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Systematic Review

Brain functional connectivity network studies of acupuncture: a systematic review on resting-state fMRI

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ABSTRACT

Background: Functional magnetic resonance imaging (fMRI) is a novel method for studying the changes of brain networks due to acupuncture treatment. In recent years, more and more studies have focused on the brain functional connectivity network of acupuncture stimulation.
Objective: To offer an overview of the different influences of acupuncture on the brain functional connectivity network from studies using resting-state fMRI.
Search strategy: The authors performed a systematic search according to PRISMA guidelines. The database PubMed was searched from January 1, 2006 to December 31, 2016 with restriction to human studies in English language.
Inclusion criteria: Electronic searches were conducted in PubMed using the keywords "acupuncture" and "neuroimaging" or "resting-state fMRI" or "functional connectivity".
Data extraction and analysis: Selection of included articles, data extraction and methodological quality assessments were respectively conducted by two review authors.
Results: Forty-four resting-state fMRI studies were included in this systematic review according to inclusion criteria. Thirteen studies applied manual acupuncture *vs.* sham, four studies applied electro-acupuncture *vs.* sham, two studies also compared transcutaneous electrical acupoint stimulation *vs.* sham, and nine applied sham acupoint as control. Nineteen studies with a total number of 574 healthy subjects selected to perform fMRI only considered healthy adult volunteers. The brain functional connectivity of the patients had varying degrees of change. Compared with sham acupuncture, verum acupuncture could increase default mode network and sensorimotor network connectivity with pain-, affective- and memory-related brain areas. It has significantly greater connectivity of genuine acupuncture between the periaqueductal gray, anterior cingulate cortex, left posterior cingulate cortex, right anterior insula, limbic/paralimbic and precuneus compared with sham acupuncture. Some research had also shown that acupuncture could adjust the limbic-paralimbic-neocortical network, brainstem, cerebellum, subcortical and hippocampus brain areas.
Conclusion: It can be presumed that the functional connectivity network is closely related to the mechanism of acupuncture, and central integration plays a critical role in the acupuncture mechanism.

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1. Introduction

Acupuncture has been used as a traditional medicine in China for over 2000 years [1], and is now rapidly gaining popularity in Western alternative and complementary medicine practice for its undeniable therapeutic effects [2]. Exploring the mechanism of acupuncture has been a hot topic in the research of alternative and complementary medicine.

Since the 1970s, many studies in animal models have shown that the integration of the central nervous system is involved in the effect of acupuncture [3]. In the last 20 years, extensive functional magnetic resonance imaging (fMRI) research has focused on the study of the neurophysiological mechanism of acupuncture. Using neuroimaging technologies, researchers have been able to examine the acupuncture process in the brain noninvasively [4]. fMRI is a new method to quantify how acupuncture affects changes in the brain network [5–8]. Many resting-state fMRI (rs-fMRI) studies have indicated that acupuncture regulates the activity of some cortical and subcortical brain regions [9–11].

This review presents a summary of current studies about brain functional connectivity networks in acupuncture research. The authors discussed aspects of study participants, acupoints, acupuncture methods, research methodology and their associated challenges. For this purpose, the study outcomes are discussed in several subgroups. The results provide an overview of changes in functional connectivity networks stimulated by different acupuncture acupoints or methods.

2. Methods

2.1. Literature search

The authors adopted a systematic search strategy according to the PRISMA guidelines [12]. Electronic searches were performed in PubMed using the keywords "acupuncture" and "neuroimaging" or "resting-state fMRI" or "functional connectivity". Then the articles were screened by title and abstract. The PubMed database was initially searched from January 1, 2006 to December 31, 2016 with restriction to human studies in English language.

2.2. Eligibility criteria

Original studies of acupuncture on the brain functional connectivity network using rs-fMRI were included in this review. We excluded meta-analyses, reviews, non-fMRI studies, non-needle acupuncture studies and non-functional connectivity studies.

2.3. Study selection

Initially, studies were screened for relevance using the title and abstract. Repeated studies, reviews, unrelated studies and works without available full text were excluded. Then, the full texts of potential studies were assessed following the inclusion and exclusion criteria. The study characteristics and variables of interest were then transferred to Excel [7]. The following data were extracted: publishing data (including author, publication year, title and journal), methodology (including number of participants, number of intervention groups, and number of treatment sessions), needling details (including acupuncture style: manual/electro; acupuncture points: unilateral/bilateral), control intervention (including types of control intervention, and size of intervention groups), technology (technical device, and data processing method) and outcomes (including findings, group differences, increase/decrease, and activation/deactivation).

3. Results

3.1. Study inclusion

A literature search was conducted, including publications from 2006 to 2016. Our search terms retrieved 136 records. After screening the title and abstract, the number was reduced to 83 articles. A further 39 articles were excluded when the full text failed to meet the inclusion criteria, leaving 44 articles for use in this study (Fig. 1). The publication year of all articles is shown in Fig. 2.

3.2. Result tables

A comparison of all included studies with regard to acupoints used, control intervention, number of participants, outcomes and so forth can be found in Table 1.

3.3. Participants

A total of 44 studies with 1 191 participants were divided as follows: 19 studies [13–31] with 574 healthy subjects, 14 studies [32–45] with 289 subjects affected by nervous system diseases, 6

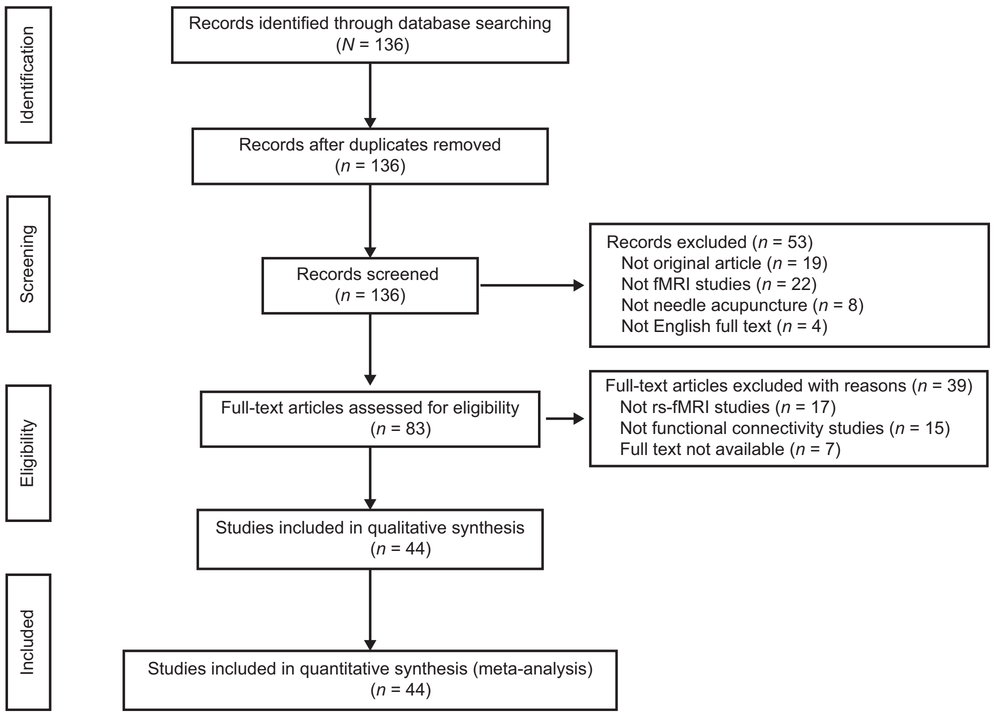

Fig. 1. Flow chart of this review fMRI: functional magnetic resonance imaging; rs-fMRI: resting-state fMRI.

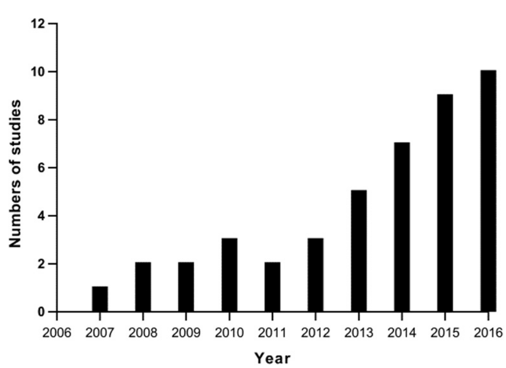

Fig. 2. Numbers of brain functional connectivity network studies of acupuncture in the last 10 years.

studies [4,46–50] with 189 subjects affected by motor system diseases and 5 studies [51–55] with 139 affected by various other diseases (Table 2).

3.3.1. Healthy subjects

A total of 574 subjects were included in 19 studies [13–31] that only used healthy adult volunteers for fMRI studies. Acupuncture increased limbic-paralimbic-neocortical network/default-mode network (DMN)/sensorimotor network (SMN) connectivity of healthy subjects, and the correlations between limbic/paralimbic and subcortical regions, including the insula, amygdala, anterior cingulate cortex (ACC), precuneus and thalamus [13–31].

3.3.2. Nervous system diseases

Out of the 44 trials, 14 studies focus on nervous system diseases: 3 studies with 31 stroke patients [32–34], 3 studies with 45 Bell's palsy patients [35–37], 3 studies with 112 migraine patients [38–40], 2 studies with 12 mild cognitive impairment (MCI) patients [41,42], 1 study with 14 Alzheimer's disease patients [43] and 2 studies with 75 major depressive disorder patients [44,45]. The significant enhancement of hippocampus, amygdala and insula after acupuncture may be associated with the effects of acupuncture on MCI [41]. Acupuncture could enhance cooperation of bilateral sensorimotor networks, stimulate the contralateral sensorimotor network and modulate the sensorimotor network of the ipsilesional hemisphere in stroke patients [32]. Compared with healthy control, migraine without aura patients showed reduced functional connectivity between the periaqueductal gray (PAG) and rostral ACC (rACC)/medial prefrontal cortex (mPFC), key areas for improving pain modulatory system [38,39]. The effects of acupuncture on brain response of Bell's palsy were closely connected with clinical course. It is indicated that brain response to acupuncture was also correlated to the condition of brain functional connectivity [36]. The effect of acupuncture as antidepressant treatments may have been achieved through the limbic system, especially the amygdala and the ACC [45].

3.3.3. Motor system diseases

One study with 13 carpal tunnel syndrome patients [4], one study with 18 low-back pain patients [46] and 4 studies with 158 chronic osteoarthritis patients [47–50] were selected. The fMRI signal of the amygdala decreased significantly and the signal in the lateral hypothalamus increased after acupuncture on carpal tunnel syndrome patients [4]. Compared with healthy controls, the DMN in low-back pain patients was found to have less connectivity in the mPFC, dorsolateral prefrontal cortex, ACC and precuneus [46]. The connectivity between medial frontal cortex and PAG in knee osteoarthritis patients with chronic pain is associated with clinical severity [49].

3.3.4. Other diseases

One study with 8 functional dyspepsia (FD) patients [51], 2 studies including 60 hypertension patients [52,53], one study with

Table 1
Experimental details of 44 articles.

Study	Acupoints used	Subjects	Region of interest
Feng et al., 2011 [13]	Right ST36	14 healthy subjects	Ninety cortical and subcortical regions
Dhond et al., 2008 [14]	Left PC6	15 healthy subjects	DMN and SMN
Qin et al., 2008 [15]	ST36	18 healthy students	Contralateral amygdala
Liu et al., 2009 [16]	Left GB37	28 healthy subjects	PCC and precuneus
Hui et al., 2009 [17]	Right LI4, ST36 and LR3	48 healthy subjects	LPNN
Hui et al., 2010 [18]	Right LI4, ST36 and LR3	52 healthy subjects	LPNN
Qiu et al., 2010 [19]	LR3	38 healthy subjects	Right posterior cingulate, and left secondary somatosensory cortex
Zyloney et al., 2010 [20]	Right LI3 and LI4	77 healthy subjects	PAG
Liu et al., 2011 [21]	ST36	14 healthy subjects	Limbic system
Fang et al., 2012 [22]	CV4 and CV12	21 healthy subjects	Whole-brain
You et al., 2013 [23]	Right ST36	28 healthy subjects	SFG, ACC, PCC, STG, AG, IPL, and middle temporal gyrus
Jiang et al., 2013 [24]	Left ST36	18 healthy subjects	DMN and SMN
Nierhaus et al., 2015 [25]	ST36	22 healthy subjects	PCC and secondary somatosensory cortex
Liu et al., 2015 [26]	Right SP6	16 healthy subjects	Cerebellum posterior lobe
Shi et al., 2016 [27]	BL40	16 healthy subjects	PCC
Qiu et al., 2012 [28]	Right LR3	12 healthy subjects	Occipital lobe, declive, supramarginal gyrus, precuneus, and postcentral gyrus
Lin et al., 2016 [29]	LI4	58 healthy subjects	DMN
Zhang et al., 2016 [30]	LR3 plus KI3	57 healthy subjects	Brodmann area 6
Long et al., 2016 [31]	ST36	22 healthy subjects	Secondary somatosensory cortex
Chen et al., 2014 [32]	TE5	24 patients with ischemic stroke	Bilateral motor, somatosensory, and basal ganglia areas
Bai et al., 2014 [33]	Left GB34	9 patients with ischemic stroke	Left primary motor cortex
Zhang et al., 2014 [34]	Left GB34	8 stroke patients and 10 healthy subjects	Bilateral PCC
He et al., 2014 [35]	LI4	20 healthy subjects and 28 patients with BP	Primary somatosensory area
Wu et al., 2015 [36]	LI4	20 healthy subjects and 28 patients with BP	ACC
Bian et al., 2016 [37]	LI4	22 healthy subjects and 17 patients with BP	Middle frontal gyrus, primary motor cortex, and cingulate motor area
Zhao et al., 2014 [38]	Active acupoint (bilateral SJ5, GB20, GB34, GB40), inactive acupoints (SJ22, PC7, GB37, SP3)	80 MwoA patients without aura	
Li et al., 2015 [39]	Bilateral TE23, GB8, GB20, EX-HN5, LI4, LR3, TE5,GB34, and GB41	12 MwoA patients and 12 healthy subjects	Brain regions changed in MWoA patients; left precentral gyrus
Li et al., 2016 [40]	GB34, GB40 and TE5; GB33, GB42, TE8; ST36, ST42 and LI6	100 MwoA patients and 46 healthy subjects	PAG
Feng et al., 2012 [41]	KI3	12 MCI patients and 12 healthy subjects	Ninety cortical and subcortical regions
Chen et al., 2013 [42]	Right KI3	12 MCI patients and 12 healthy subjects	Dorsolateral prefrontal cortex and hippocampus
Wang et al., 2014 [43]	LI4 and LR3	14 AD patients and 14 healthy elders	Bilateral hippocampus
Deng et al., 2016 [44]	GV20	29 patients with major depressive disorder and 29 healthy subjects	Precuneus/PCC
Wang et al., 2016 [45]	CV12, CV10, CV6, CV4, KL17 and ST24	46 female depressed patients	Amygdala
Napadow et al., 2007 [4]	LI4	13 CTS patients and 12 healthy subjects	
Li et al., 2014 [46]	BL23, Ah Shi point, GV3, BL40 and KI3	10 healthy subjects and 18 patients with LBP	DMN
Chen et al., 2014 [47]	GB34, SP9, GB39, SP6, ST35 and Xi Yan	30 patients with chronic osteoarthritis	Left pMPFC
Chen et al., 2015 [48]	GB34, SP9, GB39, SP6, ST35 and Xi Yan	30 patients with knee osteoarthritis	SMN, ECN, and RFPN
Egorova et al., 2015 [49]	GB34, SP9, GB39, SP6, ST35 and Xi Yan	44 patients with knee osteoarthritis	PAG
Hashmi et al., 2014 [50]	LI3 and LI4	42 patients with chronic knee pain	Prefrontal cortex
Fang et al., 2015 [51]	ST36, KI3, GB41, PC6, and HT 7	8 patients with FD and 10 healthy subjects	Pregenual ACC, sub-ACC, MTL-hippocampus, IPL, and anterior insula
Chen et al., 2013 [52]	GV20, GV23, EXHN1, ST9, LI11, PC6, LI4, ST36, SP6, LR3	30 patients with hypertension	Hypothalamus
Zheng et al., 2016 [53]	LR3	30 patients with hypertension	Hypothalamus
Von Deneen et al., 2015 [54]	ST36 and SP9	19 overweight (10 for acupuncture treatment and 9 for minimal sham acupuncture treatment)	Amygdala and hypothalamus
Bao et al., 2016 [55]	ST25 (both sides), CV6 and CV12	52 patients with Crohn's disease and 36 healthy subjects	Voxel sets within 6-mm spheres around clusters peak

ACC: anterior cingulate cortex; AD: Alzheimer's disease; AG: angular gyrus; BP: Bell's palsy; CTS: carpal tunnel syndrome; DMN: default-mode network; ECN: executive control network; FD: functional dyspepsia; IPL: inferior parietal lobule; LBP: low-back pain; LPNN: limbic-paralimbic-neocortical network; MCI: mild cognitive impairment; MTL: medial temporal lobe; MwoA: migraine without aura; PAG: periaqueductal gray; PCC: posterior cingulate cortex; pMPFC: posterior medial prefrontal cortex; RFPN: right frontoparietal network; SFG: Superior frontal gyrus; SMN: sensorimotor network; STG: superior temporal gyrus.

19 overweight patients [54] and one study with 52 Crohn's disease patients [55] were selected. For all of the regions of interest (including pregenual ACC, sub-ACC, medial temporal lobe-hippocampus, inferior parietal lobule and anterior insula), subportions of the networks' connectivity were reduced in FD patients after acupuncture, but still close to normal subjects. The alleviation of gastrointestinal symptoms and signs after acupuncture may be a result of improvement in the brain-gut axis of FD patients [51]. Acupuncture could modulate the heart function via complex brain networks such as the cerebral cortex, hypothalamus and brainstem

Table 2
Participants included in reviewed literature.

Disease	Number of studies	Number of subjects
Healthy	19	574
Nervous system diseases		
Stroke	3	31
Bell's palsy	3	45
Migraine	3	112
Mild cognitive impairment	2	12
Alzheimer's disease	1	14
Major depressive disorder	2	75
Motor system diseases		
Carpal tunnel syndrome	1	13
Low-back pain	1	18
Chronic osteoarthritis	4	158
Other diseases		
Functional dyspepsia	1	8
Hypertension	2	60
Overweight	1	19
Crohn's disease	1	52

[52]. Decreased hypothalamus–thalamus functional connectivity after acupuncture has a negative correlation with acupuncture effects in hunger [54]. Electro-acupuncture adjusted the afferent processing network in Crohn's disease patients, whereas moxibustion primarily modulated the DMN [55].

3.4. Acupoints

Out of the 44 trials, only 25 chose one single acupuncture point, 6 used a combination of two points, and 13 studies applied a combination of 3 or more points. Point selection varied significantly and included points on both arms, both legs and the head. ST36 is the most common point utilized in 14 studies; LI4 was used in 12 studies.

3.5. Acupuncture methods

Manual acupuncture, electro-acupuncture and transcutaneous electrical acupoint stimulation (TEAS) were used as main interventions. Out of 44 studies, 13 applied manual acupuncture *vs.* sham, 4 applied electro-acupuncture *vs.* sham (Table 3), 1 study compared TEAS *vs.* sham and 9 applied sham acupoints as a control (Table 4). One study compared acupuncture *vs.* medicine, 1 study compared acupuncture *vs.* moxibustion and 12 studies did not compare among different stimulation methods or points.

3.6. Subgroup comparisons

3.6.1. Point specificity comparison

Out of the 44 trials, only 25 chose one single acupuncture point. Studies evaluating a single acupuncture point against another point or a non-acupoint were compared. These 8 studies were comprised of 1 study on GB37, 1 study on LR3, 1 study on TE5 and 5 studies on ST36.

(1) GB37. Liu et al. [16] found that brain network responses to acupuncture at GB37 and KI8 were different. The results showed that overlap of spatial patterns, after acupuncture at these two points, was focused on posterior cingulate cortex (PCC) and precuneus. Two contrary regulation modes in the DMN were detected, while PCC/precuneus was used as seed point.

(2) LR3. Qiu et al. [28] found that the coherence characteristic curves of wavelet transforms in the declive, precuneus, postcentral gyrus and occipital lobe, after acupuncture at LR3, are different from those of sham acupoints. Further, the influence of acupuncture on brain response existed during the resting state and lasted for 5 min.

Table 3
Studies using sham acupuncture as a control.

Study	Stimulation	Control stimulation
Napadow et al., 2007 [4]	Acupuncture	Sham acupuncture
Dhond et al., 2008 [14]	Manual acupuncture	Sham acupuncture
Qin et al., 2008 [15]	Acupuncture	Sham acupuncture
Hui et al., 2009 [17]	Manual acupuncture	Tactile stimulation
Hui et al., 2010 [18]	Acupuncture *deqi*	Tactile stimulation
Feng et al., 2012 [41]	Manual acupuncture (deep acupuncture)	Superficial acupuncture
Jiang et al., 2013 [24]	Manual acupuncture, electro-acupuncture, TEAS	Sensory control stimulation
Chen et al., 2013 [42]	Deep acupuncture	Superficial acupuncture
Hashmi et al., 2014 [50]	Acupuncture	Sham acupuncture
Von Deneen et al., 2015 [54]	Acupuncture	Sham acupuncture
Shi et al., 2016 [27]	Deep needling	Shallow needling
Li et al., 2016 [40]	Acupuncture	Sham acupuncture
Wang et al., 2016 [45]	Acupuncture and fluoxetine	Sham acupuncture and fluoxetine
Zyloney et al., 2010 [20]	Electro-acupuncture	Sham electro-acupuncture
Fang et al., 2012 [22]	Electro-acupuncture	Sham electro-acupuncture
Bao et al., 2016 [55]	Electro-acupuncture	Moxibustion

TEAS: transcutaneous electrical acupoint stimulation.

Table 4
Studies using sham acupoints as control.

Study	Acupoints used	Stimulation	Control points
Liu et al., 2011 [21]	ST36	Verum acupuncture	Non-meridian point
Feng et al., 2011 [13]	Right ST36	Manual acupuncture	Non-acupoint
Qiu et al., 2012 [28]	Right LR3	Acupuncture	Sham acupoints
You et al., 2013 [23]	Right ST36	Manual acupuncture	Non-meridian point
Chen et al., 2014 [32]	TE5	Acupuncture	Non-acupoint
Nierhaus et al., 2015 [25]	ST36	Acupuncture	Two control points
Zheng et al., 2016 [53]	LR3	Manual acupuncture	Sham point
Zhang et al., 2016 [30]	LR3 plus KI3	Acupuncture	LR3 plus sham acupoint or LR3 alone
Long et al., 2016 [31]	ST36	Acupuncture	Two control points

(3) TE5. Chen et al. [32] found that acupuncture at TE5 could enhance cooperation of bilateral sensorimotor networks, stimulate the contralateral sensorimotor network and modulate the sensorimotor network of the contralateral hemisphere of stroke patients. In addition, there were many differences between verum acupuncture and sham, but the difference between non acupoint and TE5 was little.

(4) ST36. Feng et al. [13] found that the limbic/paralimbic areas proved to be network hubs after acupuncture at ST36. Liu et al. [21] found that the insula was involved in the mechanism of acupuncture at ST36. You et al. [23] confirmed that the PCC was a DMN hub and only within the δ and γ bands following ST36 stimulation. Nierhaus et al. [25] found more marked activation in the insula and secondary somatosensory cortex, as well as deactivation in the precuneus after acupuncture at ST36. Comparing with the two control points, the functional connectivity analysis of acupuncture at ST36 showed increased connectivity to the right precuneus. Long et al. [31] found that functional connectivity was highly concentrated in the middle temporal gyrus and parahippocampal gyrus following acupuncture at ST36.

3.6.2. Comparison of verum acupuncture vs. sham acupuncture

Out of 44 studies, 20 studies used sham acupuncture, including non-insertive cutaneous stimulation, tactile stimulation and superficial acupuncture. Verum acupuncture means that acupoints are stimulated with a manual technique that generates a *deqi* sensation.

The connectivity between DMN with pain-, affective- and memory-related brain areas was increased after verum acupuncture. Furthermore, significant functional connectivity can be seen between PAG and several brain areas during genuine electro-acupuncture, such as the ACC, mPFC, middle cingulate cortex, PCC, precuneus and left postcentral gyrus [20].

3.6.3. Comparison of different stimulation intensities

As shown in Table 5, 3 studies designed a comparison of different acupuncture intensities. Compared with sham acupuncture, obvious connectivity can be seen between left posterior medial prefrontal cortex and PAG, rACC, anterior mPFC and ventral striatum, after longitudinal acupuncture treatment [47]. The executive control network showed stronger connectivity and SMN showed reduced connectivity with rACC/mPFC following acupuncture stimulation [48,49].

Table 5
Studies on different stimulation intensities.

Study	Stimulation	Control
Chen et al., 2014 [47]	Six acupoints: ST35 and Xi Yan	Six non-acupoints
Chen et al., 2015 [48]	Six acupoints: ST35 and Xi Yan	Six non-acupoints
Egorova et al., 2015 [49]	Six acupoints: ST35 and Xi Yan	Six non-acupoints

4. Discussion

Neuroimaging, as an effective means to explore the central mechanism of acupuncture's effects, is widely used in acupuncture research. In recent years, instead of focusing on the changes in a single brain area during acupuncture, the researchers have focused more on the relationships among brain areas. The development of medical imaging has provided a good technical platform for the study of acupuncture mechanism. Brain connection is one of the most popular concepts in neuroscience at present, it can be seen from the neurons (microscale), groups of neurons (mesoscale) to entire brain areas (large scale). These techniques help to describe the brain organization and mechanism of operation. Because of the limitation of the existing imaging techniques, the research of brain connectivity is mainly focused on the large-scale level, that is, the region of interest is selected as the network node in the brain connection network. Resting-state functional connectivity of the brain network reflects the inherent and spontaneous neural activity of the brain activity pattern; it is one of the most important technologies for assessing brain function, and has good clinical applicability.

A total of 44 articles were enrolled in this review and changes in brain functional connectivity from acupuncture treatment were measured. Acupuncture can cause changes in the brain functional connectivity network under physiological conditions. Acupuncture at different acupoints can lead to different changes in brain functional connectivity. The brain functional connectivity of the patients had varying degrees of change. There are differences in the brain functional connectivity network between acupoints and non-acupoints or different acupoints. The differences also could be found in the functional connectivity network of different acupuncture manipulations, different needling depths and different stimulation intensities. Compared with sham acupuncture, verum acupuncture could increase DMN connectivity with pain-, affective- and memory-related brain areas, as well as SMN connectivity with pain-related brain areas. The limbic/paralimbic brain areas were confirmed to be network hubs after acupuncture. Furthermore, increased connectivity was mostly correlated with the limbic/paralimbic and subcortical regions after acupuncture, while decreased connectivity was mostly correlated with the sensory and frontal cortices.

Also, the brain functional connectivity was different in several diseases. The results demonstrated that the increased and decreased connectivity was correlated with some areas after acupuncture. Acupuncture could modulate the heart function via complex brain networks including the cerebral cortex, hypothalamus and brainstem [52]. Several frontal and temporal brain areas showed decreased hippocampal connectivity in patients with Alzheimer's disease. Most hippocampus-related regions showed increased connectivity after acupuncture in patients with Alzheimer's disease [43]. The significant enhancement of functional connectivity in memory-related brain areas after acupuncture may be associated with the effect of acupuncture on MCI [41]. According to our results, it can be presumed that the functional connectivity network of the brain is closely related to the mechanism of acupuncture, and central integration is involved in the mechanism of the acupuncture effect.

Recently, connectomics has been developed as a new research hotspot for studying acupuncture mechanisms [8]. The "connectome" holds that the human brain is highly self-organized, with regional networks to interconnect and interact. These connectomics studies not only give us a better understanding of the human brain, but also take a new approach to revealing the mechanism underlying acupuncture's effects. Even though many studies about neurophysiologic correlates have been done, it is still at a preliminary stage, and the specific effects of acupuncture mechanisms on the central nervous system are still unknown [56].

Although this review provides a detailed, structured overview of the current literature on brain functional connectivity networks and acupuncture, the data evaluation encountered difficulties that are hard to avoid in fMRI and acupuncture mechanism research. Every research question, every fMRI device, every analysis method and every verum and control acupuncture intervention holds its own risk of bias when conducting studies about the brain functional connectivity network of acupuncture mechanisms. There are also some differences between the experimental design and the clinical application of acupuncture. Therefore, more consistent methodology protocols are recommended for future studies. The researchers should closely follow the STRICTA guidelines [57] in designing and reporting acupuncture mechanism research. Although the research on the mechanism of brain functional connectivity network is increasing, the research in this field should pay attention to several aspects in the future. The changes of brain functional connectivity network following acupuncture should be observed repeatedly. More attention should be paid to diseases that have good therapeutic effect with acupuncture treatment. When the seed point correlation is used to construct functional connectivity, the appropriate brain area should be selected as the region of interest according to clinical effect. As far as possible, to carry out large sample studies, experimental design and analysis methods need to be further standardized.

5. Conclusion

This review provides an overview of 44 neuroimaging studies, including trials with healthy subjects, and patients with nervous system diseases, motor system diseases and other diseases. The results of this review show that acupuncture could increase DMN, SMN connectivity with pain-, affective- and memory-related brain areas. Verum acupuncture showed significantly greater connectivity between the PAG, ACC, left PCC, insula, limbic/paralimbic and precuneus compared with sham acupuncture. Some research also indicated that the limbic-paralimbic-neocortical network, brainstem cerebellum, subcortical and hippocampus brain areas could be regulated by acupuncture. However, the changes of brain functional connectivity caused by acupuncture need to be further studied. In the future, results from standardized experimental design and analysis methods with larger sample sizes are needed to reach more definitive conclusions.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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