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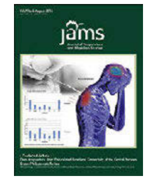

REVIEW ARTICLE

Does Acupuncture Alter Pain-related Functional Connectivity of the Central Nervous System? A Systematic Review

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Abstract
Acupuncture has been studied for several decades to establish evidence-based clinical practice. This systematic review aims to evaluate evidence for the effectiveness of acupuncture in influencing the functional connectivity of the central nervous system in patients with musculoskeletal pain. A systematic search of the literature was conducted to identify studies in which the central response of acupuncture in patients with musculoskeletal pain was evaluated by neuroimaging techniques. Databases searched were AMED, CINAHL, Cochrane Library, EMBASE, MEDLINE, PEDro, Pubmed, SCOPUS, SPORTDiscuss, and Web of Science. Included studies were assessed by two independent reviewers for their methodological quality by using the Downs and Black questionnaire and for their levels of completeness and transparency in reporting acupuncture interventions by using Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) criteria. Seven studies met the inclusion criteria. Three studies were randomized controlled trials (RCTs) and four studies were nonrandomized controlled trials (NRCTs). The neuroimaging techniques used were functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Positive effects on the functional connectivity of the central nervous system more consistently occurred during long-term acupuncture treatment. The

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results were heterogeneous from a descriptive perspective; however, the key findings support acupuncture's ability to alter pain-related functional connectivity in the central nervous system in patients with musculoskeletal pain.

1. Introduction

Acupuncture is an ancient healing modality used for a range of diseases, including pain disorders [1]. Current evidence demonstrates that acupuncture effects are predominately attributable to its physiological mechanisms rather than to a placebo effect [2,3]. Peripheral, central, and neurohormonal responses are different physiological mechanisms that are triggered in the human body by stimulating muscle afferent fibers during needle manipulation [4].

Since the mid-1990s, the interest in investigating the central response of acupuncture with neuroimaging techniques has been growing [5]. Functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), electroencephalography, and magnetoencephalography provide a means to monitor the effects of acupuncture on the functional connectivity of the human brain [6].

Functional connectivity is fundamental for understanding the nature of brain function [7]. Neuroimaging has immensely increased the knowledge of pain processing in the central nervous system (CNS) [8,9]. The current evidence indicates that several cortical and subcortical areas constitute the pain matrix: primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insular cortex (IC), anterior cingulate cortex (ACC), amygdala, prefrontal cortex (PFC), and thalamus [10]. However, there is a difference between the brain areas activated during acute pain and during chronic pain [11]. The intensity of pain in chronic pain states such as chronic back pain, fibromyalgia, osteoarthritis, and chronic regional pain syndrome are highly correlated with abnormal plasticity (i.e., functional changes or alterations in the connectivity of brain areas) [12,13].

Neuroimaging acupuncture studies have detected brain activation in the IC, thalamus, ACC, S1, S2, inferior frontal cortex, superior temporal cortex, superior temporal gyrus, and cerebellum; and have detected brain deactivation in the medial prefrontal cortex, subgenual ACC, caudate, amygdala, posterior cingulate cortex, thalamus, parahippocampus, and cerebellum [14]. However, most studies were performed on healthy individuals [6,14—16]. Whether these findings can be extrapolated to patients with pain remains unclear [17]. However, such findings serve as background knowledge and provide a rationale for studies involving patients.

Investigating acupuncture central response will help to underpin the clinical efficacy of acupuncture analgesia, which can be related to an alteration in the functional connectivity of the CNS and restoration of normal plasticity, followed by the reduction of pain. Therefore, the aim of this systematic review was to evaluate the evidence for the effectiveness of acupuncture on influencing the functional connectivity of the CNS in patients with musculoskeletal pain.

2. Methods

2.1. Protocol and registration

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. The protocol was not preregistered.

2.2. Selection criteria

2.2.1. Types of studies

Randomized controlled trials (RCTs) and nonrandomized studies (i.e., observational studies, lab-based experimental studies, case-control studies, cohort studies) published in peer-reviewed journals were included in this review. Non-English language publications were excluded because of the anticipated time constraints of this review.

2.2.2. Types of study participants

Individuals with acute or chronic musculoskeletal pain syndromes were included. There were no restrictions based on sex.

2.2.3. Types of intervention

Studies using acupuncture or electroacupuncture were included. There were no restrictions based on the selection or number of acupuncture points used. Studies using other types of acupuncture such as ear acupuncture, moxibustion, acupressure, laser acupuncture, and dry needling were excluded.

2.2.4. Types of comparators

Studies using sham acupuncture or no intervention as a comparator were included in this review.

2.2.5. Types of outcome measures

Studies that assessed functional connectivity using one of the following brain imaging techniques were included: fMRI, PET, SPECT, electroencephalography, and magnetoencephalography. Brain activity markers (e.g., voxels) were quantified according to the brain imaging technique used in the studies included.

2.2.6. Assessment time frame

No restriction was applied to the assessment time frame.

2.3. Search strategy

A comprehensive literature search from the database' inception was performed on March 17, 2015 in the following databases: MEDLINE (1946 to March 17, 2015), AMED (1985 to March 17, 2015), EMBASE (1947 to March 17, 2015), Pubmed (1950 to March 17, 2015), CINAHL (1981 to March 17, 2015), Cochrane Library, Web of Science (1900 to March 17, 2015), SCOPUS (1960 to March 17, 2015), and SPORTDiscus (1960 to March 17, 2015). The same search strategy was used in subject-based databases, as shown in Appendix 1. Search terms in Appendix 2 were combined using Boolean logic as an advanced search in keyword databases. Search strategies were established in consultation with a university librarian to cover all potentially relevant studies. In addition, Google Scholar, Physiotherapy Evidence Database (PEDro; 1966 to March 17, 2015), five relevant journals (*Journal of Alternative and Complementary Medicine*, *Acupuncture in Medicine*, *Complementary Therapies in Medicine*, *Journal of Acupuncture and Meridian Studies*, and *Evidence-Based Complementary and Alternative Medicine*), and reference lists of previous systematic reviews were manually searched to retrieve relevant studies.

2.4. Selection of studies

All studies obtained by the systematic search were exported and saved into reference management software (EndNote X7; Thomson Reuters, New York, NY, USA). Duplicates were removed. Two independent reviewers, who were blinded to each other, assessed the eligibility of all studies by first screening the titles, followed by screening the abstracts, and finally screening the full-texts with the aforementioned selection criteria. Any disagreements regarding study inclusion between the two reviewers were resolved through discussion. A third reviewer was consulted for a consensus if further disagreements persisted. Agreement between the two reviewers on the final selection of studies was assessed by Cohen's *kappa* statistics.

2.5. Data extraction

One reviewer extracted the data from the included studies and the second reviewer checked the extracted data to ensure accuracy. Any disagreements were resolved through discussion. The authors of the studies were not contacted to provide missing data.

The following data were extracted from each included study: (1) study design; (2) study participants' demographics (e.g., number, sex, age, groups, and diagnosis); (3) details of interventions (based on STRICTA guidelines [19]); (4) brain imaging technique and assessment time frame; and (5) results (e.g., brain area, and brain activity markers).

The data were also categorized into long-term and short-term intervention periods, as follows: (1) brain imaging technique; (2) diagnosis; (3) activated/deactivated brain areas; and (4) reported reduction in pain.

For the purpose of this systematic review, long-term intervention involved multiple sessions of acupuncture and short-term intervention involved one session of acupuncture.

2.6. Assessment of methodological quality

All included studies were assessed for methodological quality using a modified Downs and Black quality index, which was originally developed to assess the methodological quality of RCTs and NRCTs [20]. Similar to the method used in other studies [21,22] a modified version of the original index was used. Items #8 and #27 were omitted; the results were finalized with 25 of 27 items for the RCTs and 21 of 27 for NRCTs. For the purpose of this review, a study was considered of high quality if it scored $>$ 75% of the total criteria; moderate quality if it scored 50–74%; and low quality if it scored $<$ 50% [21–23]. All studies were also assessed for their level of completeness and transparency in reporting acupuncture interventions, based on the STRICTA checklist [19]. Two reviewers independently performed the assessments in a standardized manner; they were unblinded to details of the studies. Any disagreements between the reviewers were resolved by consensus and a third reviewer was consulted if disagreements persisted.

3. Results

3.1. Study selection

The process of study selection using the PRISMA flow diagram is depicted in Fig. 1. The search was conducted on March 17, 2015 and retrieved 1,957 potential relevant records. After removing duplicates, 1,558 records remained. Of these, 1,542 records were excluded after screening the titles and abstracts. The full-text articles of the remaining 16 studies were assessed for eligibility. After a discussion on items of disagreement, a consensus was reached. Seven studies met the inclusion criteria and were included in this systematic review. A good agreement (*kappa* = 0.613) was observed on the final selection of the studies [24].

3.2. Study characteristics

Table 1 summarizes the characteristics of all seven included studies. Three studies were RCTs [25–27] and four studies were NRCTs [28–31]. All studies were published in English in peer-reviewed journals. The years of publication, ranged from 2005 to 2014.

3.2.1. Study population

One hundred and ninety-one individuals were involved in the seven studies. Of these, 163 individuals were patients with an age range of 31–60 years. The clinical conditions were osteoarthritis [25,31], chronic low back pain [28], carpal tunnel syndrome [26,29,30], and fibromyalgia [27]. The minimum pain duration was 3 months in five studies [25,26,28–30], 1 year in one study [27], and not reported in one study [31].

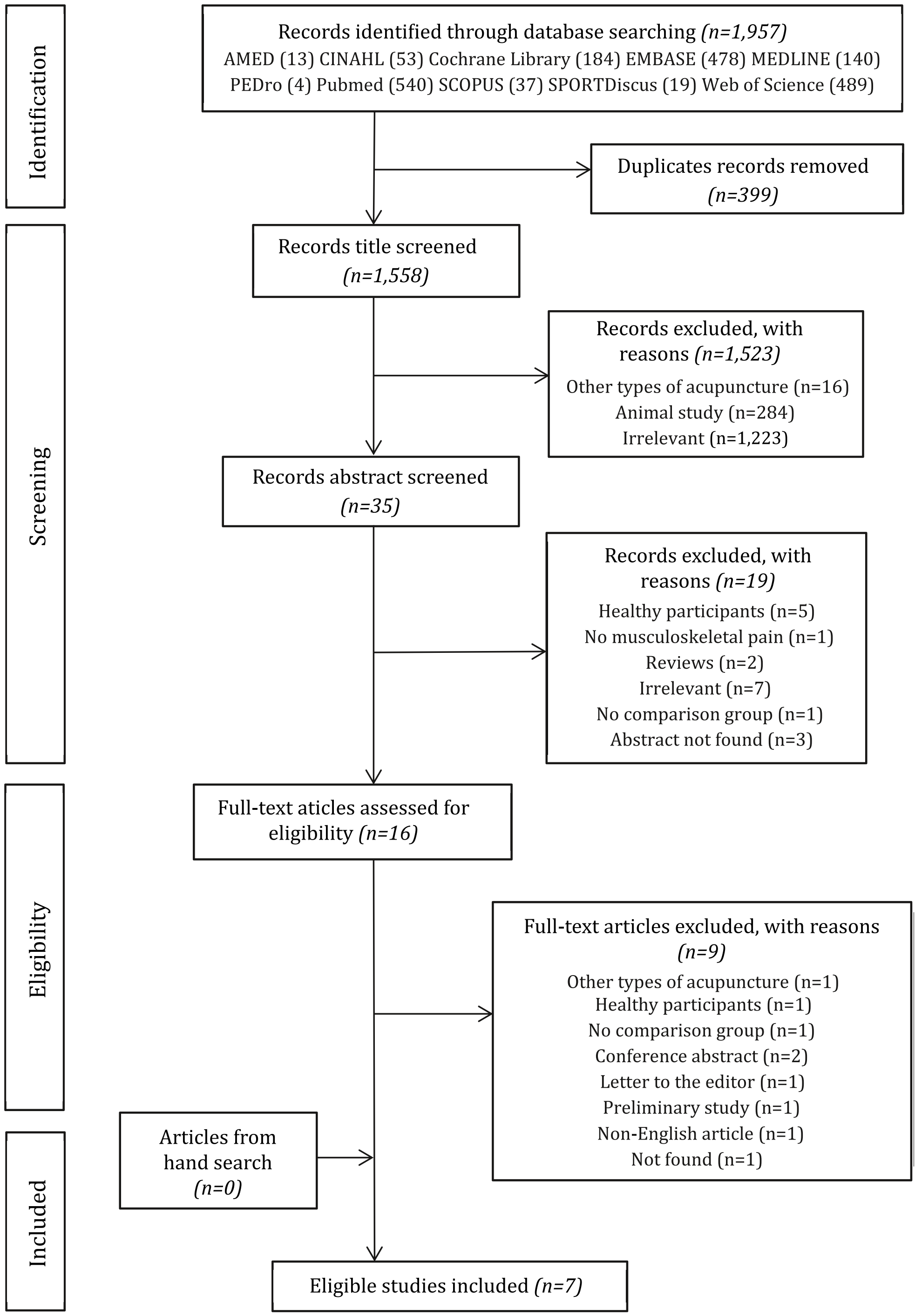

Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

3.2.2. Interventions

There were variations in interventions between the studies. Four studies used acupuncture [25,27,28,31], one study used electroacupuncture [26], and two studies combined acupuncture and electroacupuncture [29,30]. The intervention period ranged from 4 weeks to 5 weeks in five studies [25,27–30], and patients were treated for 6–13 sessions. Two studies [26,31] reported a single intervention. There were also diversities in comparison interventions. These included sham acupuncture or electroacupuncture [25–27,31], and healthy individuals with no acupuncture [28–30].

3.2.3. Brain imaging technique and assessment time frame

Among the seven studies, five studies used fMRI [25,26,28–30] and two studies used PET [27,31] as the brain imaging technique for assessing functional connectivity. There were several variations on the assessment time frame used in each study. Two studies [26,31] did the

Table 1 Characteristics of the included studies.

Study & Year	Study design	Participants	Interventions	BIT & Assessment time frame	Results
Chen et al. [25], 2014	RCT	*N*: 30 (F 13) Age: 58 ± 8 Groups (*n*): Verum A (20); Sham A (10) Diagnosis: Knee osteoarthritis	EXP: KO Verum A CONT: KO Sham A Session: 6 IP: 1 month	fMRI Baseline (pre-acupuncture treatment 1) Follow-up at 25 days (pre- acupuncture treatment 6)	Fisher-Z connectivity values: PAG [$F(2,27) = 8.637$, $p = 0.001$], rACC [$F(2,27) = 8.885$, $p = 0.001$], ventral striatum [$F(2,27) = 3.931$, $p = 0.032$], anterior MPFC [$F(2,27) = 6.927$, $p = 0.004$]
Maeda et al. [26], 2013	RCT	*N*: 59 (F 49) Age: 49.1 ± 9.8 Groups (*n*): Verum EA (40); Sham EA (19) Diagnosis: Carpal tunnel syndrome	EXP: CTS Verum EA CONT: CTS Sham EA Session: 1 IP: NA	fMRI During treatment	Voxels: Activation [S2(R) 7869, S2(L) 7029, pSMA(R) 602, Th(R) 563]; Deactivation [OCG(L) 924, MPFC(R) 945, ITG(R) 2633, S1(R) 2233]
Harris et al. [27], 2009	RCT	*N*: 20 (F 20) Age: 44.3 ± 13.6 Groups (*n*): TCA (10); Sham A (10) Diagnosis: Fibromyalgia	EXP: FM TCA CONT: FM Sham A Session: 9 IP: 1 month	PET Baseline (pre-acupuncture treatment 1 and 9) Follow-up (post-acupuncture treatment 1 and 9)	Voxels: Long-term [dACC 185, Amyg 2417, CAU 23, dCC(R) 192, dCC(L) 225, DLPFC 351, PUT 158, tmpole 1037]; Short-term [Amyg 1556, CAU(R) 212, CAU(L) 140, NAC 1004, dCC 178, sgACC(R) 399, sgACC(L) 120, IC 540, dlTh 547]
Li et al. [28], 2014	Quasi-experimental	*N*: 20 CLBP (F 10, M 10) (age: 38.1 ± 6.4); 10 HP (F 5, M 5) (age: 37.7 ± 5.1) Groups (*n*): Patient (20); Control (10) Diagnosis: Chronic low back pain	EXP: CLBP A CONT: HP no A Session: 12 IP: 1 month	fMRI Baseline (CLBP pre-acupuncture treatment 1/HP) Follow-up at 4 weeks (CLBP post- acupuncture treatment 12/HP)	DMN connectivities of DLPFC, MPFC, ACC, and precuneus. Mean number of voxels with DMN properties: Control (2,047), Patient baseline (1,739), Patient after treatment (1,998)
Napadow et al. [29], 2007	Quasi-experimental	*N*: 10 CTS (F 6) (age: mean: 51.1, range: 31–60); 9 HP (F6) (age: mean: 46.9, range: 32–59) Groups (*n*): CTS (10); HP (9) Diagnosis: Carpal tunnel syndrome	EXP: CTS A/EA CONT: HP no A/EA Session: 13 IP: 5 weeks	fMRI Baseline (CTS pre-acupuncture treatment 1 with electrical stimulation D2/D3/D5; HP with ele ctr ical stimulation D2/D3/D5); Follow-up at 5 weeks (CTS post- acupuncture treatment 13 with electrical stimulation D2/D3/D5; HP with electrical stimulation D2/D3/D5)	Voxels: Deactivation (S1 127.45, PrCG 9.57, S2 72.61)

(*continued on next page*)

Table 1 (*continued*)

Study & Year	Study design	Participants	Interventions	BIT & Assessment time frame	Results
Napadow et al. [30], 2007	Quasi-experimental	*N*: 10 CTS (F 6) (age: mean: 51.1, range: 31–60); 9 HP (F6) (age: mean: 46.9, range: 32–59) Groups (*n*): CTS (10); HP (9) Diagnosis: Carpal tunnel syndrome	EXP: CTS A/EA CONT: HP no A/EA Session: 13 IP: 5 weeks	fMRI Baseline (CTS pre-acupuncture treatment 1 with verum/sham LI4; HP with verum/sham LI4) Follow-up at 5 weeks (CTS post- acupuncture treatment 13 with verum/sham LI4; HP with verum/sham LI4)	Z-score: Long-term [ACC -3.27, Amyg -3.79, LatHypothA 3.37, IC(R) -3.54, IC(l)-3.95, MPFC -3.37, S1 -4.37] Short-term (ACC -3.70, Amyg -4.33, CC -3.30, LatHypothA 2.88, S1 -4.08, Th -2.85, IC -3.16, M PFC -4.15, DLPFC-3.00)
Pariente et al. [31], 2005	Single-blind, randomized crossover	*N*: 14 (F 11, M 3) Age: 59.4 ± 5.7 Groups (*n*): RA (14); SN (14); OP (14) Diagnosis: 1st metacarpophalangeal osteoarthritis	EXP: 1stMO RA CONT: 1stMO SN/1stMO OP Session: 1 IP: NA	PET During treatment	Z-score: ACC (4.17)DLPFC (4.21)IC (3.86)midbrain (3.63)

1stMO = 1st metacarpophalangeal osteoarthritis; A = acupuncture; ACC = anterior cingulate cortex; Amyg = amygdala; BIT = brain imaging technique; CAU = caudate; CC = cingulate cortex; CLBP = chronic low back pain; CONT = control group; CTS = carpal tunnel syndrome; D2 = digit 2; D3 = digit 3; D5 = digit 5; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; EA = electroacupuncture; EXP = experimental group; F = female; FM = fibromyalgia; fMRI = functional magnetic resonance imaging; HP = healthy participants; ITG = inferior temporal gyrus; KO = knee osteoarthritis; L = left; LatHypothA = lateral hypothalamic area; M = male; MPFC = medial prefrontal cortex; NA = not applicable; OCG = occipital gyrus; OP = overt placebo; PAG = periaqueductal gray; PET = positron emission tomography; PrCG = precentral gyrus; pSMA = presupplementary motor area; PUT = putamen; R = right; RA = real acupuncture; rACC = rostral anterior cingulate cortex; RCT = randomized controlled trial; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SN = streitberger needles; TCA = traditional Chinese acupuncture; Th = thalamus; tmpole = temporal pole.

Table 2 Reported brain areas in patients after long-term acupuncture intervention.

Study	BIT	Diagnosis	*Areas* activated/*deactivated*	Reported reduction of pain
Chen et al [25]	fMRI	KO	ACC, MPFC, PAG, Ventral striatum	Yes
Li et al [28]	fMRI	CLBP	ACC, DLPFC, MPFC, Precuneus	Yes
Napadow et al [29]	fMRI	CTS	*PrCG, S1, S2*	Not reported
Napadow et al [30]	fMRI	CTS	*ACC, Amyg*, Hyp, *IC, MPFC, S1*	Not reported
Harris et al [27]	PET	FM	ACC, Amyg, CAU, CC, DLPFC, PUT, tmpole	Yes

The bold font indicates activation to acupuncture; italic font indicates deactivation to acupuncture.
ACC = anterior cingulate; Amyg = amygdala; CAU = caudate; CC = cingulate cortex; DLPFC = dorsolateral prefrontal cortex; Hyp = hypothalamus; IC = insular cortex, MPFC = medial prefrontal cortex; PAG = periaqueductal grey; PrCG = precentral gyrus; PUT = putamen; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; tmpole = temporal pole.

Table 3 Reported brain areas in patients after short-term acupuncture intervention.

Study	BIT	Diagnosis	*Areas* activated/*deactivated*	Reported reduction of pain
Maeda et al [26]	fMRI	CTS	IC, IFG, *ITG*, MFG, *OCG*, *PFC*, PMC, pSMA, *S1*, *S2*, SMG, STG, Th	Yes
Napadow et al [30]	fMRI	CTS	*ACC, Amyg, CC, DLPFC*, Hyp, *IC, MPFC, S1, Th*	Not reported
Pariente et al [31]	PET	1st MO	ACC, DLPFC, IC, midbrain	No
Harris et al [27]	PET	FM	ACC, Amyg, CAU, CC, IC, NAC, Th	No

The bold font indicates activation to acupuncture; italic font indicates deactivation to acupuncture.
ACC = anterior cingulate; Amyg = amygdala; CAU = caudate; CC = cingulate cortex; DLPFC = dorsolateral prefrontal cortex; Hyp = hypothalamus; IC = insular cortex; IFG-inferior frontal gyrus; ITG = inferior temporal gyrus; MFG = middle frontal gyrus; MPFC = medial prefrontal cortex; NAC = nucleus accumbens; OCG = occipital gyrus; PFC = prefrontal cortex; PMC = premotor cortex; pSMA = presupplementary motor area; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SMG = supramarginal gyrus; STG = superior temporal gyrus; Th = thalamus.

assessment during treatment and the other five studies [25,27–30] varied between assessing preacupuncture and postacupuncture treatment, which were all performed at different time frames and number of sessions.

3.2.4. Measures of brain activity

Four studies reported brain activity using voxels [26,29], two studies used *z*-scores [30,31], and one study used the Fisher *z* value [25]. Deactivation/activation variability between studies, lack of information on the neuroimaging data reports, and different ways of reporting the data were issues when comparing the outcomes.

3.3. Neuroimaging acupuncture effects in the CNS

To have a better understanding of the reported effects of acupuncture on the CNS, the included studies were grouped separately into studies reporting brain areas after a long-term intervention period (Table 2) and studies reporting brain areas after a short-term intervention period (Table 3). Furthermore, five of the seven studies assessed pain, and four studies reported a significant reduction in pain after the intervention period.

Tables 2 and 3 reveal some similarities and differences in brain areas that are reportedly activated or deactivated in the included studies. Figs. 2 and 3 show the similarities among the studies for the most commonly reported brain areas (i.e., ACC, amygdala, IC, S1, S2, thalamus, and PFC) in long-term and short-term acupuncture intervention, respectively. Among the seven studies, PFC was the most commonly reported brain area (85%), followed by the ACC (71%) and IC (57%), regardless of the length of acupuncture intervention.

3.4. Quality assessment of the included studies

Appendix 3 shows the methodological assessment of the included studies using a modified Downs and Black questionnaire [20]. Six studies had a high methodological quality

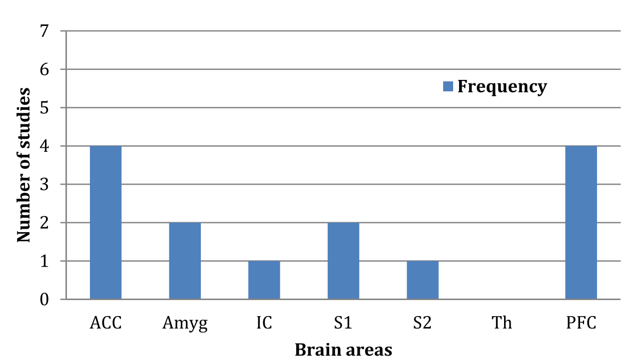

Figure 2 Most common reported brain areas in long-term acupuncture intervention. ACC = anterior cingulate cortex; Amyg = amygdala; IC = insular cortex; PFC = prefrontal cortex; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; Th = thalamus.

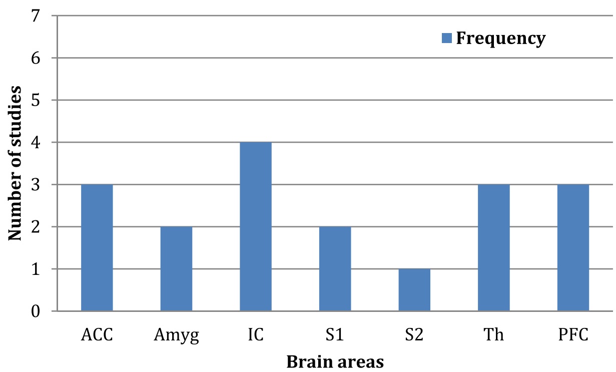

Figure 3 Most common reported brain areas in short-term acupuncture intervention. ACC = anterior cingulate cortex; Amyg = amygdala; IC = insular cortex; PFC = prefrontal cortex; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; Th = thalamus.

(i.e., the range was 76–95%) and one study had a moderate quality (72%). The most common flaws were lack of information regarding sample selection and recruitment.

3.4.1. Standards for reporting interventions in clinical trials of acupuncture

Appendix 4 shows the assessment for the level of completeness and transparency to report acupuncture interventions of the included studies, based on the STRICTA checklist [19]. All studies adequately addressed acupuncture rationale. The most common missing information included depth of needle insertion, needle retention time, and needle type.

4. Discussion

This is the first systematic review that summarized the potential influence of acupuncture on pain-related functional connectivity of the CNS in individuals with musculoskeletal pain. The current findings strengthen the evidence from previous systematic reviews indicating that acupuncture can modulate activity in multiple cortical and subcortical brain areas [5,15,16].

All studies included in this review showed important brain activation after acupuncture treatment. The most common reported areas among the studies were the ACC, amygdala, IC, S1, S2, Th, and PFC. These areas overlap the pain matrix [9,10]. Furthermore, several previous neuroimaging studies on the pain matrix have proven the existence of abnormal connectivity in cortical and subcortical brain regions in patients with chronic pain, even with different pain locations and etiology [13,32]. It should be emphasized that the patients of the seven studies included in this systematic review were in a chronic pain state.

Results of the five studies looking at the long-term response of acupuncture effects reported positive findings on reversing the abnormal plasticity [25,27–30], which means that functional changes or alterations in the connectivity occurred on the reported brain areas. Furthermore, in three of these studies, reductions in clinical pain were positively correlated with restoring normal plasticity [25,27,28].

Findings of the four studies that investigated the short-term response of acupuncture effects demonstrated brain activation of the pain matrix. However, the conclusion of a reversal of abnormal connectivity cannot be drawn from a short-term intervention period [26,27,30,31]. In addition, the reduction in clinical pain was positively correlated in just one of these studies [26]. It is worth mentioning that the two studies that investigated both responses of acupuncture effects demonstrated more relevant changes in long-term interventions than in short-term interventions [27,30].

Different conclusions can be drawn with regard to the comparators used in the included studies. Studies that used sham acupuncture in patients demonstrated that sham acupuncture did not restore abnormal connectivity and significant pain reduction did not occur [25–27,31]. On the contrary, studies that used sham acupuncture in healthy participants found that healthy individuals responded differently to sham acupuncture than patients [29,30]. A study conducted by Napadow et al [30] demonstrated that processing in the brain after verum acupuncture differs between patients and healthy individuals.

The overall methodological quality of the studies was high, according to the Downs and Black index; however, neuroimaging data were consistently poorly reported. Reporting these data are essential to draw more meaningful conclusions regarding activation or deactivation of certain brain areas. In nearly all studies, some information regarding STRICTA was missing such as needle retention time, depth of insertion, and needle type. This information is necessary for the standardization and reproducibility of acupuncture treatments. Shi et al [33] indicated in their review that issues such as needling sensation, acupuncture manipulation, and needle retention time have relevant influences on the therapeutic effects of acupuncture.

The studies included in this systematic review were highly heterogeneous with regard to their study design, their aims, and their quality of reporting from a descriptive perspective. Despite this fact, the key findings in the current review support the theory that acupuncture can alter pain-related functional connectivity of the CNS in patients with chronic pain. It is also important to highlight the positive correlation between functional connectivity changes and pain reduction reported by three studies.

4.1. Generalization of findings

The findings can be generalized as follows: (1) functional connectivity changes among patients with chronic pain have been reported; (2) restoration of normal functional connectivity is correlated with pain reduction; and (3) brain response to acupuncture between healthy individuals and patients differs.

4.2. Limitations

One of the most noticeable limitations of this review is the limited number of included studies. In addition, the study designs and the manner of reporting neuroimaging data were variable. We did not include non-English studies; therefore a language bias may be present.

4.3. Future directions

There are several challenges that acupuncture neuroimaging studies must overcome to provide an understanding of the central mechanism of acupuncture. First, more studies investigating the long-term effects of acupuncture on patients in chronic pain states need to be performed. Furthermore, standardization for reporting acupuncture interventions (STRICTA) [19] and neuroimaging data (e.g., Biomedical Informatics Research Network) [34] should be enhanced among researchers.

5. Conclusion

The findings of the seven studies included in this review support the theory that acupuncture can alter pain-related functional connectivity of the CNS. The main implications of this review for clinical practice are that acupuncture is proven to cause important changes in chronic pain states and that acupuncture efficacy in chronic pain patients is achieved by long-term intervention.

Disclosure statement

The author declares to have no conflicts of interest and no financial interests related to the material of this manuscript.

Acknowledgments

This systematic review was not supported by any funding source.

Appendices

Appendix 1. Search strategy

Concept 1	Concept 2	Concept 3
1. Acupunc*.mp.	8. Pain	13. Functional connectivity.mp.
2. Acupuncture	9. Musculoskeletal pain or musculoskeletal diseases	14. Neuroimaging
3. Acupuncture therapy or acupuncture points or acupuncture analgesia	10. Chronic pain	15. exp Functional neuroimaging
4. Electroacupuncture	11. Acute pain	16. Central nervous system or brain
5. Acupuncture needle.mp.	12. or/811	17. Magnetic resonance imaging
6. Acupuncture needling.mp.		18. Electroencephalography
7. or 16		19. Positron emission tomography
		20. Magnetoencephalography
		21. Tomography, emission computed, single photon
		22. or 1321
		23. and 7,12,22

Appendix 2. Search terms

Search terms category	Acupuncture	Pain	Functional connectivity
MeSH keywords	Acupuncture, acupuncture points, acupuncture therapy, acupuncture analgesia, electroacupuncture, acupuncture needle, acupuncture needling.	Pain, musculoskeletal pain, chronic pain, acute pain, musculoskeletal diseases.	Functional connectivity, neuroimaging, functional neuroimaging, brain mapping, connectome, magnetic resonance imaging, electroencephalography, positron emission tomography, magnetoencephalography, tomography emission computed single photon, central nervous system, brain.

Appendix 3. Modified Downs and Black questionnaire scores

Study type	Study	Item no. 1	2	3	4	5	6	7	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	No.	Total %	Quality rating
RCT	Chen et al [25]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	UD	Y	Y	UD	Y	Y	Y	Y	Y	Y	UD	Y	Y	Y	N	21/25	84	High
	Maeda et al [26]	Y	Y	Y	Y	Y	Y	Y	Y	Y	UD	UD	Y	N	N	Y	Y	Y	Y	Y	UD	UD	Y	UD	Y	Y	18/25	72	Moderate
	Harris et al [27]	Y	Y	Y	Y	Y	Y	Y	Y	Y	UD	UD	Y	Y	UD	Y	Y	Y	Y	Y	UD	UD	Y	UD	Y	Y	19/25	76	High
Non-RCT	Li et al [28]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	UD	Y	NA	NA	Y	Y	Y	Y	Y	Y	UD	NA	NA	Y	Y	18/21	85	High
	Napadow et al [30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	UD	UD	Y	NA	NA	Y	Y	Y	Y	Y	UD	UD	NA	NA	Y	Y	17/21	80	High
	Napadow et al [29]	Y	Y	Y	Y	Y	Y	Y	Y	N	UD	UD	Y	NA	NA	Y	Y	Y	Y	Y	UD	UD	NA	NA	Y	Y	16/21	76	High
	Pariente et al [31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	UD	Y	NA	NA	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	Y	20/21	95	High

The scores are as follows: high, >75%; moderate, 50–74%; low, ≤ 50%; N = 0; UD = 0; Y = 1.
N = no; NA = not applicable; RCT = randomized controlled trial; NRCT = nonrandomized trial; UD = unable to determine; Y = yes.

Appendix 4. Standards for Reporting Interventions in Clinical Trials of Acupuncture checklist

Type of Study	Study	Acupuncture rationale			Details of needling							Treatment regimen		Other components of treatment		Practitioner background	Control interventions	
		1a	1b	1c	2a	2b	2c	2d	2e	2f	2g	3a	3b	4a	4b	5	6a	6b
RCT	Chen et al [25]	Y	Y	Y	Y	Y	Y	Y	Y	Y	NM	Y	Y	NA	NA	NM	Y	Y
	Maeda et al [26]	Y	Y	Y	Y	Y	NM	Y	Y	NM	Y	Y	NA	NA	NA	P	Y	P
	Harris et al [27]	Y	Y	Y	Y	Y	NM	Y	Y	NM	NM	Y	NM	NA	NA	NM	Y	P
Non-RCT	Li et al [28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	Y	Y
	Napadow et al [30]	Y	Y	Y	Y	Y	NM	Y	Y	NM	NM	Y	Y	NA	NA	P	Y	Y
	Napadow et al [29]	Y	Y	Y	Y	Y	NM	Y	Y	NM	NM	Y	Y	NA	NA	P	Y	Y
	Pariente et al [31]	NM	Y	Y	Y	Y	NM	Y	Y	Y	Y	Y	NA	NA	NA	NM	Y	P

N = no; NA = not applicable; NM = not mentioned; NRCT = nonrandomized trial; P = partially; RCT = randomized controlled trial; Y = yes.

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