to empty their bladders	rs-fMRI, T1-weighted MRI	MNI	0	
S8	Xinfei Huang (2021) China Huang et al., 2021	CP/ CPPS	Non-RCT	19/32	38.11 ± 9.02	—	—	T1-weighted MRI, DTI	MNI	0	0
S9	Yan Xu (2021) China Xu et al., 2021	CP/ CPPS	Non-RCT	19/32	38.11 ± 9.02	—	—	T1-weighted MRI, DTI	MNI	0	0

Table 2: Diagnostic criteria of the study.

No.	Diagnostic criteria
S1	Patients who had pelvic discomfort/pain for three or more months within the last six months; an overall score of 15 or greater of 43 points on the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), including 1 or more on the pain subscale of this index or current pain.
S2	In accordance with European Association of Urology guidelines, patients with CPPS complained about pain perceived in structures related to the pelvis for at least three months without proven infection or other obvious pathology. Inclusion criteria were a NIH-CPSI total score of 15 or greater, NIH-CPSI pain subscale eight or greater.
S3	CP/CPPS patients had to report an unpleasant sensation of pain, pressure, or discomfort perceived to be related to the bladder and/or pelvic region for most of the time during the most recent three months.
S4	Patients had complaints about pelvic pain at least three months within the last six months; the NIH-CPSI total score was 15 or greater.
S5	In accordance with the European Association of Urology guidelines, all patients with chronic pelvic pain syndrome (CPPS) enrolled in this study reported pain perceived in structures related to the pelvis for at least three months without proven infection or other related pathologies.
S6	Meets National Institutes of Health diagnostic criteria for CP/CPPS.
S7	According to the category of National Institutes of Health, CP/CPPS was defined as urological pain or discomfort in the pelvic region sustained for no less than three months during the preceding six months that is associated with lower urinary symptoms and not in consort with a urinary tract bacterial infection.
S8	Based on the NIH-CPSI, patients with at least three months of persistent pelvic pain, urinary symptoms, and/or sexual dysfunction can make the diagnosis of CP/CPPS after excluding obvious etiologies such as active UTIs.
S9	The patient had pain and discomfort in the pelvic region for more than three months; NIH–CPSI score ≥15; normal white blood cell count and negative bacterial culture on routine prostate massage.

Four studies (S2, S4, S5, S6) discovered changes in the anterior cingulate cortex (ACC) in CP/CPPS patients versus healthy subjects. Two of these studies (S4, S6) revealed changes in the ACC function, with a significant decrease in the ReHo value of the bilateral ACC and a significant negative correlation between the degree of activation of the bilateral ACC and the National Institutes of Health-chronic prostatitis symptom index (NIH-CPSI) scale pain score. Another study (S2) demonstrated changes in ACC structure, including a significant decrease in volume and an increase in density in the gray matter of the left ACC brain. Another study (S5) revealed that CBF was downregulated in the anterior cingulate cortex of patients.

Three studies (S1, S3, S4) found insula (INS) changes in CP/CPPS patients versus healthy subjects. One study (S4) revealed structural changes in the INS and a significant reduction in ReHo in the insula cortex of CP/CPPS patients. Two studies (S1, S3) correlated the functional changes in INS, functional activation within the patient's right anterior insula, and pelvic-motor connectivity to the right posterior insula with pain intensity in CP/CPPS.

Three studies (S1, S8, S9) found changes in the structure of the postcentral gyrus (PoCG), precentral gyrus (PreCG), and precuneus (PCUN) in CP/CPPS patients, all with significant increases in the values of the local efficiency attributes. The overall efficiency value of the left PoCG increased. The NIH-CPSI scale total score, the pain and discomfort symptom score, and the impact of symptoms on quality of life score all had a positive correlation with the local efficiency of the left PCUN.

Two studies (S1, S5) found increased CBF in the left dorsomedial and right dorsolateral prefrontal cortex resulting in functional changes in the dorsolateral prefrontal cortex (DLPFC).

Two studies (S4, S6) revealed changes in thalamus (THA) function, including significantly higher ReHo values and homogeneity in the right thalamic area and a significant positive correlation between the degree of activation in the right thalamic area and the NIH-CPSI scale pain score.

Two studies (S5, S7) found changes in medial prefrontal cortex (mPFC) function and increased CBF in patients' left medial and right dorsolateral prefrontal cortex.

Two studies (S7, S9) revealed structural changes in the middle frontal gyrus, orbital (ORBmid), median, and paracingulate gyrus (DCG), supplementary motor area (SMA), right superior temporal gyrus (STG), left superior marginal gyrus (SMG), left superior parietal gyrus (SPG), left posterior cingulate gyrus (PCG), and paracentral lobule (PCL) in CP/CPPS patients. The right middle frontal gyrus (orbit) is inefficient in CP/CPPS patients, implying a disruption in the connection of the entire brain to the right middle frontal gyrus (orbit). Local efficiency attribute values increase significantly in the left paracingulate gyri, supplementary motor area, right superior temporal gyrus, left supramarginal gyrus, left superior parietal gyrus, and left posterior cingulate gyrus. The overall efficiency of the left paracingulate gyrus and left posterior cingulate gyrus is improved. The NIH-CPSI scale total score, pain and discomfort symptom scores, and symptom impact on quality of life scores were all positively correlated with the right supplementary motor area (Table 3).

A total of 207 subjects were included in the ALE analysis, consisting of 9 studies, 29 foci, and a total of 2 significant clusters. Cluster 1 included the insula and superior temporal gyrus, and cluster 2 consisted mainly of the cingulate gyrus region (Table 4 and Figure 2).

4. Discussion

4.1. A Narrative Review of Nine Studies on MRI of the Brain in Patients with CP/CPPS. A narrative review of nine studies on brain MRI in CP/CPPS patients revealed a close

Table 3: Nine studies of functional or structural brain changes in patients with CP/CPPS.

Brain area (abbreviations)	Brain area (full name)	Number of studies	Functional/ structure	Sign	Literature name
ACC.L	Anterior cingulate cortex	Four studies	Functional/ structure	↓	S2, S4, S5, S6
ACC.R	Anterior cingulate cortex	Three studies	Functional/ structure	↓	S2, S4, S6
INS.R	Insula	Three studies	Functional	↓	S1, S3, S4
PoCG.L	Postcentral gyrus	Three studies	Functional	—	S1, S7, S9
PreCG.L	Precental gyrus	Three studies	Functional	—	S1, S7, S9
PCUN.L	Precuneus	Three studies	Functional	—	S1, S7, S9
INS.L	Insula	Two studies	Functional	↓	S1, S4
DLPFC.R	Dorsolateral prefrontal cortex	Two studies	Functional/ structure	↑	S1, S5
THA.R	Thalamus	Two studies	Functional	↑	S4, S6
mPFC.L	Medial prefrontal cortex	Two studies	Functional/ structure	↑	S5, S8
ORBmid.R	Middle frontal gyrus, orbital part	Two studies	Functional	↓	S7, S9
DCG.L	Median cingulate and paracingulate gyri	Two studies	Functional	↑	S7, S9
DCG.R	Median cingulate and paracingulate gyri	Two studies	Functional	↑	S7, S9
SMA.L	Supplementary motor area	Two studies	Functional	—	S7, S9
SMA.R	Supplementary motor area	Two studies	Functional	—	S7, S9
PCG.L	Posterior cingulate gyrus	Two studies	Functional	—	S7, S9
SPG.L	Superior parietal gyrus	Two studies	Functional	—	S7, S9
SMG.R	Supramarginal gyrus	Two studies	Functional		S7, S9
PCL.L	Paracentral lobule	Two studies	Functional	↑	S7, S9
STG.R	Superior temporal gyrus	Two studies	Functional		S7, S9
MTG.L	Middle temporal gyrus	One study	Functional/ structure	—	S1
MTG.R	Middle temporal gyrus	One study	Functional/ structure	—	S1
Frontal. L	Orbital frontal cortex	One study	Functional/ structure	—	S1
Frontal.R	Orbital frontal cortex	One study	Functional/ structure	—	S1
MFG.L	Middle frontal gyrus	One study	Structure		S2
VPC.R	Ventrolateral parietal cortex	One study	Functional/ structure	—	S1
VPC.L	Ventrolateral parietal cortex	One study	Functional/ structure	—	S1
PPC.L	Posterior parietal cortex	One study	Functional/ structure	—	S1
PPC.R	Posterior parietal cortex	One study	Functional/ structure	—	S1
IFGoperc.R	Inferior frontal gyrus, opercular part	One study	Functional	—	S3
THA.L	Thalamus	One study	Functional/ structure	—	S1
Brainstem. R	Brainstem	One study	Functional		S4
Brainstem. L	Brainstem	One study	Functional	—	S4
mPFC.R	Medial prefrontal cortex	One study	Functional		S4
HIP.R	Hippocampus	One study	Functional/ structure	—	S5
Cerebellum anterior lobe.L	Anterior cerebellum lobe.	One study	Functional	—	S8
PoCG.R	Postcentral gyrus	One study	Functional/ structure	—	S1
PreCG.R	Precental gyrus	One study	Functional/ structure	—	S1
PHG.R	Parahippocampal gyrus	One study	Functional	—	S9

L: left hemisphere; R: right hemisphere.

Table 4: ALE analysis results.

Cluster #	MNI coordinates X	Y	Z	ALE ($\times 10^{-3}$)	p	Z	Hemisphere	Label
1	48	2	−6	9.10	6.90E−05	3.811792	R	Insula
	52	2	−2	9.07	7.11E−05	3.804371	R	Superior temporal gyrus
	56	14	8	9.06	9.36E−05	3.735753	R	Precentral gyrus
	42	−4	4	9.06	9.36E−05	3.735753	R	Claustrum
	50	−6	2	9.06	9.36E−05	3.735753	R	Insula
	66	−2	6	9.06	9.36E−05	3.735753	R	Superior temporal gyrus
	34	24	0	8.71	1.14E−04	3.68467	R	Insula
	44	14	−4	8.33	1.99E−04	3.541374	R	Insula
2	8	14	30	16.28	1.09E−07	5.182729	R	Cingulate gyrus
	−6	28	24	14.10	1.52E−06	4.667913	L	Cingulate gyrus
	−10	18	24	9.53	3.96E−05	3.947112	L	Cingulate gyrus

L: left hemisphere; R: right hemisphere.

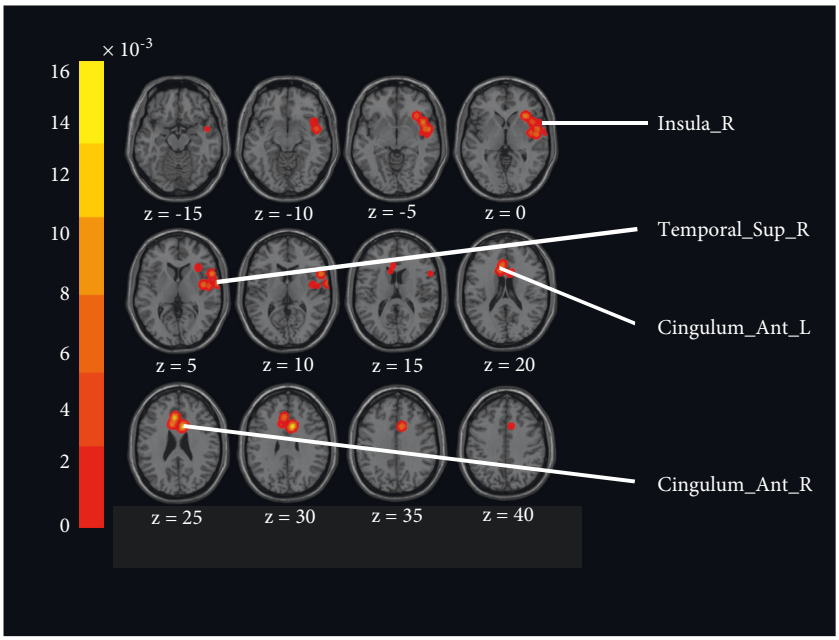

Figure 2: ALE analysis results.

association of clinical pelvic pain symptoms with functional or structural changes in brain regions, including left ACC, right ACC, right INS, right STG, and left PCUN in male CP/CPPS patients.

This systematic review found structural changes in the ACC in CP/CPPS patients in four studies (S2, S4, S5, S6). The ACC is a critical brain region component of the neural substrate involved in pain processing [11]. Lin et al. (S4) found that in CP/CPPS patients, regional homogeneity (ReHo) was significantly decreased in the ACC, insula cortex, and right medial prefrontal cortex but significantly increased ReHo in the brainstem and right thalamus. These findings demonstrate that nociceptive information is correlated to these brain regions. Furthermore, emerging evidence shows that noxious stimuli are transmitted indirectly to the ACC via at least three major projection systems [12]. The first comes from the thalamus, where nociceptive input from the medial thalamus is received by ACC neurons [13, 14]. The amygdala sends the second nociceptive message to the ACC. Other pain-related cortical areas, including the insula cortex, are the third source of nociceptive input to the ACC. Lin et al. (S4) showed decreased ReHo in bilateral ACCs and INCs, indicating impaired downstream pain inhibition in CP/CPPS. Furthermore, an impaired pain modulation system could explain the pain symptoms of CP/CPPS by decreasing downstream pain inhibition or increasing pain vulnerability. It is also possible that AC1-triggered cAMP signaling contributes to synaptic changes associated with chronic pain in the ACC. Mordasini et al. (S2) demonstrated a significant decrease in brain gray matter volume and an increase in density in CP/CPPS patients with left ACC, suggesting that this mechanism is involved.

Three studies (S1, S3, S4) found structural changes in the INS of CP/CPPS patients. Two studies (S1, S3) found functional activation of the right anterior insula in CP/CPPS patients. Mounting evidence from pain studies shows that the insula capitol cortex, which plays a critical role in chronic pain, is the brain region most consistently activated [15–17].

The insula cortex plays a role in both the sensory-discriminative and affective-motivational aspects of nociceptive processing [18]. According to the findings of Xu et al. (S9), the anterior insula (AI) cortical area was primarily associated with pain-induced affective feelings, whereas the posterior insula (PI) cortical area was associated with sensory information of nociception [19]. Pain information elicits an emotional response through this pathway, which activates the downstream pain modulation system. Farmer et al. (S1) demonstrated that pain information in the insula cortical area might influence brain activity other than the primary clinical symptoms of CP/CPPS. The posterior insula cortical area receives nociceptive afferents primarily from the ventral posterior inferior nucleus and the thalamus ventromedial posterior nucleus, both of which receive input from spinothalamic neurons of lamine I [20]. The degree of activation of the posterior insula cortical area was most consistent with chronic pain progression [21]. Kutch et al. (S3) revealed that the functional connectivity between the motor cortex and the posterior insula is potentially one of the most critical markers of the altered brain function in CP/CPPS patients, representing changes in the integration of visceral sensory and motor processing.

Three studies (S1, S8, S9) found structural changes in PCUN in CP/CPPS patients. Positive correlations were found between the local efficiency of the left PCUN and the NIH-CPSI scale total score, pain and discomfort symptom score, and symptom impact on quality of life score. These findings demonstrate that the higher the local efficiency of the left PCUN, the more severe the patient's pain symptoms. The PCUN is the functional core of the posterior DMN [22], and it is in charge of self-processing and internal sensing, as well as pain sensitivity and pain threshold determination.

4.2. Discussion of the Results Based on ALE. The ALE result suggests significant INS, STG, and ACC changes in patients with CP/CPPS. In S9, the ratio of STG network efficiency is more significant in patients than in healthy individuals. Robust evidence [23] suggests that the STG may play a role in encoding experimental pain memory and that the STG is involved in memory bias associated with experimental pain memory. Stimulation of the STG affected the motivational-emotional component of the pain experience but not the sensory discrimination component, highlighting the role of the cortical region in the emotional memory of experimental pain.

Chronic pelvic pain syndrome is a centralized pain syndrome associated with central nervous system changes. Abnormal regulation and output of the hypothalamic-pituitary-adrenal (HPA) axis are frequently related to centralized pain disorders. The HPA axis is the primary stress response system, and its activation induces cortisol production and immune response dampening. Patients with centralized pain syndromes frequently have hypercortisolism or hypocortisolism, and evidence of altered downstream signaling from the HPA axis, including increased mast cell (MC) infiltration and activation, can cause sensitization of nearby nociceptive afferents. Increased peripheral input via nociceptor activation can result in "hyperalgesic priming" and "wind-up," which may eventually cause central sensitization via long-term potentiation in the central nervous system [24]. CP/CPPS pain is not only felt near the prostatic organ but also in the L5-S2 sacral innervation area associated with vesicourethral innervation, and central sensitization of the L5-S2 sacral nerve segments may be a cause of CP/CPPS pain [25].

Studies reviewed herein revealed that critical regions played a role in pain relief. Opioid signaling in the anterior cingulate cortex, activation of midbrain dopamine neurons, and dopamine release in the nucleus accumbens are all required for the rewarding effect of pain relief [26]. The ventral anastomotic insular region (RAIC) is part of the anterior insula. A study by Zhang [27] revealed that chronic pain increases the excitability of RAIC pyramidal neurons, and activation of cannabinoid receptors within the RAIC can significantly inhibit mechanical touch-evoked pain in mice. Moreover, RAIC may be involved in regulating dopamine in the vomeronasal nucleus, thereby inhibiting injury perception [28]. Stimulation of the STG with a single pulse of TMS (virtual disruption paradigm) prevents exaggeration of memory for painful events when administering electrical pain stimulation [23].

5. Conclusion

The changes in brain regions of CP/CPPS patients are primarily concentrated in the left ACC, right ACC, right INS, right STG, and left PCUN. The ACC receives pain signals via the thalamus, amygdala, and insula cortex, and the regional homogeneity of bilateral ACC in CP/CPPS patients is significantly reduced. Patients with CP/CPPS have functional activation in the right anterior insula. Pain significantly impacts the anterior insula in CP/CPPS patients, with altered functional connectivity between the motor cortex and the PI. The higher the local efficiency of the left PCUN, the worse the pain symptoms in CP/CPPS patients. The network efficiency ratio was greater in STG patients than in healthy individuals, and STG was involved in the memory bias associated with experimental pain memory.

The present systematic review has some limitations. The studies included were nonrandomized controlled trials, and due to the limitations of the study design, selection and measurement bias could not be avoided. The contribution analysis of ALE suggested that cluster 1 was provided by S1, S3, and S4, of which S3 had a high contribution; Cluster 2 was provided by S2, S4, S5, and S6, of which S4 and S6 had a high contribution; S8 and S9 have not made any contribution between cluster 1 and cluster 2 (Table 1). This may be related to the quality of the references. Due to the number limitation of the included references, this study investigated the potential changes in the brain regions of CP/CPPS patients through the ALE method and provided the quality was suitable for the study, which provided ideas for future studies.

Despite the high prevalence of pain in CP/CPPS patients, current neuroimaging studies provide only a limited

understanding of pain mechanisms. There is ample opportunity to advance our understanding of CP/CPPS-related pain mechanisms and future CP/CPPS treatment. More attention should be paid to these brain regions with targeted studies on targeted drugs for pain relief in CP/CPPS. The use of functional and advanced structural MRI techniques to compare differences between CP/CPPS patients and healthy individuals has the potential to advance research in this critical area.

Data Availability

The data used in this study are all included in this paper and are open to all readers.

Disclosure

Yifan Zhao, Jiaqi Lin, and Ye Dong are the co-first authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Yifan Zhao, Jiaqi Lin, and Ye Dong designed the study and drafted the manuscript. Peihai Zhang and Zilei Tian revised the study design and the manuscript. Yan Ye, Ziyang Ma, and Shengli Xia participated in the design of the search strategy and data extraction. Xiaopeng Huang and Diang Chen formed the data synthesis and analysis plan. All authors have read and approved the publication of the final manuscript. Yifan Zhao, Jiaqi Lin, and Ye Dong contributed equally to this paper.

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Supplementary Materials

Supplementary Table 1: Chinese search terms. (*Supplementary Materials*)

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Review Article

Neuroimaging Mechanism of Cognitive Behavioral Therapy in Pain Management

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Purpose. To review the recent neuroimaging studies on cognitive-behavioral therapy (CBT) for pain management, with the aim of exploring possible mechanisms of CBT. *Recent Findings.* Current studies can be divided into four categories, mixed pain, fibromyalgia, migraine, and experimental pain, based on the type of disease included, with the same or different changes of brain regions after CBT intervention. According to structural and functional MRI analyses, changes of brain gray matter volume, activation and deactivation of brain regions, and intrinsic connectivity between brain regions were observed after CBT sessions. The brain regions involved mainly included some areas related to cognitive and emotional regulation. After comparison, the DLPFC, OFC, VLPFC, PCC and amygdala were found to be recurrent in multiple studies and may be key regions for CBT intervention in pain management. In the treatment of mixed chronic pain, CBT may decrease the gray matter volume of DLPFC, reduce ICN connection of OFC within the DAN network, and increase fALFF of the PCC. For FM intervention, CBT may activate the bilateral OFC and VLPFC, while in migraine, only the right OFC, VLPFC, and DLPFC were found to be more activated after CBT. In addition, the differential action of the left and right amygdala has also been shown in the latest study of migraine. In heat-evoked pain, CBT may increase the deactivation of the PCC, the connectivity between the DMN and right VLPFC, while diminishing the deactivation of VLPFC. *Summary.* After CBT, the brain showed stronger top-down pain control, cognitive reassessment, and altered perception of stimulus signals (chronic pain and repeated acute pain). The DLPFC, OFC, VLPFC, PCC, and amygdala may be the key brain regions in CBT intervention of pain.

1. Introduction

Cognitive-behavioral therapy (CBT) came out in the 1960s, which is a structured psychotherapeutic intervention that targets maladaptive cognitive factors to reduce negative affect [1]. Since then, it has been extensively used in the treatment of psychiatric disorders, such as depression, anxiety disorders, and personality disorders [2]. In recent years, numerous studies have demonstrated its application value in nonpsychiatric disorders, including irritable bowel syndrome, insomnia, and chronic pain conditions, such as migraine and fibromyalgia. CBT is available for all ages, from children to the elderly, and the treatment modality has evolved from one-on-one communication to team therapy, from face-to-face communication to telephone therapy, and the newly explored online therapy. It can be seen that CBT is a treatment with great clinical application value.

In recent years, pain, the fifth vital sign, has developed into a global problem [3]. Chronic pain can even last for decades, severely affecting physical and mental health. The importance of nonpharmacological treatment of chronic pain has become increasingly significant due to problems such as addiction to painkillers. Pain and its neural representation are highly affected by cognitive factors [4–6]. Clinical studies on CBT and chronic pain have proliferated. With the development of neuroimaging techniques, it has been increasingly used to conduct studies about CBT to explore the mechanisms of CBT for pain management. In

this review, we intend to review the recent neuroimaging studies on CBT for pain management, with the aim of exploring possible mechanisms of CBT, improving the CBT process to increase clinical efficacy, and providing a basis for reversing chronic pain in the future.

2. Method

In September 2021, we searched PubMed and Web of Science. We searched the mentioned database using search terms including "CBT" AND "pain," "CBT" AND "fMRI" AND "pain," "CBT" AND "pain" AND "imaging," "cognitive" AND "pain" AND "imaging," and "cognition" AND "pain" AND "imaging." We mainly selected literature from 2016 to 2021. In addition, the early literature that were frequently cited and of high value were also cited. The reference lists for included studies were manually screened by members to minimize the omission of potentially eligible articles.

3. Structural and Functional Changes of the Brain due to CBT

In recent 2 years, a large number of clinical studies had taken CBT as a management measure of different kinds of pain, including mixed unlocated chronic pain [7–18], back pain [19, 20], low back pain [21–26], chronic pancreatitis [27], fibromyalgia [28, 29], functional abdominal pain [30], trigeminal neuralgia [31], haemophilia pain [32], osteoarthritis pain [33–35], perioperative pain [36–39], orofacial pain [40], diabetic peripheral neuropathic pain [41], and provoked vestibulodynia [42]. Previous studies on structural changes in the brain of patients with chronic pain indicated the presence of neuroplasticity in areas associated with the experience and anticipation of pain [43]. In the past few years, there has been growing interest in studying changes in brain structure and connectivity after CBT interventions for pain to explore the underlying mechanism. Previous studies of the neuroimaging mechanism can be classified according to the type of pain enrolled, including mixed diagnosis and pain with clear diagnosis and experimental irritation.

3.1. Mixed Diagnosis of Pain. Several studies have shown a correlation between gray matter (GM) reduction in some regions (including volume or density) and the duration or intensity of pain [44–48]. According to former research studies, Seminowicz et al. [49] conducted a study that enrolled 26 patients (chronic pain (CP), $n = 13$; healthy controls (HC), $n = 13$). Patients in the CP group received 11 times, 90-minute weekly CBT group sessions, and were scanned twice by anatomical MRI before and after these CBT sessions. Voxel-based morphometry (VBM) analysis was conducted on MRI data. After CBT sessions, results showed that GM volume (GMV) in the bilateral dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and some other sensory, motor, and affective areas increased, while GMV in the left supplementary motor area (SMA) reduced. They also found that increased GMV in prefrontal and parietal areas was related to decreased pain catastrophizing, which is regarded as an important target for the treatment of CP in the latest research [15]. These results suggested that after CBT, the brain has a stronger top-down control of pain and a cognitive reassessment of pain and a change in the perception of noxious signals. Notably, in this early study, they rigorously performed analyses on the exclusion of depression and natural changes of GM density (GMD) across time. These factors are not taken into account in many later studies.

Shpaner et al. [50] conducted a randomized control trial (RCT) and enrolled 38 participants with chronic musculoskeletal pain, who were divided into the CBT group ($n = 19$) and educational materials group (EDU, $n = 19$). They observed changes in intrinsic functional connectivity (iFC) of the brain after 11 weeks of CBT by using functional MRI (fMRI). The results showed that after CBT, iFC between the anterior default mode network (DMN) and amygdala/periaqueductal gray (PAG) decreased, which was related to the prepost change in self-efficacy for coping with symptoms ($\rho = -0.329$, $P = 0.044$). And, iFC between the basal ganglia (BG) network and right secondary somatosensory (S2) cortex increased, which was revealed to the decrease in pain symptoms ($\rho = -0.343$, $P = 0.035$) and the increase in other clinical results such as self-efficacy for pain management ($\rho = 0.574$, $P < 0.001$) [50]. CBT patients also had increased posttherapy fractional amplitude of low-frequency fluctuations (fALFF) in the bilateral posterior cingulate cortex (PCC) and the cerebellum. In addition, they examined the possible confounding influence of medication and menstrual cycle.

Yoshino et al. [51] used resting-state functional magnetic resonance imaging (R-fMRI) to examine neural changes after CBT (CP, $n = 29$; age-matched HC, $n = 30$). After a weekly 12-session CBT, abnormal intrinsic connectivity network (ICN) connections in CP patients normalized, including the orbitofrontal cortex (OFC), inferior parietal lobule within the dorsal attention network (DAN), and the paracentral lobule within the sensorimotor network. Interestingly, inspired by the previous studies on posttreatment prediction [52, 53], they also conducted relevant experiments. Among them, higher ICN connection strength in OFC was associated with a greater decrease in pain intensity. The lower ICN connectivity strength in the dorsal posterior cingulate cortex within the DAN was related to positive CBT-related clinical improvements.

3.2. Fibromyalgia. The study of Jensen et al. [54] is the earliest published neuroimaging study on the therapeutic mechanisms of CBT for chronic pain, which was reported in 2012. This randomized, 12-week, waiting-list controlled clinical trial enrolled 43 female participants with fibromyalgia (FM) syndrome (CBT $n = 25$; controls $n = 18$). FMRI during pressure-evoked pain was assessed twice before and after 12-week CBT. The analysis showed that CBT activations in the ventrolateral prefrontal cortex (VLPFC) and lateral orbitofrontal cortex increased, which were associated with executive cognitive control. The change in anxiety was

significantly positively related to the VLPFC activation ($r = 0.67$, $P < 0.05$, 2-tailed). In addition, they found that coherence between the VLPFC and thalamus was increased. In former studies, thalamic activity was decreased in FM [52, 55, 56] and other CP conditions [57]. So, it was suggested that CBT may also influence the thalamus and other lower structures of the brain.

Shipman [58] enrolled 16 high-catastrophizing FM patients (CBT, $n = 8$; EDU, $n = 8$). An innovation over previous studies is that they performed a total of three times fMRI scans, at baseline, posttreatment, and 6-month follow-up, in order to observe the persistence outcomes of CBT. The result showed that resting state connectivity between the primary somatosensory cortex (S1) and anterior/medial insula was reduced after CBT, which was correlated with concurrent treatment-related reductions in catastrophizing [59]. Furthermore, a clear potential sequential association was shown in this study. Changes in catastrophizing and insula-S1 connectivity occurred after the 1-month CBT sessions, while the pain interference changed significantly at 6-month follow-up. This sequential association provided us with the potential for fMRI to be used as an early marker tool to identify the benefits of long-term treatment.

Interestingly, McCrae et al. [60] had compared the changes of nerve activation in pain response after traditional CBT for pain (CBT-P) and CBT for insomnia (CBT-I). They enrolled 32 patients with FM who underwent an experimental pain protocol during fMRI before and after CBT-P or CBT-I or waitlist control period. The fMRI analysis indicated that 12 regions showed significant interactions after CBT intervention. Activation decreased in 8 regions after CBT-I and in 3 regions after CBT-P, which was assessed by blood oxygen level-dependent (BOLD) response to pain. The better sleep improvement from CBT-I may account for this difference. Later, they conducted the latest study which innovatively regarded arousal and insomnia as mediating mechanisms in CBT for pain. McCrae et al. [61] enrolled 130 female participants with comorbid FM and insomnia, and carried out direct interventions with CBT-I. Similar to the design of Lazaridou et al., they planned structural and functional MRI scans 4 times to observe the persistence effects. They focused on central sensitisation (CS), which is an important character of FM [62, 63]. They proposed that CBT-I had the effect of reducing arousal, improving sleep, and reversing the negative hypothalamic-pituitary-adrenal (HPA) and central nervous system (CNS) changes (i.e., reversing CS) that sustain CP [61]. The data of this RCT have not been collected yet; it is believed that the publication of the full trial results will provide a deeper understanding of the intervention mechanism of CBT-I.

3.3. Migraine. Unlike most current CP research studies, Nahman-Averbuch et al. [64] recruited 18 adolescents with migraine in the clinical trial (15 females, age 15.1 ± 2.1 years). These adolescents underwent an 8-week CBT with their parents. The results showed a decrease in headache frequency from 15 ± 7.4 per month to 10 ± 7.4 per month after CBT sessions ($P < 0.001$). Similar to former studies, they found changes both in brain activation and functional connectivity. According to fMRI analysis, CBT resulted in activation of the OFC, VLPFC, and DLPFC regions on the right side of the brain, increased connectivity between the amygdala and paracingulate gyrus, PFC, and occipital cortex, but led to bilateral deactivation of the cerebellum. Additionally, the reduction in headache was correlated with bilateral activation of the occipital cortex, lingual gyrus, angular gyrus, and superior parietal lobule.

Interestingly, in this study, headache reduction was associated with opposite changes in left and right amygdala connectivity. The decrease in headache after CBT was associated with increased connectivity between the left amygdala and the occipital cortex and the reduced connectivity between the right amygdala and the paracingulate gyrus and DLPFC [64]. The amygdala is regarded as a key region in nociceptive processing and is highly connected to other pain regions such as the PFC, thalamus, anterior cingulate cortex, insula, and PAG [65, 66]. Changes in the amygdala function and structure have also been found in previous studies in adults suffering from migraine [67–69]. The amygdala and PFC are structurally and functionally related [70–73], and the amygdala has an inhibitory action and can disable the activity of MPFC [66, 74, 75]. This finding indicated that the left and right amygdala may have different roles in pain processing. It is suggested that CBT decreased the compensatory action of the right amygdala on the DLPFC. While the antinociceptive action of the left amygdala on the dorsal medial prefrontal cortex (DMPFC) was increased after CBT.

3.4. Experimental Pain. In contrast to the above studies that recruited patients, Kucyi et al. [76] recruited 30 healthy participants (CBT $n = 17$; control $n = 13$) to undergo equal amounts of heat-evoked pain, and they used the identical subjective reported pain levels before and after treatment. The fMRI analysis showed that there were pain-evoked deactivations in regions of the default mode network (DMN), including the bilateral posterior cingulate cortex (PCC)/precuneus (PCU), medial prefrontal cortex (MPFC), and lateral parietal cortex (LPC). There were no statistically significant group differences before intervention ($P < 0.05$), but after the intervention, the deactivation was significantly lower in the control group compared to the CBT group ($P < 0.05$). This means that repeated pain exposure eradicated DMN deactivation in the nonintervened ones but CBT could reverse the effect. Moreover, reduced deactivation of the right ventrolateral prefrontal cortex (VLPFC) of the executive control network and increased spontaneous functional connectivity between the DMN and right VLPFC was observed in the CBT group. Former studies suggested that changes in MPFC activity and connectivity were related to development of CP [77, 78]. In addition, patients with CP showed a lack of DMN deactivation during painful stimulation, which was recovered after successful analgesic treatment [79]. It can be seen that chronic or repeated acute pain exposure could lead to decreased pain-induced DMN

Table 1: Comparison of findings on neuroimaging changes in CBT for pain-related disorders.

Type	Journal year	L/R	Regions	Structural changes	Functional changes	+/−	References
Mixed	2013	B	**DLPFC***, PPC	GMV	—	−	Seminowicz et al. [49]
		L	SMA	GMV	—	−	
	2014	B	Anterior **DMN*** and the **amygdala***/PAG	—	iFC	−	Shpaner et al. [50]
		R	BG network and the right S2	—	iFC	+	
		B	**PCC***, the cerebellum	—	fALFF	+	
	2018	B	**OFC*** within the **DAN***	—	ICN connection	−	Yoshino et al. [51]
			IPL within the **DAN*** and PCL within the sensorimotor network	—	ICN connection	+	
FM	2012	B	**VLPFC***, **OFC***	—	Activation	+	Jensen et al. [54]
	2016	B	S1 and anterior/medial **insula***	—	Connectivity	−	Lazaridou et al. [59]
	2021	B	STG, IFG	—	Activation	−	McCrae et al. [60]
		R	**Insula***, MOG, lentiform nucleus, **cingulate gyrus***	—	Activation	−	
		L	ANG, MFG, IOG, MTG	—	Activation	−	
Migraine	2020	R	**OFC***, **VLPFC***, **DLPFC***	—	Activation	+	Nahman-Averbuch et al. [64]
		L	The left **amygdala*** and the occipital cortex	—	Connectivity	+	
		R	The right **amygdala*** and the paracingulate gyrus and **DLPFC***	—	Connectivity	−	
Heat-evoked	2016	B	**PCC***, PCU, MPFC, LPC	—	Deactivation	+	Kucyi et al. [76]
		B	**VLPFC***	—	Deactivation	−	
		R	**DMN*** and right **VLPFC***	—	Connectivity	+	

The bolded and asterisked markers mean that the brain region was repeatedly mentioned in multiple studies. L: left; R: right; B: bilateral; GMV: gray matter volume; iFC: intrinsic functional connectivity; fALFF: fractional amplitude of low-frequency fluctuations; ICN: intrinsic connectivity network; DLPFC: dorsolateral prefrontal cortex; PPC: posterior parietal cortex; SMA: supplementary motor area; DMN: default mode network; PAG: periaqueductal gray; BG: basal ganglia; S2: the secondary somatosensory cortex; PCC: posterior cingulate cortex; OFC: orbitofrontal cortex; DAN: dorsal attention network; IPL: inferior parietal lobule; PCL: paracentral lobule; VLPFC: ventrolateral prefrontal cortex; S1: the primary somatosensory cortex; STG: superior temporal gyrus; IFG: inferior frontal gyrus; MOG: middle occipital gyrus; ANG: angular gyrus; MFG: middle frontal gyrus; IOG: inferior occipital gyrus; MTG: middle temporal gyrus; PCU: precuneus; MPFC: medial prefrontal cortex; LPC: lateral parietal cortex.

deactivation, but this decline can be prevented/reversed by CBT or analgesic treatment.

4. Discussion

The aforementioned studies showed that CBT may relieve mixed chronic pain, fibromyalgia, migraine, and heat-stimulated pain by causing structural or functional changes in multiple brain regions. The main mechanisms of CBT are given in Table 1 and Figure 1. Previous studies mainly used Brodmann area for brain region partitioning; still, some also used anatomical automatic labelling (AAL), which may lead to crossover in the results. As given in Table 1, some key regions were repeatedly observed in several studies, including the DLPFC, OFC, VLPFC, PCC, and amygdala.

DLPFC was the only region showing both functional and structural alterations, suggesting that CBT may relieve mixed pain by decreasing GMV of DLPFC, and be therapeutic for migraine by activating the right DLPFC and weakening its association with the right amygdala. OFC and VLPFC had also shown their importance in the mechanism of CBT-P, which are adjacent to DLPFC. The findings suggested that CBT may treat FM and migraine by activating the right or bilateral OFC and VLPFC. In addition, CBT may reduce ICN connection of OFC within the DAN network in mixed pain treatment and reduce deactivation of VLPFC and enhance its connectivity with the DMN in heat-evoked pain intervention. Moreover, CBT may relieve mixed pain by reducing iFC between the medial prefrontal cortex and the amygdala, which is an important component of the anterior DMN. The reduction in the volume of SMA and the decreased activation of the MFG and IFG may also be associated with the relief of mixed pain or FM due to CBT.

Functional changes in the PCC, cingulate gyrus, and paracingulate gyrus were also found in the above four types of pain studies. It is suggested that CBT may treat mixed pain by increasing fALFF of the PCC, relieve heat-evoked pain by increasing its deactivation, intervene in FM by reducing the activation of the right cingulate gyrus, and treat migraine by reducing the association of the paracingulate gyrus with the right amygdala.

The differential action of the left and right amygdala has gradually emerged as research progresses. While earlier studies showed a decrease in iFC of the amygdala and the anterior DMN due to CBT, the latest study showed that the left and right amygdala had opposed alterations in connectivity with other regions. It is implied that CBT-P may treat migraine by increasing the connectivity between the left amygdala and the occipital lobe and decreasing the connectivity between the right amygdala and the paracingulate gyrus and DLPFC. The amygdala and the lentiform nucleus are important components of the BG. The therapeutic effects of CBT may also be associated with enhanced iFC between the BG network and the right S2 as well as diminished activation of the right lentiform nucleus.

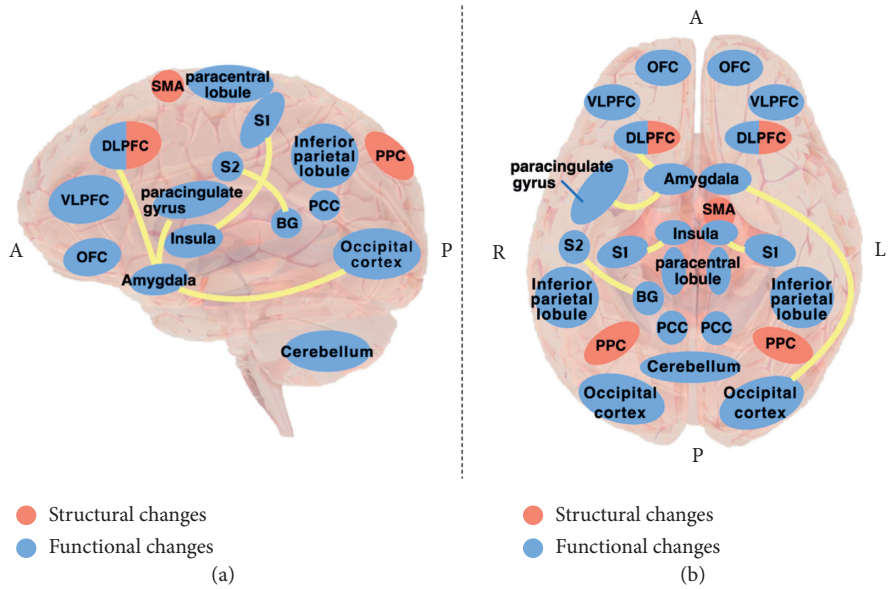

Figure 1: Illustration of the main mechanisms of CBT in pain management. (a) Side perspective view. (b) Bottom perspective view. Abbreviations are annotated after Table 1.

The following problems exist in the published studies. (1) Several studies enrolled patients with mixed diagnoses of pain. Small number of subjects led to the lack of subgroup analysis of each diagnosis. Different types of pain may cause different central imaging changes, and the therapeutic effects of CBT may be different. (2) Only a few studies had considered the mediating role of insomnia, medication, menstrual cycle, depression, and other factors. These neuroimaging changes after CBT may be confounded with the performance of mood and insomnia improvement, and the causal relationship is difficult to clarify. (4) Only a few studies controlled or matched for pain levels. It is speculated that the therapeutic effect of CBT may be associated with pain severity, based on the current clinical study findings. Published studies had not shown changes in the brain areas in patients with ineffective clinical symptom improvement, which are common in the real world, and lacked subgroup analyses of different pain levels.

Future trend: (1) in the future, subgroup analysis of different types of pain should be designed to reduce the confounding factors of different types of pain. (2) Future research needs to reduce the mixed effects of insomnia and emotions (depression and anxiety). (3) fMRI can be used to predict the curative effect of CBT according to the level and stage of pain and the structural connection state of the inherent brain region. (4) Neuroimaging studies can be designed to make improvements of CBT. It is possible to refine whether patients with certain clinical characteristics can benefit specifically after strengthening some stages of the CBT session. Neuroimaging studies can guide innovation in the form of CBT by comparing the effects of online-offline and individual-team brain stimulation.

5. Conclusions

Current studies of neuroimaging mechanisms of CBT used structural and functional MRI to analyze changes in brain gray matter volume, activation and deactivation of brain regions, and intrinsic connectivity between brain regions. The involved networks contained the DMN, DAN, and sensorimotor network. Pain is a multidimensional sensory and emotional experience associated with anxiety, depression, and insomnia. The current findings indicated that many brain regions responsible for cognition and emotion were involved in the mechanism of CBT, including the frontal cortex, parietal cortex, occipital cortex, somatosensory cortex, basal ganglia, amygdala, cerebellum, insula and cingulate gyrus. After CBT, the brain showed stronger top-down pain control, cognitive reassessment, and altered perception of stimulus signals (chronic pain and repeated acute pain). In order to get more accurate results in future studies, separate analyses for a specific type of pain could be considered to rule out the influence of mixed factors such as different kinds of pain, anxiety, depression, and insomnia.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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Review Article

A Narrative Review of Neuroimaging Studies in Acupuncture for Migraine

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Acupuncture has been widely used as an alternative and complementary therapy for migraine. With the development of neuroimaging techniques, the central mechanism of acupuncture for migraine has gained increasing attention. This review aimed to analyze the study design and main findings of neuroimaging studies of acupuncture for migraine to provide the reference for future research. The original studies were collected and screened in three English databases (PubMed, Embase, and Cochrane Library) and four Chinese databases (Chinese National Knowledge Infrastructure, Chinese Biomedical Literature database, the Chongqing VIP database, and Wanfang database). As a result, a total of 28 articles were included. Functional magnetic resonance imaging was the most used neuroimaging technique to explore the cerebral activities of acupuncture for migraine. This review manifested that acupuncture could elicit cerebral responses on patients with migraine, different from sham acupuncture. The results indicated that the pain systems, including the medial pain pathway, lateral pain pathway, and descending pain modulatory system, participated in the modulation of the cerebral activities of migraine by acupuncture.

1. Introduction

Migraine is a chronic neurological disease characterized by recurrent headaches and neurological symptoms [1]. As the third most prevalent disorder and the seventh highest specific cause of disability worldwide [2, 3], migraine not only affects the quality of life (QoL) and productivity of patients [4] but also results in a high financial burden to society [5]. Recently, acupuncture has been widely used as an alternative or complementary treatment for migraine with its efficacy and safety. Using the neuroimaging techniques to explore the underlying mechanism of acupuncture for migraine has also attracted the increasing interest of investigators.

Since the first neuroimaging study about acupuncture for migraine was published in 2008, nearly 30 studies have been emerged to improve the understanding of acupuncture for migraine with real-time visualized evidence. However, the designs and results of these studies showed significant differences. For example, some research studies concentrated on study designs from different perspectives, such as different manipulation modalities of acupuncture and different subtypes of migraine; several studies applied different neuroimaging scanning techniques or used different analytical methods. The various study designs may partly contribute to different results which affect the clinical application to some degree. Therefore, this review aimed to analyze the study design and summarize the main results of the published neuroimaging studies in acupuncture for migraine to deepen the understanding of the cerebral mechanism of acupuncture for migraine and provide reference and guidance for future research.

2. Methods

2.1. Searching Strategy. Data collections were conducted in three English language databases (PubMed, Embase, and Cochrane Library) and four Chinese language databases (Chinese National Knowledge Infrastructure, CNKI; Chinese Biomedical Literature database, CBM; the Chongqing VIP database, VIP; and the Wanfang database, WF) from database inception up to 31st Dec 2020, with the combination of the main keywords: neuroimaging, acupuncture, and pain; studies about migraine were selected. The retrospective searching was performed on reference lists of included articles. Details of search terms were depicted and modified for each database in Supplementary Table 1.

The article was included if [1] the studies were original articles, [2] the patients were diagnosed with migraine, [3] acupuncture was the intervention method, and [4] neuroimaging techniques were used to investigate the cerebral changes elicited by acupuncture (Supplementary Table 1).

The article was excluded if [1] it was a duplicate article or [2] it was the irrelevant article, review, case report, protocol, only abstract, editorial letter, retracted article, and animal experiment. Studies not fulfilling each of the above criteria were excluded (Supplementary Table 1).

Supplementary Figure 1 shows the flow diagram of the literature search and screening process.

2.2. Data Extraction and Analysis. The published year, the institution of corresponding authors (Supplementary Table 2 and Supplementary Figure 2), study design (types of migraine, interventions (manipulation modality and course of treatments), types of control, and clinical scales of migraine) (Supplementary Table 3), and the related neuroimaging information (neuroimaging scanning techniques, analytical methods of neuroimaging data, and the results of brain regions involved in acupuncture analgesia for migraine) (Supplementary Table 4) were extracted.

3. Results

Twenty-eight original articles were included in this review.

3.1. The Basic Information of the Studies. The first acupuncture-neuroimaging study for migraine was published in 2008. All the twenty-eight studies were published by Chinese researchers. The top three corresponding affiliations were Chengdu University of TCM (11 studies) [6–16], Dongzhimen Hospital of Beijing University of TCM (5 studies) [17–21], and Xidian University (3 studies) [22–24].

3.2. The Subtypes of Migraine Patients. Twenty studies (71%) enrolled migraine patients without aura [6–8, 11, 14–29]. Four studies (14%) did not describe the subtypes of migraine [12, 30–32], three studies (11%) enrolled chronic migraine patients [9, 10, 33], and one study (4%) enrolled the patients with menstrual migraine [13] (Figure1(a)).

3.3. The Acupuncture Intervention. Twenty studies (71%) focused on the long-term efficacy of acupuncture for migraine [6–8, 11, 13, 15–17, 20, 22–25, 27–33]; eight studies (29%) adopted performed treatment session to explore the immediate efficacy of acupuncture for migraine [9, 10, 12, 14, 18, 19, 21, 26] (Figure1(b)).

Twenty-one (75%) studies were designed to concentrate on the central mechanisms of acupuncture for migraine. Among them, nine studies (32%) were designed as the self-control model (pre vs. posttreatment) [9, 10, 15, 18–21, 28, 29], nine studies (32%) explored the differences in cerebral responses between verum acupuncture (VA) and sham acupuncture (SA) [6–8, 12, 13, 16, 26, 27, 33], and the remaining three studies for different acupuncture intensities or different acupoints. Other studies concentrated on the central mechanisms of acupuncture for different conditions of migraine (Figure1(d)).

Seventeen studies used the visual analogue scale (VAS) to assess the pain intensity of migraine [6–8, 11–15, 17, 20, 22–24, 27–29, 33]. Besides, the condition of migraine such as frequency of migraine attacks (8 studies) [6–8, 11, 13, 16, 20, 29], migraine attack duration (7 studies) [20, 22–24, 28, 30, 31], migraine days (6 studies) [11, 15, 22–24, 29], and migraine intensity (3 studies) [13, 30, 31] was also assessed. Two studies adopted the disease-specific scale, Migraine-Specific Quality of Life Questionnaire (MSQ), to evaluate the QoL of migraine [22, 25] (Figure1(c)).

3.4. Neuroimaging Scan and Data Analysis. Twenty studies selected magnetic resonance imaging (MRI) to explore the cerebral responses of acupuncture for migraine [6–8, 11, 13, 15–29]; among these studies, fifteen studies applied functional magnetic resonance imaging (fMRI) [6–8, 11, 13, 15, 16, 18–21, 26–29], five studies applied diffusion tensor imaging (DTI) [17, 22–25], four studies used positron emission tomography-computed tomography (PET-CT), and four studies selected proton magnetic resonance spectroscopy (H-MRS) to investigate the metabolic ration of H-MRS to explore the cerebral responses of acupuncture for migraine (Figures 1(e) and 1(f)) [30–33].

Functional integration analysis (functional connectivity, independent component analysis, and functional brain network) (9 studies) were the common analytical methods applied in the fMRI [7, 8, 13, 16, 19, 20, 24, 28, 29] and followed by functional segregation analysis (amplitude of low-frequency fluctuations/fractional amplitude of low-frequency fluctuations, ALFF/fALFF; regional homogeneity, ReHo) (7 studies) [6, 11, 15, 18, 21, 26, 27]. Tract-based spatial statistics (TBSS) was the common analytical method applied in the DTI. Besides, the statistical parametric mapping (SPM) software was applied to assess the brain glucose metabolism alterations of acupuncture for migraine [9, 10, 12, 14]. Furthermore, three studies used multiple analytical methods [8, 22, 24] and four studies selected machine learning [15, 16, 22, 24].

The cerebral responses to acupuncture for migraine are given in Supplementary Table 4. The high-frequency reported brain regions are shown in Figure 2.

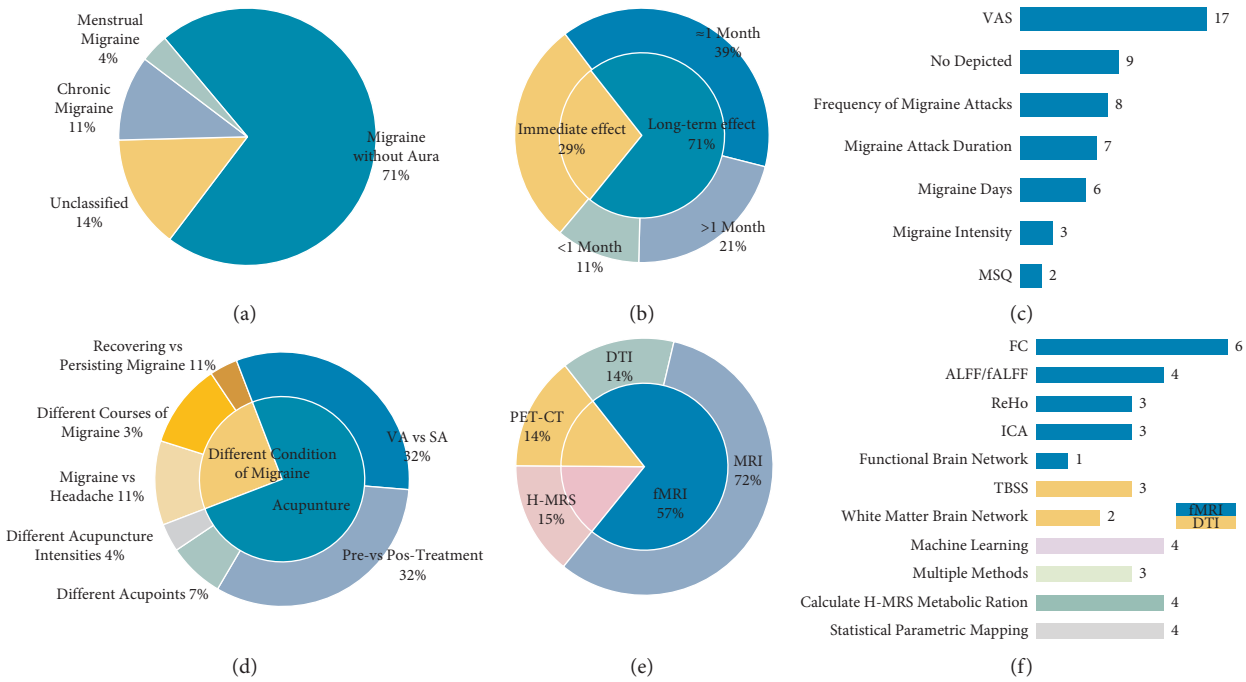

Figure 1: The study design of included studies. (a) The proportion of different types of migraine. (b) The proportion of treatment session. (c) The proportion of clinical variables of migraine. (d) The proportion of control types. (e) The proportion of scanning techniques. (f) The proportion of analysis methods of neuroimaging data. VA, verum acupuncture; SA, sham acupuncture; VAS, visual analogue scale; MSQ, Migraine-Specific Quality of Life Questionnaire; H-MRS, proton magnetic resonance spectroscopy; PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; ALFF, amplitude of low-frequency fluctuations; FC, functional connectivity; ReHo, regional homogeneity; ICA, independent components analysis; TBSS. tract-based spatial statistics.

4. Discussion

Since neuroimaging techniques were used to explore the mechanisms of acupuncture, the central mechanism of acupuncture for migraine has gradually drawn the attention of investigators. Since the first study explored the central mechanism of acupuncture for migraine, 28 studies have been published during the past 15 years. From the beginning, these articles simply concentrated on the self-control design of the cerebral activities, gradually developed to explore the different cerebral activities of the acupuncture efficacy (such as VA and SA), and now paid attention to the different cerebral activities of acupuncture for subtypes or stages of the migraine. These articles significantly improved the understanding of acupuncture for migraine with real-time visualized evidence.

4.1. The Study Design of Acupuncture-Neuroimaging Studies for Migraine. The design of the acupuncture-neuroimaging study for migraine could be divided into four categories according to the contents.

First, at the early stage, these studies [8–10, 18–21, 28, 29] mainly designed the self-controlled trial to investigate whether acupuncture could elicit cerebral responses on patients with migraine, accounting for more than one-third of studies. Although these studies only set one group to observe the cerebral signal changes comparing the brain activities at the baseline with that at the end of acupuncture therapy, these studies provided preliminary references for future studies. However, this kind of design had limitations what factors (such as the efficacy of acupuncture and moxibustion, placebo effect of acupuncture, or the natural course of migraine) caused the alterations of cerebral activities were still unclear.

Second, people gradually tended to investigate whether the cerebral changes elicited by acupuncture were different from those by SA, to explore the different cerebral activities between the acupuncture efficacy and placebo efficacy. The majority of these studies selected functional connectivity (FC) to analyze the neuroimaging data. FC has developed to the popular direction of the neuroimaging analytical method in recent years. However, few kinds of research concentrated on the depth, the intensities of acupuncture stimulation, or other factors that influenced the efficacy of acupuncture for migraine.The application of FC based on the specific ROI of the brain, rather than the whole brain, is a substantial limitation of these studies. Thus, it is valuable to explore the central mechanism of acupuncture for migraine from different perspectives including the influencing factors and large-scale whole brain networks.

Third, some studies investigated the central mechanism of acupuncture therapy for some subtypes (menstrual migraine or some stages of migraine). That means investigators mostly focused on the central mechanisms of acupuncture for specific subtypes of migraine. It has been proved that the

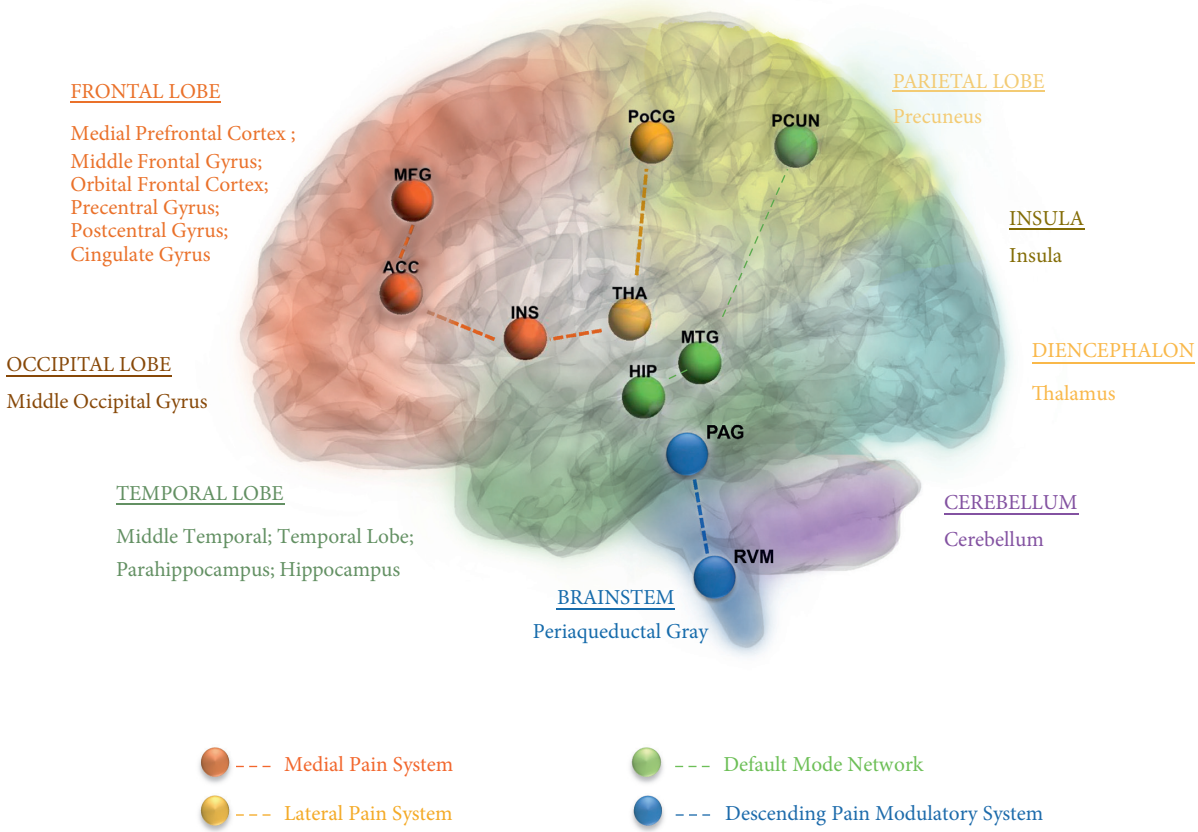

Figure 2: The main findings of acupuncture for migraine by neuroimaging techniques. The different shadow colors represent the different functional classifications of the brain. The high frequent reported areas that have been affected by acupuncture for migraine in the included studies were noted with different colors. The different color nodes represent the different pathways or networks. ACC, anterior cingulate cortex; DMN, default mode network; HIP, hippocampus; INS, insula; MFG, middle frontal gyrus; MTG, medial temporal gyrus; PAG, periaqueductal gray; PCUN, precuneus; PoCG, postcentral gyrus; RVM, rostral ventromedial medulla.

cerebral activities of the ictal or interictal phase of the migraine existed differently [34–36]. The migraine with aura, chronic migraine, different phases of migraine was hardly explored. Therefore, future studies can explore other subtypes of migraine and apply the experimental pain to model the different phases of migraine to fully explore the cerebral responses to acupuncture for migraine.

Fourth, with the application of the machine learning (ML) algorithm in neuroimaging studies, people gradually began to predict the efficacy of acupuncture for migraine with neuroimaging data by the multivariate pattern analysis method. In this review, four studies applied ML to explore the structural and functional properties of the brain whether it can contribute significant information to predict the efficacy of acupuncture for migraine at the individual level [15, 16, 22, 24]. Unlike the univariate group-level statistics, ML can predict the efficacy of acupuncture for migraine with valid multivariate characteristics and provide specific clinical guidance at the individual level, which has gradually attracted increasing attention by researchers in recent years. Therefore, integrating ML and neuroimaging techniques will be the hot direction to identify neural "biomarkers" from neuroimaging data automatically at the individual level and predict the acupuncture efficacy for migraine.

Of the included studies, VAS was the most used scale for pain assessment for migraine. Besides, the clinical efficacy of migraine mostly focused on symptoms such as the frequency, intensity, and attack duration of migraine. Only five studies applied emotional scales and two studies applied disease-specific scales, MSQ, to assess the emotion and QoL of migraine patients. The pain experience is multifaceted and complex, encompassing multiple dimensions including psychological, cognitive, perception, affective, and behavior [37]. Except for the pain, the impaired functioning, psychological responses, and participant ratings of overall improvement are also associated with migraine [38–40]. Therefore, the multidimensional characteristics of migraine such as psychological, physical functioning, and participant ratings of overall improvement should be assessed simultaneously to explore the central mechanisms of the analgesic efficacy of acupuncture for migraine.

4.2. The Neuroimaging Methods Applied in the Acupuncture for Migraine. In this review, the neuroimaging techniques

including MRI, PET, and H-MRS were applied. fMRI was the most commonly used technique to explore the cerebral activities of acupuncture for migraine. fMRI indirectly measures brain activity based on the blood oxygenation level-dependent effect [41], PET-CT relies on the exogenous tracer for measuring the functional and metabolic changes [42], and H-MRS explores the neurochemical changes of the brain [43]. Only one study combing DTI and fMRI to explore the cerebral alterations of acupuncture for migraine [20] ofthe included studies. Multimodal neuroimaging can integrate the strengths of each imaging modality and make the data cross-validation.

Therefore, future studies can combine the multimodal neuroimaging techniques to detect the dynamic brain activity of acupuncture for migraine to make the results complementary and cross-validation. For example, combine molecular imaging such as H-MRS with fMRI to detect cerebral activities from the molecular and functional levels. H-MRS can be a complementary neuroimaging technique to fMRI, which can identify static as well as dynamic levels of specific brain neurotransmitters that likely relate to the fMRI signal involved in pain processing and modulation of acupuncture for migraine [44]. Besides, combing fMRI with electroencephalography can provide complementary information of brain activity (hemodynamic and electrophysiological, respectively) with the spatiotemporal resolution, which can be applied to detect the dynamic cerebral activities of acupuncture for the whole migraine attacks.

4.3. Pain Pathways Participating in the Acupuncture for Migraine. The neuroimaging studies about acupuncture for migraine demonstrated that acupuncture modulates a widely distributed network of brain areas including the frontal lobe, temporal lobe, occipital lobe, parietal lobe, diencephalon, brainstem, and cerebellum (Figure 2). According to the high frequency of altered brain regions, the important pain pathways related to the acupuncture for migraine of the included studies were clarified (Figure 2).

4.3.1. The Medial Pain System Participating in the Cerebral Responses to Acupuncture for Migraine. In this review, the included studies have suggested that the regions of the medial pain system, including the anterior cingulate cortex (ACC), insula, and middle frontal gyrus (MFG), are participating in the cerebral responses to acupuncture for migraine (Figure 2(b), orange nodes). The medial pain pathway projects to the limbic system including the ACC and insula via the medial thalamus participating in the process of motivational-affective aspects, cognitive-evaluative aspects, and memory of pain [45, 46]. Chronic pain can lead to persistent emotional disorders such as anxiety, fear, and influence brain processing on many levels [47–49]. Cumulative evidence suggested that ACC contributed to the response to the process of anxiety and fear of pain [50, 51] and insula involved in the processing of the emotional motivation dimension of pain [52, 53]. MFG is often referred to as the dorsolateral prefrontal cortex (dlPFC) [54], dlPFC is a core putative target for modulation of pain-related fear responses [55]. Previous studies suggested that the altered function of the regions of the medial pain system participates in the pathology of migraine [56, 57]. In this review, the key regions of the medial pain system are involved in the modulation of acupuncture for migraine, which indicated that acupuncture may exert its therapeutic efficacy on migraine by modulating the medial pain system.

4.3.2. The Lateral Pain System Participating in the Cerebral Responses to Acupuncture for Migraine. The thalamus cortex is known to be a relay center for the processing of nociceptive inputs, and the thalamus can be divided into medial and ventrobasal parts [58]. Pathways from the medial thalamus project diffusely to wide areas of the cortex and together make up the medial pain system. The ventrobasal thalamus receives input from the ascending tract, sends fibers to the primary and secondary somatosensory areas of the cerebral cortex, and makes up the lateral pain system. The postcentral gyrus (PoCG) was a part of secondary somatosensory areas of the cerebral cortex. The lateral pain system was where refined localization and discrimination of pain occurred. The altered thalamus and PoCG involved in the lateral pain system pointed to abnormal pain processing and modulation in migraine [59–61]. After summarizing the neuroimaging results of acupuncture for migraine, thalamus and PoCG were the high-frequency regions that can be regulated by acupuncture for migraine. Therefore, the lateral pain pathway (Figure 2(b), yellow nodes) processing the localization and discrimination of pain was also the important region of acupuncture for migraine.

Besides, the results indicated that the key regions of default DMN [62] (Figure 2(b), green nodes), including the media prefrontal cortex, cingulate cortex, precuneus, medial temporal lobe, insula, and hippocampus, are involved in the cerebral responses to acupuncture for migraine. DMN is associated with attention, memory, prospection, and self-referential processing [63–65]. Recent studies showed that altered DMN is associated with many chronic pain conditions [66–68], and it is the primary network affected by chronic pain [69]. Previous studies have also found that DMN plays an important role in pain modulation of migraine [70–72]. In this review, most regions of DMN are involved in the modulation of acupuncture for migraine, which indicated that acupuncture may exert its therapeutic effects by modulating the distributed regions for migraine.

4.3.3. The Descending Pain System Participating in the Cerebral Responses to Acupuncture for Migraine. Disruption of the balance of descending pain modulation associated with chronic pain has been confirmed [73, 74]. The well-known descending pain systems majorly contained periaqueductal gray (PAG) and rostral ventromedial medulla (RVM). PAG is the primary region in controlling the modulation of the descending pain modulatory system in the brainstem [75, 76] and affects descending pain modulation primarily through its reciprocal connections with RVM [77]. The descending pain system is significantly implicated in the dysfunction of the descending pain modulatory pathways in

migraine [78–80]. The PAG and RVM were activated after the treatment of acupuncture in this review, which suggested that the functions of the descending pain system were not only a response to migraine but also an underlying brain pathway that was perhaps at the core of modulating the pain of migraine.

Further analysis of the relation between the study designs and results indicated that the medial pain pathway was the core altered region during VA vs. SA control modality about the long-term effect [6–8, 12, 13, 16, 26, 27, 33]. The results indicated that the role of the medial pain system, which mainly participated in the pain-related emotional response, was one of the key modulations of acupuncture for migraine. Additionally, the results about adopting one treatment session to explore the immediate-efficacy acupuncture for migraine [9, 10, 12, 14, 18, 19, 21, 26] mainly concentrated on the lateral pain system. The results manifested that the lateral pain system was another key pathway processing the sensation of pain involving the modulation for acupuncture. In other words, the pain experience has a multidimensional nature. The modulation of acupuncture was multimodal rather than unidimensional, which contained the medial pain system for processing the emotion loop, lateral pain system for processing the sensory loop, and descending pain system for inhibiting pain.

5. Conclusion

This review mainly overviewed the study design and main findings of acupuncture for migraine by neuroimaging techniques. This review manifested that acupuncture could elicit cerebral responses on patients with migraine and different from SA. Current studies began to use the ML to predict the efficacy of acupuncture for migraine. In the future, researchers can promote the integration of clinical and neuroimaging data with a bigger sample size to predict the efficacy of acupuncture for migraine and provide specific clinical guidance at the individual level.

Abbreviation

TCM: Traditional Chinese medicine
VA: Verum acupuncture
SA: Sham acupuncture
VAS: Visual analogue scale
MRI: Magnetic resonance imaging
fMRI: Functional magnetic resonance imaging
DTI: Diffusion tensor imaging
PET-CT: Positron emission tomography-computed tomography
H-MRS: Proton magnetic resonance spectroscopy
ALFF/fALFF: Amplitude of low-frequency fluctuations/fractional amplitude of low-frequency fluctuations
ReHo: Regional homogeneity
SPM: Statistical parametric mapping
ML: Machine learning
DMN: Default mode network
MwoA: Migraine without aura
MSQ: Migraine-Specific Quality of Life Questionnaire
QoL: Quality of life
ACC: Anterior cingulate cortex
dlPFC: Dorsolateral prefrontal cortex
PoCG: Postcentral gyrus
MFG: Middle frontal gyrus
PAG: Periaqueductal gray
RVM: Rostral ventromedial medulla.

Data Availability

The datasets of this study can be requested from the first author at mapeihong@stu.cdutcm.edu.cn.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Peihong Ma, Xiaohui Dong, and Yuzhu Qu contributed equally to this article. Fang Zeng designed the study.Peihong Ma, Xiaohui Dong, and Yuzhu Qu participated in screening studies. Yuke Teng and Kunnan Xie extracted the data from the included studies. Zhaoxuan He, Shirui Cheng, and Zilei Tian analyzed the data. Peihong Ma, Ruirui Sun, and Tao Yin drafted the manuscript. Siyi Yu and Fang Zeng revised the draft. All authors have read and approved the publication of the final manuscript.

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Supplementary Materials

Supplementary Table 1. Full search strategy for each of the electronic databases queried. Supplementary Table 2. The basic information of the included studies. Supplementary Table 3. The study design of the included studies. Supplementary Table 4. The neuroimage information of the included studies. Supplementary Figure 1. The flow diagram of the literature search and screening process. Supplementary Figure 2. The basic information of the included studies. A. The annual distribution of included studies. B. The institution distribution of included studies. (*Supplementary Materials*)

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