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REVIEW

Acupuncture-Related Therapy for Knee Osteoarthritis: A Narrative Review of Neuroimaging Studies

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Abstract: Acupuncture has been widely applied for treating knee osteoarthritis (KOA). Numerous studies have found that acupuncture can effectively alleviate KOA symptoms. With the advancement of neuroimaging techniques, integrating neuroimaging with in-depth investigations of acupuncture mechanisms has emerged as a hot topic in traditional Chinese medical neuroscience research. This review aimed to analyze the study design and main findings from neuroimaging studies of acupuncture-related therapy for KOA to provide a reference for future research. Original studies were sourced from English databases (PubMed, Embase, and Cochrane Library) and Chinese databases (Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, the Chongqing VIP database, and Wanfang database). As a result, thirteen articles were ultimately included in this review. Functional magnetic resonance imaging was the most frequently used neuroimaging technique to explore cerebral responses to acupuncture-related therapy for KOA. Findings suggested that acupuncture-related therapy could regulate some brain regions in patients with KOA. Specifically, for acupuncture, it showed that the medial pain pathway and the limbic system were involved in the regulation of KOA. Meanwhile, moxibustion induced a wide range of functional activity throughout the entire brain.

Keywords: acupuncture-related therapy, knee osteoarthritis, cerebral response, neuroimaging study

Introduction

Osteoarthritis of the knee (KOA), the most prevalent joint disorder, is characterized by the loss of articular cartilage, progressive degeneration, pain, and physical dysfunction.[1,2] Approximately 30% of individuals over 45 years old have radio-graphic evidence of KOA, and nearly half of them exhibit knee symptoms.[3] Besides its significant impact on physical disability,[4] KOA is also associated with an increased risk of all-cause mortality.[5,6] Patients with KOA spend an average of over $10,000 in direct medical costs for this osteoarthritis throughout their lifetimes.[3] The management of KOA spans non- or pharmacologic interventions, orthopedic aids, and surgery. Based on the treatment guidelines,[7–9] acupuncture is recommended for the management of KOA symptoms. As a traditional complementary therapy originating in China, acupuncture-related therapy has been utilized for thousands of years to address knee-related disorders. According to traditional Chinese medicine theory, acupuncture and moxibustion are the most important components of acupuncture-related therapy. Specifically, acupuncture is characterized by inserting a metal needle into a subcutaneous acupoint, mainly including manual acupuncture, electro-acupuncture, auriculoacupuncture, and more.[10] Moxibustion is identified as igniting moxa on the skin of an acupoint to produce warmth and cause redness

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around the peripheral.[11] Clinically, acupuncture and moxibustion can be used alone or in combination to treat certain chronic diseases.[12] Substantial studies have found that acupuncture-related therapy is beneficial to KOA.[13–15]

Advances in neuroimaging technologies for pain research have provided insights into cerebral mechanisms of acupuncture for KOA. For instance, KOA patients have exhibited abnormalities in brain functional activity and connectivity, such as the periaqueductal gray, raphe nuclei, medial frontal cortex, and bilateral hippocampus, while acupuncture could regulate these abnormalities to control KOA.[16,17] Since the publication of the first neuroimaging study on acupuncture-related treatment for KOA in 2013,[18] 13 neuroimaging studies have been conducted in the past decade, supporting the effect of acupuncture on central regulation. These neuroimaging studies have described specific research methods, such as verum acupuncture (also known as real acupuncture, involving the insertion of a metal needle into an acupoint) and sham acupuncture (involving the use of a placebo needle device to prevent penetration of the skin at an acupoint or sham acupoint), heat-sensitive moxibustion and sham moxibustion, different neuroimaging techniques and analysis methods. Furthermore, they have reported different brain responses elicited by acupuncture. For instance, research has revealed that acupuncture could enhance functional connectivity (FC) between dorsal raphe and striatum,[17] in the right frontoparietal network and the executive control network with the rostral anterior cingulate cortex/medial prefrontal cortex.[19]

Therefore, we summarized these available neuroimaging studies of acupuncture-related therapy for KOA, reviewed the methodological issues and the core regulated brain regions involved in acupuncture analgesia for KOA. Furthermore, this review provided prospects for future neuroimaging research on acupuncture-related therapy for KOA.

Materials and Methods

Literature Search

The literature search was performed in the following databases from inception up to March 31, 2023 and updated on October 10, 2023: PubMed, Embase, Cochrane Library (CENTRAL), Chongqing VIP Chinese Science and Technology Periodical Database, Wanfang database, Chinese Biomedical Literature Database, and Chinese National Knowledge Infrastructure, without language restrictions. In addition, reference lists of related publications were checked for potentially applicable studies. A combination of MeSH terms, free-text terms, synonyms, and subject headings related to "knee osteoarthritis", "acupuncture", "moxibustion", and "neuroimaging" were included in this strategy. The search strategy for PubMed is shown in Supplementary Table 1. Equivalent search terms were used in other databases.

Study Selection and Data Extraction

Studies were selected and included based on population, intervention, comparison, outcome and study design if they met the following criteria: 1) conducted among patients with KOA, 2) applied acupuncture and/or moxibustion as interventions, and 3) utilized neuroimaging techniques to explore cerebral responses. Conversely, animal studies, reviews, conference abstracts, commentaries, editorials, protocols, and clinical studies using experimental pain models were excluded.

Two reviewers (Ying Peng and Yan Xiong) independently screened all titles and abstracts, followed by full texts to identify eligible articles. The information of eligible articles was extracted by the two reviewers and then cross-checked by a third reviewer (Xiaohui Dong), including first author's name, publication year, controls, sample size, interventions, neuroimaging modality and conditions, analytical methods, and outcomes of neuroimaging data. Any disagreements were resolved through discussion, with Yuzhu Qu serving as a judge if no agreement was reached.

Data Analysis

A descriptive analysis was conducted to summarize the methodological issues of the published A&M neuroimaging studies on KOA and cerebral responses elicited by A&M.

Results

Study Selection and Description

A total of 312 potential articles were initially identified using the primary search strategy. After removing duplicates and screening titles, abstracts, and full texts, 13 eligible clinical neuroimaging trials were ultimately included in this review (Figure 1). These

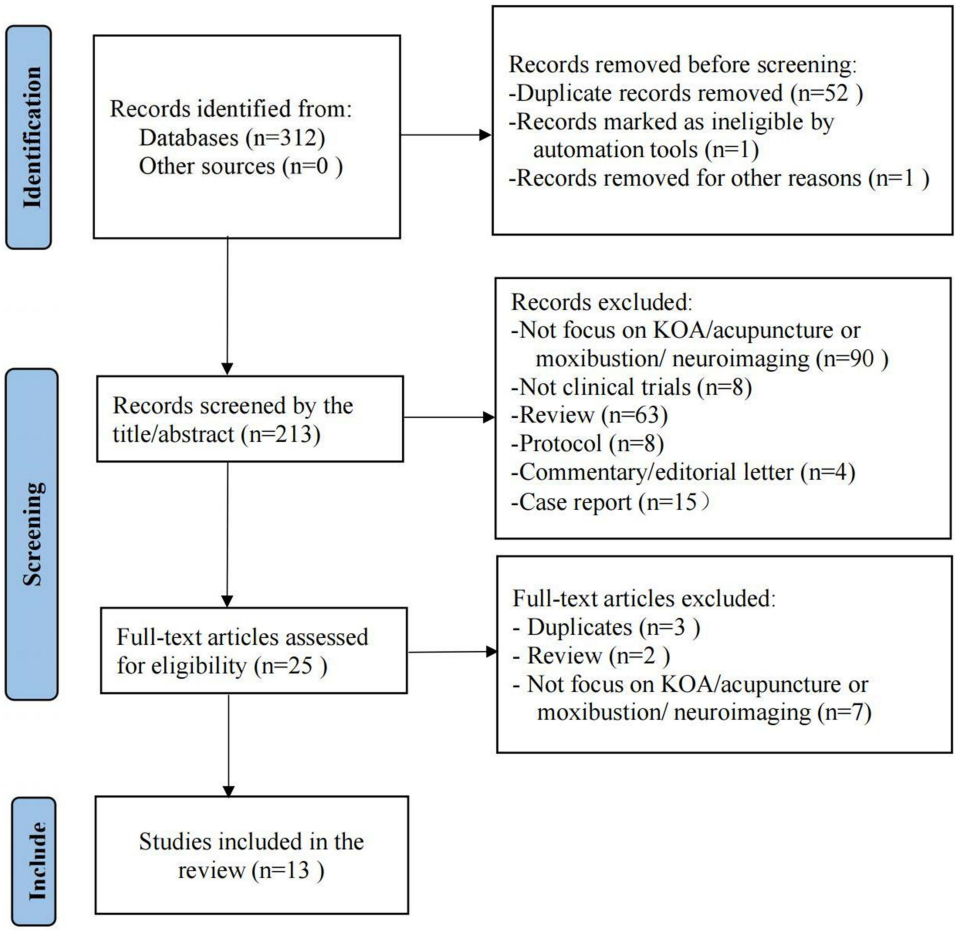

Figure 1 Flow diagram of this review.

articles were published between 2013 and 2023. Among them, six studies were conducted in the United States (Studies 1–6),[19–24] and the remaining seven studies were carried out in China (Studies 7–13).[25–31] Ten studies used acupuncture (eight used manual acupuncture, and two used electro-acupuncture), while three studies used moxibustion. Additionally, 12 studies applied blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD-fMRI) as the neuroimaging tool, and one study used EEG (Study 13). Characteristics of included studies are shown in Table 1.

Participants

This review included a total of 561 KOA participants and 131 healthy subjects. The age of patients with KOA ranged between 40 and 69.4 years. The duration of KOA varied from 0.33 to 19 years (not stated in half of these studies).

Acupuncture-Related Interventions

Ten studies used acupuncture for KOA. Among them, three studies (Studies 1, 5, and 8) focused on the immediate effect of acupuncture, with a single treatment duration ranging from 6 to 25 minutes. Seven studies (Studies 2, 3, 4, 6, 7, 9, and 10) examined the long-term effect of acupuncture, employing 6 to 30 treatment sessions over 2 to 8 weeks, with each session lasting 25 to 30 minutes. The other three studies (Studies 11–13) focused on the immediate effect of moxibustion for KOA, with a single treatment duration of 30 minutes. The most frequently used acupoints for KOA were Dubi (ST35), Xiyan (EX-LE4 and EX-LE5), Yanglingquan (GB34), Yinlingquan (SP9), Xuanzhong (GB39), and Sanyinjiao (SP6). Almost all of included studies (except Study 1) stated the acquisition of needle sensation (*deqi*) or moxibustion sensation during each treatment session.

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Table 1 Characteristics of the 13 Included Studies

No. Study (Year)	Sample Size (Male)	Patients Age	Duration (Years)	Intervention	Groups	Design	Clinical Outcome	Imaging Modality/ Condition	Analytical Approaches	Overall Risk of Bias
1. Hashmi et al (2014)[26]	KOA 42 (17)	57.9±7.2	4.6±3.2	Electro-Acu	VA vs SA	RCT	1) Psychological condition 2) KOOS	BOLD-fMRI/resting	Brain network ReHo	Some concerns
2. Chen et al (2014)[19]	KOA 30 (17)	58±8	11±8	Manual Acu	Low dose VA vs High dose VA vs SA	RCT	1) KOOS 2) MASS	BOLD-fMRI/resting	FC Corticla thickness	Some concerns
3. Chen et al (2015)[25]	KOA 30 (17)	58±8	11±8	Manual Acu	Low dose VA vs High dose VA vs SA	RCT	1) KOOS 2) MASS	BOLD-fMRI/resting	ICA FC	Some concerns
4. Egorova et al (2015)[16]	KOA 30 (17)	57.5±8.3	11±8	Manual Acu	Low dose VA vs High dose VA vs SA	RCT	KOOS	BOLD-fMRI/resting	FC	Some concerns
5. Gollub et al (2018)[20]	KOA 43 (19)	58.7±7.4	N/A	Electro-Acu	VA vs SA	RCT	Expectancy rating	BOLD-fMRI/resting state	ReHo	Some concerns
6. Kong et al (2018)[21]	KOA 46 (19)	60.9±7.2	N/A	Manual Acu	Boosted Acu vs Standard Acu vs Usual treatment	RCT	1) KOOS 2) Expectancy rating	BOLD-fMRI/resting state	FC	Some concerns
7. Qu et al (2021)[22]	KOA 80 (28) HC 80 (30)	52.7±4.6	N/A	Manual Acu	KOA vs HC	Non-RCT	1) BPI 2) Lysholm	BOLD-fMRI/resting state	ALFF	Moderate
8. Gao et al (2021)[17]	KOA 15 (7) HC 15 (4)	59.1±10.3	≥0.33	Manual Acu	KOA vs HC	Non-RCT	VAS (pain)	BOLD-fMRI/resting state	FC	Moderate
9. Wang et al (2023)[23]	KOA 74	45–65	≥0.5	Manual Acu	VA vs SA vs Waiting-list	RCT	1) 11-point NRS 2) WOMAC 3) SF-MPQ 4) Psychological measures	BOLD-fMRI/resting state	Cortical thickness / subcortical volume; fALFF; Brain network; Machine learning	Low
10. Zhou et al (2023)[24]	KOA 149 (35) HC 36 (13)	51.4	2.4	Manual Acu	VA vs SA vs Celecoxib vs Placebo vs Waiting-list vs HC	RCT	1) VAS (pain) 2) SF-MPQ 3) WOMAC 4) SF-12	BOLD-fMRI/resting state	FC	Low
11. Xie et al (2013)[18]	KOA 30	45–65	N/A	Mox	N/A	Non-RCT	N/A	BOLD-fMRI/resting state	fALFF; ReHo	Moderate
12. Zheng et al (2015)[27]	KOA 42 (24)	56.7±6.5	N/A	Mox	N/A	Non-RCT	N/A	BOLD-fMRI/pre-post moxibustion	fALFF; FC	Moderate
13. Huang et al (2019)[28]	KOA 30	40–65	4.5±0.9	Mox	N/A	Non-RCT	1) KOOS 2) WOMAC	EEG/task	Power spectral density	Moderate

Notes: The low dose and high dose referred to the difference in the number of acupoints in the acupuncture prescription, and the high dose group had four more acupoints than the low dose group with only two acupoints. The RoB 2 and ROBINS-I were used for assessment the risk of bias of randomized controlled trials and non-randomized controlled trials included in this review, respectively.

Abbreviations: KOA, knee osteoarthritis; HC, healthy control; Acu, acupuncture; Mox, moxibustion; VA, verum acupuncture; SA, sham acupuncture; RCT, randomized controlled trial; KOOS, Knee Injury and Osteoarthritis Outcome Score; BPI; VAS, Visual Analog Scale; 11-point NRS, the 11-point Numerical Rating Scale; WOMAC, the Western Ontario and McMaster Universities Arthritis Index; MPQ/SF-MPQ, McGill Pain Questionnaire/Short-Form McGill Pain Questionnaire; SF-12, 12-Item Short Form Survey; FC, functional connectivity; ReHo, regional homogeneity; ALFF/fALFF, amplitude of low-frequency fluctuations/fractional amplitude of low-frequency fluctuations.

Neuroimaging Scan and Data Analysis

Twelve studies (Studies 1–12) applied BOLD-fMRI with resting scans to investigate brain responses, followed by functional segregation analysis (regional homogeneity, ReHo; amplitude of low-frequency fluctuations/fractional amplitude of low-frequency fluctuations, ALFF/fALFF), functional integration analysis (functional connectivity, FC; independent component analysis, ICA; brain network), and structural analysis (cortical thickness; sub-cortical volume). Study 13 utilized EEG with a task condition to analyze the power spectral density of the central region in KOA patients.

Cerebral responses of acupuncture-related therapy for KOA are shown in Table 2. Frequently reported brain regions included the prefrontal cortex (PFC, including the medial, lateral, dorsolateral, and orbital PFC), cingulate gyrus (anterior cingulate cortex, ACC; rostral ACC, rACC;), temporal gyrus, periaqueductal grey (PAG), insula, thalamus, hippocampus, parahippocampal gyrus, and nucleus accumbens (NAc) (Figure 2).

Results of Risk-of-Bias Assessments

The risk-of-bias assessment in clinical neuroimaging research is not well established. In this review, based on previous acupuncture neuroimaging reviews,[32] the risk-of-bias was assessed using the RoB 2 and ROBINS-I for RCTs and non-RCTS, respectively, as shown in Table 1. Among the eight RCTs, two studies were rated as having a "low" overall risk of bias (Studies 9 and 10). The remaining six were rated as having a "some concerns" due to acupuncturists always being aware of group assignments; it is concerning that there was no reporting on whether outcome evaluators were blinded to the group assignment (Study 1–6). The five included non-RTCs were rated as having a "moderate" overall risk of bias, also because it was not clear whether outcome evaluators were aware of participants' interventions (Study 7–8 and 11–13).

Discussion

Over the past decade, there has been increased attention given to explore the cerebral mechanism of acupuncture for KOA by neuroimaging techniques. To date, 13 articles measuring brain activities have been considered, providing visualized evidence for a deeper understanding of the central mechanism of acupuncture in treating KOA.

Neuroimaging Techniques and Analysis Methods Applied in Acupuncture-Related Therapy for KOA

Since the 1990s, neuroimaging techniques, particularly fMRI (12 out of the 13 included studies), have been widely applied to explore the central mechanisms of acupuncture-related therapy. fMRI offers advantages such as good spatiotemporal resolution,[29] timely and visualized imaging, non-invasion,[30] and lack of radiation[31] to investigate cerebral response. Within the review, ReHo, ALFF/fALFF, and FC were the most frequently used to analyze the fMRI data. ReHo reflects the consistency of functional activities of adjacent brain regions,[33] with a higher ReHo value indicating a consistent local functional activity in a brain region and a lower value implying local abnormal neural activities. Due to its good repeatability, one quarter of the included fMRI studies used ReHo to explore the central mechanism of acupuncture for KOA. In this review, one-third of the included fMRI studies used ALFF/fALFF as an indicator of neuronal activity, reflecting the spontaneous neuronal activity through the magnitude of spontaneous BOLD signal. Meanwhile, fALFF is an improvement on ALFF to avoid interference from physiological signals.[34] The abnormality of ALFF/fALFF is thought to be a candidate biomarker for the prognosis of various pain conditions.[35] More than half of the included fMRI studies in this review selected FC as an indicator of the brain network, measuring neuronal activities based on the specific region of interest of the brain, representing neural communication among brain regions.[36] These analytical methods are sensitive and reliable to be used in investigating the cerebral mechanism of acupuncture-related therapy.

Cerebral Response to Acupuncture for KOA Patients

Based on the neuroimaging results, acupuncture treatment induced brain regulation mainly in several brain regions, including PFC, ACC, insula, thalamus, nucleus NAc, hippocampus, and parahippocampal gyrus, with an increased FC in PFC-rACC/PAG. A more extensive and notable brain response was exhibited in verum acupuncture compared to sham acupuncture, including PFC, PAG, ACC, thalamus, insula, etc., with an enhanced FC in PFC-ACC/insula/PAG.

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Table 2 Brain Imaging Data of Acupuncture-Related Therapy Neuroimaging Studies in KOA

No. Study (Year)	Intervention	Control	Acupoints	Treatment Course	Needle Sensation	Brain Imaging Data
1. Hashmi et al (2014)[26]	VA	SA	LI3, LI4	25min, 1 session (1t)	*deqi* avoided	**Post-acu (vs SA)**: The FC enhanced between the ventral medial prefrontal cortex and dorsolateral prefrontal cortex, middle frontal gyrus, anterior cingulate, thalamus, hippocampus, parahippocampal gyrus, and middle temporal gyrus
2. Chen et a (2014)[19]	VA: Low dose, High dose	SA	Low dose: ST35, EX-LE5 High dose: ST35, EX-LE5, GB34, SP9, GB39, SP6 SA: six sham acupoints	25min, 6sessions (2t/w*2w+1t/w*2w)	*deqi*	**Post-acu (vs SA)**: 1) The FC increased between the left posterior medial prefrontal cortex and rostral anterior cingulate cortex, medial frontal pole and periaqueductal grey **SA (vs post-acu)**: The cortical thickness decreased in the left posterior medial prefrontal cortex
3. Chen et al (2015)[25]	VA: Low dose, High dose	SA	Low dose: ST35, EX-LE5 High dose: ST35, EX-LE5, GB34, SP9, GB39, SP6 SA: six sham acupoints	25min, 6 sessions (2t/w*2w+1t/w*2w)	*deqi*	**Post-acu (vs SA)**: 1) The FC increased between the right frontoparietal network and rostral anterior cingulate cortex, and medial prefrontal cortex 2) the FC increased between the executive control network and rostral anterior cingulate cortex, medial prefrontal cortex, and left insula
4. Egorova et al (2015)[16]	VA: Low dose, High dose	SA	Low dose: ST35, EX-LE5 High dose: ST35, EX-LE5, GB34, SP9, GB39, SP6 SA: six sham acupoints	25min, 6 sessions (2t/w*2w+1t/w*2w)	*deqi*	**Post-acu (vs SA)**: 1) The FC increased between the periaqueductal gray and medial frontal cortex 2) The FC decreased between the periaqueductal gray and hippocampus
5. Gollub et al (2018)[20]	VA	SA	LI3, LI4	25min, 1 session (1t)	*deqi*	**Post-acu (vs SA)**: 1) The ReHo values increased in the left postcentral and precentral gyrus 2) The ReHo values decreased in the bilateral dorsal anterior cingulate cortex, bilateral medial prefrontal cortex, right secondary somatosensory cortex, supramarginal gyrus, right superior temporal gyrus, right inferior parietal lobule, and left insula, and left operculum
6. Kong et al (2018)[21]	VA (with expectancy)	VA (standard), Usual treatment	ST35, EX-LE5, GB34, SP9, GB39, SP6	30min, 10 sessions (2t/w*2w+1t/w*6w)	*deqi*	**Post-acu (vs standard/usual treatment)**: The FC increases between the nucleus accumbens and medial prefrontal cortex, rostral anterior cingulate cortex, and dorsolateral prefrontal cortex
7. Qu et al (2021)[22]	VA	N/A	EX-LE5	30min, 30 sessions (1t/d*30d)	*deqi*	**Pre-acu (vs HC)**: 1) The ALFF values increased in the bilateral frontal gyrus, right inferior frontal gyrus, fusiform gyrus and insular lobe, left anterior cuneiform lobe, superior marginal gyrus, middle temporal gyrus and inferior temporal gyrus 2) The ALFF values decreased in right superior frontal gyrus, left middle occipital gyrus/superior occipital gyrus, hippocampus, thalamus, and amygdala **Post-acu (vs Pre-acu)**: 1) The ALFF values increased in the central anterior gyrus and the cingulate gyrus, the right temporal gyrus and the occipital gyrus 2) The ALFF values decreased in the prefrontal cortex

8. Gao et al (2021)[17]	VA	N/A	EX-LE5	6min 50s, 1 session (1t)	*deqi*	**Post- acu (vs HC)**: 1) The FC of periaqueductal gray decreased in the right lingual gyrus 2) The FC of dorsal raphe nuclei increased in right putamen 3) The FC of medial raphe nuclei decreased in the right cerebellum
9. Wang et al (2023)[23]	VA	SA, Waiting-list	ST35, EX-LE4, LR8, GB33, SP6, SP10, KI3, Ashi point	30min, 12 sessions (3t/w*4w)	*deqi*	**Post-acu (vs SA/waiting-list)**: 1) Structural metrics remained stable 2) The fALFF values increased in posterior cingulate cortex and precuneus
10. Zhou et al (2023)[24]	VA	SA, Celecoxib, Placebo, Waiting-list	ST35, EX-LE4, GB34, SP4	30min, 10 sessions (5t/w*2w)	*deqi*	**Post-acu (vs celecoxib/placebo)**: The FC increased between the ventrolateral periaqueductal gray and right dorsolateral prefrontal cortex and angular **Post-acu (vs waiting-list)**: The FC increased between the ventrolateral periaqueductal gray and right dorsolateral prefrontal cortex and precuneus
11. Xie et al (2013)[18]	Mox	N/A	ST35	30min, 1 session (1t)	Mox sensation	**Post-mox (vs pre-mox)**: 1) The fALFF values increased in the right cerebrum, extra-nucleus, left cerebellum, left cerebrum and white matter 2) The fALFF values decreased in the precentral gyrus, frontal lobe and occipital lobe 3) The ReHo values increased in the thalamus, extra-nucleus and parietal lobe 4) The ReHo values decreased in the right cerebrum, left cerebrum and frontal lobe
12. Zheng et al (2015)[27]	Mox	N/A	ST35	1 session (1t)	Mox sensation	**Post-mox (vs pre-mox)**: 1) the fALFF values increased in parietal precuneus, posterior cingulate cortex, anterior cerebellum, central hemisphere, and white matter 2) The fALFF values decreased in superior temporal gyrus and occipital cuneiform 3) The FC enhanced between the bilateral ventral-posterolateral nuclei and hippocampus, posterior lobe, and midbrain 4) The FC decreased between the bilateral ventral-posterolateral nuclei and prefrontal and posterior occipital lobes
13. Huang et al (2019)[28]	Mox	N/A	ST35	20min, 2 sessions (2t/w)	Mox sensation	**Post-mox (vs pre-mox)**: The average power densities increased in the bilateral frontal regions, parietal region and occipital region

Abbreviations: VA, verum acupuncture; SA, sham acupuncture; t/w, time/week; t/d, time/day; Mox, moxibustion; FC, functional connectivity.

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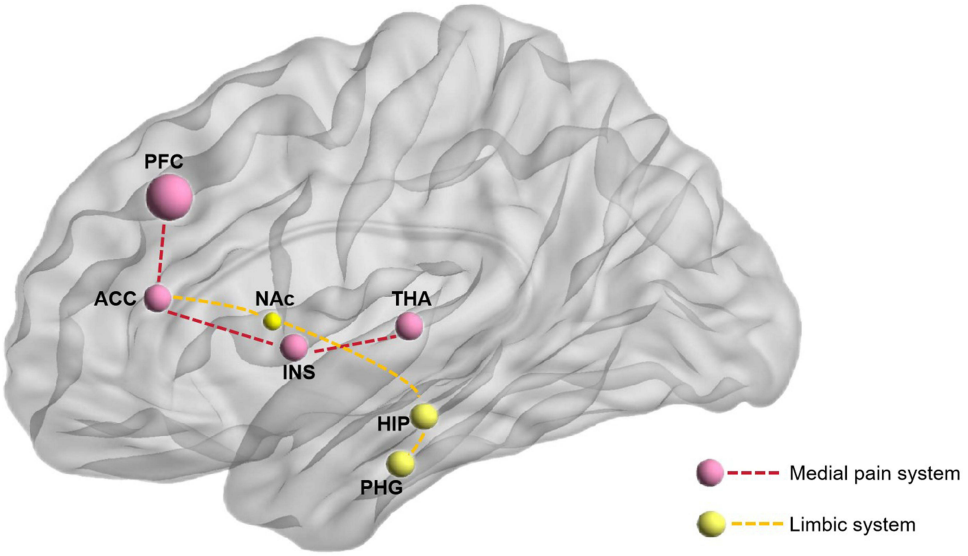

Figure 2 The main brain regions of acupuncture for KOA based on neuroimaging studies.
Note: The high frequency regulated brain regions by acupuncture had been colored with different notes and edges.
Abbreviations: PFC, prefrontal cortex; ACC, anterior cingulate gyrus; INS, insula; THA, thalamus; NAc, nucleus accumbens; HIP, hippocampus; PHG, parahippocampal gyrus.

KOA patients with chronic pain experience abnormal brain functional activity in somatosensory, affective, and cognitive, involving multiple brain regions and networks associated with the pain processing systems.[37–39] Öztürk et al found that KOA patients with chronic pain exhibited abnormal functional activity of the dorsolateral PFC (dlPFC).[40] Liu et al demonstrated that KOA patients showed dysregulated FC between the hippocampus and thalamus/superior frontal gyrus.[41] Furthermore, Barroso et al revealed that KOA pain was linked to disruption of whole-brain and local FC, with major nodal connectivity changes identified in the primary somatosensory cortex/primary motor cortex, parahippocampal gyrus, and insula.[36] In this review, studies showed that acupuncture activated lateral and orbital PFC and insula/putamen and regulate FC among PFC, ACC, thalamus, insula, PGA, etc. These brain regions, including the thalamus, ACC, and PFC, are thought to participate in processing motivation-affective, cognitive-evaluative, and memory aspects of pain,[42–45] which are associated with the medial pain system. The medial pain system originates from pain-specific neurons in the superficial dorsal horn of the spinal cord, projects via thalamus to ACC and insula, and transmits the cognitive-emotional component of pain to the PFC.[42] The thalamus is a relay station for transmitting pain information to the PFC, which is the key to pain awareness.[46] Previous research demonstrated that KOA with chronic pain caused altered FC of the thalamus to several brain regions, which also correlated with negative affect in these brain regions.[39] ACC is crucial for responding to pain-related anxiety and fear,[47–49] and KOA pain is connected to the abnormal FC of ACC to other brain areas.[50] While the PFC receives ascending, nociceptive input, it also exerts a substantial top-down control role in pain sensation, which relies on its connections to hippocampus, PAG, thalamus, amygdala, etc.[51–53] Although the altered functional activity of these brain regions was represented in KOA, the abnormality could be reversed once pain is controlled by acupuncture. Thus, the findings suggested that the medial pain system is involved in the central response to acupuncture for KOA pain relief in regulating cognitive, memory, and emotion.

According to the included neuroimaging studies, acupuncture was found to regulate abnormal functional activity in the cortical structure (the cingulate gyrus) and subcortical structures (hippocampus, parahippocampal gyrus, and NAc) of patients with KOA. This regulation was associated with the limbic system, which plays a role in the affective aspects of pain, regulating emotional and motivational responses.[54,55] Acupuncture with expectancy was found to alleviate KOA pain better than regular acupuncture, and this central mechanism was correlated with an increased FC between NAc and the medial PFC/rACC/dlPFC.[23] Since NAc and ACC are involved in emotion, motivation and reward-related behaviors,[56,57] functional changes in these regions can lead to emotional and cognitive problems in patients with KOA pain. Acupuncture could improve KOA pain by regulating these brain areas in the limbic system. Notably, these brain regions were functionally interconnected and participated in pain processing together. Acupuncture not only enhanced FC among hippocampus, parahippocampal

gyrus, PFC and ACC[21] but also increased FC between hippocampus and PAG.[16] The hippocampus is involved in forming emotional memory of pain through the Papez circuit and transmitting information to the limbic system.[58,59] Meanwhile, the parahippocampal gyrus is understood to play a role in pain sensitivity.[60] The pain sensitivity is correlated with the altered function of parahippocampal gyrus in KOA patients.[37] Studies showed that acupuncture could regulate altered functional activity of these brain regions. Acupuncture reduces the intensity of KOA pain may be correlated to regulating these regions in the limbic system to improve negative emotions. Therefore, the effect of acupuncture in treating KOA may be partly attributed to the regulation of the medial pain and limbic systems, which presents potential targets for pain modulation in KOA.

Intriguingly, it is known that psychological factors influence chronic pain to some extent.[61] Some studies have suggested that baseline psychological conditions, such as expectancy, partly determined KOA pain responses to acupuncture.[62] Hashmi et al found that the psychologically conditioned analgesia was invariant to sham versus real treatment.[26] It plays a direct role in modulating pain, independent of any direct analgesic effect of acupuncture, suggesting acupuncture may or may not be more effective than a placebo intervention in treating KOA. Although the placebo of psychological factors showed an effect on relieving pain, some studies found that psychological condition controls KOA pain through different pathways based on different treatment modalities. For instance, Gollub et al reported that expectancy similarly modulated KOA pain in both verum and sham acupuncture, while they showed different regulation patterns in brain response.[20] Therefore, these studies provide new insights into combining positive psychological factors with treatment modalities to enhance clinical efficacy.

Cerebral Response to Moxibustion for KOA Patients

Moxibustion, an important component of acupuncture therapy, is also commonly used for KOA. Similar to acupuncture, moxibustion regulated brain functional activity of KOA patients in frontal lobe, thalamus, hippocampus, cingulate cortex, and occipital lobe. It is inferred that acupuncture and moxibustion had some similarities in activating brain regions through exogenous stimulation on acupoints and meridians.[63–65] However, moxibustion differs from acupuncture in that it also showed a more extensive response in the cerebrum, midbrain, cerebellum, central hemisphere, white matter, etc. Specifically, moxibustion was found to increase the fALFF values in the cerebrum, left cerebellum, central hemisphere, extra-nucleus, and white matter, and decrease the fALFF values in precentral gyrus, frontal lobe, and occipital lobe. Additionally, moxibustion could increase the ReHo values in thalamus, extra-nucleus and parietal lobe while decrease it in the cerebrum and frontal lobe in KOA patients. The effect of moxibustion on KOA patients involves complex coordinated regulation among multiple brain regions. For example, Zheng et al reported that moxibustion for KOA increased the fALFF values in parietal precuneus, posterior cingulate cortex, anterior cerebellum, central hemisphere, and white matter while decreased the fALFF values in superior temporal gyrus and occipital cuneiform.[27] It is speculated that the central mechanism between acupuncture and moxibustion for KOA may differ to some extent. For acupuncture, it involves the process of stimulating specific acupoint by inserting metal needles and manipulates the needle, so its effect is produced by the physical stimulation that penetrates the skin.[66] While moxibustion is used to treat diseases by burning moxa, it possesses features of heat, light, moxa smoke, and drug properties.[67] The thermal product of moxibustion is an essential factor in achieving clinical effects. Moxibustion's unique thermal effect can activate local specific receptors and transmit the signal to the thermal cortical center, thereby eliciting a broad response in cerebral areas.[68] Despite moxibustion could elicit a wide cerebral response, the central mechanism of moxibustion for KOA is not yet clear. Therefore, further research is necessary to elucidate the cerebral mechanism of moxibustion in the future.

Future Perspectives

First, acupuncture-related therapy is known to have both immediate[69] and cumulative effects.[70] Some studies have explored the cerebral response caused by the immediate effect of acupuncture, and others have focused on the response elicited by its cumulative effect. However, few studies have investigated the differences in changes of cerebral response in KOA patients with different doses of acupuncture-related stimulation. It remains unclear how many intervention sessions could produce the maximum improvement in KOA symptoms and to what extent brain functional activity/structure changed. Hence, future studies could investigate the correlation between the amount of acupuncture-related stimulation and changes in cerebral activity or structure in KOA patients. Second, there may exist differences in efficacy among acupuncture, moxibustion, and other therapies, as well as their underlying mechanisms. Therefore, in the future,

the effects of different therapies on the cerebral response could be compared to identify specific therapeutic targets of acupuncture-related therapy. Third, previous studies have reported mild degeneration of white matter in patients with KOA.[18,27] However, few studies of acupuncture or moxibustion for KOA have focused on brain structure. This may be related to the short treatment course of clinical effect-acting, which is insufficient to observe significant changes in brain structure. Future research could use relatively long-term courses to investigate whether and how A&M regulates brain structure in KOA patients. Finally, it has been found that individuals' brain functional activities are continuously changing, even in the resting state.[71] Meanwhile, current studies primarily explore KOA patients' cerebral responses in a resting state after acupuncture-related stimulation. Future research could consider a task-state study design to investigate the regulation of dynamic functional brain activities by acupuncture-related therapy in KOA patients.

Conclusion

Acupuncture is effective in treating KOA, while its underlying cerebral mechanism remains unclear. This review synthesized the study design and main neuroimaging research findings on acupuncture-related therapy for KOA. The results suggested that acupuncture could regulate pain-related cerebral regions in KOA patients associated with the medial pain and limbic systems, while moxibustion could regulate a wide range of brain regions. Future neuroimaging research is needed to reveal the central mechanisms of acupuncture for KOA.

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Disclosure

The authors report no conflicts of interest in this work.

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