

# Neuroimaging Evidence of Acupuncture Treatment for Depression Over the Past Decade: A Systematic Review

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## Abstract

This systematic review aims to synthesise evidence from neuroimaging studies to illustrate that acupuncture does have measurable multi-target central actions for major depressive disorder (MDD) treatment. The key mechanisms identified in studies over the past decade, using fMRI, PET and EEG, are: Acupuncture reduces hyperconnectivity of the default mode network (DMN) and increases its anti-correlation with the salience network. In task-based imaging, there is observed reduction in hyperactivity in the amygdala in conjunction with an increase in activity in the dorsolateral prefrontal cortex. Morphometric analyses showed that sustained EAc caused an increase in gray matter in the hippocampus and prefrontal cortex. PET studies have been reported to show alterations in serotonin transporter (SERT) binding and opioid receptor (OR) availability in the limbic system following treatment. So far, although there have been a lot of clinical evidence showing the antidepressant effects of acupuncture, the neurobiological understanding of acupuncture's effects remained unclear. Existing studies suggest that there are potential neural modulation targets to consider for the pathophysiology of MDD, such as dysregulated neurotransmission, and corticolimbic connectivity; however, there have been some limitations in the studies, with small sample sizes, heterogeneous protocols, and relatively short follow-up. Further multicenter randomized controlled trials involving longitudinal imaging will be required to determine definite mechanistic and clinical standards.

**Keywords:** acupuncture; electroacupuncture; major depressive disorder; neuroimaging; fMRI; default mode network; PET; EEG; systematic review

## 1. Introduction

Major depressive disorder is a recurrent psychiatric condition characterized by persistent low mood, anhedonia, cognitive impairment, and vegetative dysfunction. It ranks among the leading causes of global disability-adjusted life years, with a lifetime prevalence estimated at approximately 15–17% in high-income countries. Despite the availability of pharmacological and psychotherapeutic interventions, a substantial proportion of patients fail to achieve full remission after initial treatment, and a meaningful fraction meet criteria for treatment-resistant depression. The attendant disability, mortality risk, and socioeconomic burden underscore the need for mechanistically informed complementary approaches.

Acupuncture, the insertion of fine metallic needles at defined anatomical loci according to traditional Chinese medicine theory, has been practiced for more than two millennia. Contemporary meta-analyses indicate that acupuncture, both as monotherapy and as an adjunct to antidepressants, produces clinically meaningful reductions in depressive symptom severity. Nevertheless, its

biological plausibility has remained contested, partly because early mechanistic research relied on peripheral biomarkers that are distal from central pathophysiology.

The emergence of multimodal neuroimaging has substantially transformed this landscape. Resting-state functional MRI, task-based fMRI, voxel-based morphometry, positron emission tomography, and high-density electroencephalography now permit non-invasive interrogation of the neural substrates implicated in depression, including corticolimbic circuits, large-scale functional networks, and monoaminergic pathways. Over the past decade, a growing body of neuroimaging studies has begun to map acupuncture's effects onto these systems. This systematic review synthesizes that evidence, evaluates methodological quality, and identifies the most pressing gaps that future research must address.

## **2. Methods**

### **2.1 Search Strategy and Eligibility Criteria**

The systematic search of literature was performed in PubMed, Web of Science, Embase and CNKI. Search was done with a combination of MeSH terms and free text words across three concept domains: the intervention (MeSH terms used were acupuncture, electroacupuncture, and manual acupuncture); the condition (MeSH terms used were depression, major depressive disorder, and depressive disorder); and the neuroimaging modality (MeSH terms used were functional MRI, resting-state fMRI, PET, electroencephalography, and voxel-based morphometry). Additional records were identified by hand searching a list of eligible articles and relevant reviews.

Studies were eligible if they enrolled adult patients fulfilling DSM-IV, DSM-5, or ICD-10 criteria for a depressive disorder; applied manual acupuncture or electroacupuncture as the primary or adjunctive intervention; compared acupuncture against sham acupuncture, waitlist control, or pharmacotherapy; and reported at least one quantitative neuroimaging outcome, including amplitude of low-frequency fluctuations, regional homogeneity, functional connectivity, gray matter volume, PET radioligand binding, or EEG spectral power. Studies were excluded if they were reviews, editorials, or animal experiments; enrolled participants with bipolar disorder, psychotic features, or active neurological disease; or lacked primary neuroimaging data.

### **2.2 Data Extraction and Quality Assessment**

Two reviewers independently screened titles and abstracts, then full texts, resolving disagreements through consensus. Extracted variables included study design, sample characteristics, acupuncture protocol, comparator, neuroimaging modality and analysis pipeline, primary outcomes, and follow-up duration. Methodological quality of randomized controlled trials was appraised with the Cochrane Risk of Bias 2.0 tool across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Non-randomized studies were assessed with the Newcastle–Ottawa Scale. Overall evidence certainty was graded using the GRADE approach for each neuroimaging outcome domain.

## **3. Results**

### **3.1 Study Selection and Characteristics**

Neuroimaging modalities included resting-state fMRI, task-based fMRI, voxel-based morphometry, PET, and EEG; some studies used more than one modality. Treatment length varied from 2 to 12 weeks and the number of treatment sessions varied from 3 to 5 times a week.

### **3.2 Resting-State fMRI: Large-Scale Network Dynamics**

#### ***3.2.1 Default Mode Network Normalization***

In major depressive disorder (MDD), the default mode network (DMN) is mechanistically associated with excessive rumination and a failure of cognitive control and is characteristically hyperactive and internally hyperconnected [1]. Resting-state fMRI studies included in the study all showed a reduction in this pathological hyperconnectivity, especially between the posterior cingulate cortex and the medial prefrontal cortex with acupuncture. Several studies have reported that this was in parallel with the reduction in depressive symptom scores and that the normalization lasted for several weeks following the end of treatment, indicating long-lasting network recalibration instead of short-term neuromodulation [2, 3].

#### ***3.2.2 Limbic-Cortical-Striatal Circuit Modulation***

In addition to the default mode network, acupuncture consistently modulated the limbic-cortical-striatal circuit, the neural substrate of reward processing, threat appraisal and emotion regulation. In patients with depression, excessive negative functional connectivity between amygdala and medial prefrontal cortex (mPFC) was reduced by electroacupuncture at GV20 and GV29, which was also inversely correlated with self-reported anhedonia severity [5]. Independent investigation showed that sustained electroacupuncture treatment led to enhanced episodic memory encoding, along with reduced contextual fear generalization, and increased connectivity of the hippocampus with lateral prefrontal regions. Thalamo-cortical connectivity analysis also revealed that connectivity between the mediodorsal thalamus and the dorsolateral prefrontal cortex was restored, which may be related to better top-down modulation of sensory gating [6].

### **3.3 Task-Based fMRI: Affective Processing and Cognitive Control**

Task-related fMRI studies explored how acupuncture modulated neural responses to activity and emotional and cognitive paradigms. In emotional facial recognition, the electroacupuncture was shown to decrease the bilateral amygdala response to fearful and sad faces in MDD patients but not in healthy controls. An increase in activation of both dorsolateral prefrontal cortex and ventrolateral prefrontal cortex was found during negative-affect processing, which is consistent with strengthened top-down reappraisal. The increase in prefrontal activation gain was associated with improvement in a cognitive emotion regulation questionnaire, indicating that acupuncture might reset the fronto-amygdalar circuits that underlie effortful emotion regulation [7]. Other studies of specific tasks showed increased activation of anterior cingulate cortex and anterior insula in affective tasks, reflecting increased interoceptive-executive integration [8].

### **3.4 Structural Neuroimaging: Gray Matter Morphometry**

The neuroplastic effects of acupuncture on gray matter architecture were studied longitudinally, focusing on the well-documented hippocampal and prefrontal volume deficits in major depressive

disorder (MDD) [9]. High-field MRI was taken at baseline and end-point in the most methodologically rigorous morphometric randomized controlled trial, which randomized patients with depression to eight-week electroacupuncture and sham. Compared with sham, the electroacupuncture group showed higher increase in the volume of gray matter in the left hippocampus and the left dorsolateral prefrontal cortex. Hippocampal volume alterations were positively related to reduction on the Hamilton Depression Rating Scale (HDRS), suggesting that hippocampal neurogenesis and/or dendritic remodeling are a basis of antidepressant response [10]. A second cohort study confirmed dorsolateral prefrontal volumetric gains after 12 weeks of manual acupuncture and also found subgenual anterior cingulate cortex volume gains, a region known to be involved in negative affect bias [11].

### **3.5 PET Neurochemistry: Monoaminergic and Opioidergic Systems**

#### **3.5.1 Serotonergic System**

In a PET study to examine central serotonin transporter binding, electroacupuncture decreased the serotonin transporter binding potential in the raphe nuclei of major depressive disorder patients compared with sham, suggesting that the availability of serotonin in synapse or regulation of serotonin receptors was changed. The complementary findings revealed similar changes in serotonin transporter in the caudate nucleus and putamen, suggesting that serotonin transporter in the striatum is involved in the mood-modulatory aspects of acupuncture.

#### **3.5.2 Endogenous Opioid System**

Manual acupuncture at LI4 and ST36 in depression patients resulted in widespread opioid receptor availability changes in anterior cingulate cortex, amygdala, nucleus accumbens and insular cortex areas that are all involved in affective valuation and pain modulation. The amount of receptor change in the anterior cingulate cortex correlated with the immediate improvements in mood, indicating that opioid receptor activation may underlie the immediate anxiolytic and antidepressant effects of acupuncture [13]. All these increase the evidence of the antidepressant effects of endogenous opioid system activation and the findings are consistent with the effects on pain reported in the acupuncture literature.

### **3.6 EEG: Cortical Oscillatory Dynamics**

EEG studies measured the effect of acupuncture on the oscillations in the cortex. In all of the included studies, acupuncture was shown to increase the alpha frequency over prefrontal and parietal areas, which has been linked to emotional relaxation, decreased vigilance to threat and improved cognitive flexibility [14]. Sham-controlled designs allowed us to confirm that these oscillatory changes were not simply due to non-specific relaxation. There was also an increase in fronto-parietal network integration in terms of theta band coherence between the frontal and parietal regions after the acupuncture procedure. Frontal alpha asymmetry (FA) is a well-known measure of approach motivation, and this asymmetry was reported to be normalized after both manual and electroacupuncture methods in several studies [15].

### **3.7 Synthesis of Mechanistic Pathways**

Acupuncture's central action on major depressive disorder can be summarized as having effects

on three mechanistic axes, with integration across each neuroimaging modality. The first is large-scale network recalibration that includes reduction of pathological default mode network hyperconnectivity, restoration of anti-correlation between default mode network and salience network, and increased recruitment of central executive network. The second is corticolimbic circuit normalization, characterized by decreased hyperreactivity of the amygdala, normalization of the connection between the hippocampus and prefrontal cortex and increased activation of the dorsolateral prefrontal cortex during affective processing. The third is neurochemical modulation, which includes the enhancement of the availability of serotonin at the synapse through modulation of serotonin transport occupancy and release of endogenous opioids in limbic affect systems. These changes are not independent – network recalibration is likely to reflect as well as mediate the neurochemical changes, and the corticolimbic balance restored is likely to provide the circuit-level substrate through which monoaminergic normalization propagates.

## **4. Discussion**

### **4.1 Toward a Multi-Network Model of Acupuncture Antidepressant Action**

Overall, the neuroimaging findings presented here suggest that acupuncture has a depressive effect by coordinated modulation of more than one neural system that are functionally coupled, but not through a single mechanistic node. Overall, acupuncture seems to exert inhibitory effects on the pathologically increased default mode network inherent activity, especially in the posterior cingulate cortex and the medial prefrontal cortex axis, and to enhance the salience-network mediated switch to central executive network engagement. This switch at the network level is related to the clinical phenomenology of depression: increased default mode activity is associated with rumination and self-referential bias, while decreased central executive network activity is associated with poorer working memory, cognitive flexibility and goal-directed behaviour [1, 16].

At the same time, acupuncture treats the limbic system at several points. Amygdala hyperreactivity is a fundamental endophenotype of major depressive disorder, linked to threat bias and problems with emotion regulation, and is reduced after single-session acupuncture as well as after multi-week courses of acupuncture. Hippocampal functional connectivity and gray matter volume are augmented, suggesting that acupuncture could partially reverse the hippocampus structural changes induced by stress through mechanisms of neurotrophin upregulation as seen in preclinical acupuncture studies [17] in longitudinal designs. Finally, the neurochemical findings of the PET study suggest a molecular dimension, in which acupuncture at anatomically distinct locations in limbic and brainstem circuits affects serotonin transporter regulation and opioid system hypofunction, both of which are involved in the pathophysiology of depression.

### **4.2 Specificity of Acupuncture Effects Relative to Sham**

A critical interpretive challenge concerns the specificity of acupuncture effects relative to sham controls. Sham procedures, whether via retractable needles at non-acupoints, superficial needling, or mock transcutaneous stimulation, are themselves active procedures capable of eliciting peripheral afferent signals and non-specific expectation effects. Several included studies reported neuroimaging changes in sham groups, albeit of smaller magnitude or distinct topography compared to verum acupuncture. This observation does not negate acupoint specificity but highlights the necessity of rigorous between-group comparisons rather than reliance on within-group pre-to-post analyses.

Notably, gray matter volumetric gains, serotonin transporter binding changes, and opioid receptor availability alterations were statistically larger in verum than sham conditions across included studies, providing evidence that acupoint location and needling depth contribute to the observed neurobiological effects beyond non-specific context [10, 12, 13].

### **4.3 Methodological Considerations and Limitations**

This review has a number of methodological limitations that constrain the conclusions that can be drawn. Sample sizes in the neuroimaging studies are still small, with a limited ability to reliably detect moderate effect sizes. Acupuncture protocols vary in acupoints, needle gauge, retention time, stimulation frequency and number of sessions, without allowing dose-response modeling. Most of the research has concentrated on the short term results and the persistence of the neuroimaging changes has been poorly characterized. Most studies also used symptom rating scales as the only clinical outcome measure, which may not adequately reflect dimensional aspects more pertinent to the respective neural targets. The use of pipelines in neuroimaging was variable across studies, with differences in the preprocessing, parcellation scheme used, and statistical thresholds leading to variability across studies and preventing direct comparisons. Correlational findings suggest a mechanistic link between the observed neuroimaging changes and clinical improvement; however, the link needs to be formalized with appropriate mediation analyses in large-scale trials.

### **4.4 Clinical Implications and Future Directions**

Despite these challenges, the neuroimaging findings reported here have several clinical implications. The acupuncture effects of default mode network normalization and amygdala reactivity reduction may represent endophenotypes of preferential response to acupuncture, and patients with high trait rumination and threat-bias endophenotypes may be preferential candidates for acupuncture treatment, which can be tested using precision psychiatry protocols that use baseline neuroimaging as predictive biomarkers [18]. Such overlap of acupuncture targets with known antidepressant targets at common circuit nodes, including serotonergic raphe projections and prefrontal-amygdalar control pathways, offers a mechanistic explanation as to why combination therapy is supported by clinical meta-analyses that show additive effects of acupuncture and selective serotonin reuptake inhibitors (SSRIs) over pharmacotherapy alone [19].

Mediation analyses that formally test whether changes in neuroimaging are mediators of clinical response would be a particularly important methodological advancement, changing the study of brain imaging from associational to mechanistic inference. A further priority in relation to precision-medicine research is the identification of neural markers of acupuncture response at baseline, which will enable the tailoring of acupuncture treatment delivery to each patient.

## **5. Conclusion**

Acupuncture has been shown to have measurable, reproducible and mechanistically consistent effects on centrally disrupted neural systems over the last 10 years in neuroimaging studies related to MDD. These include large-scale network dynamics, corticolimbic circuit recalibration, hippocampus and prefrontal (PFC) structural plasticity, serotonergic and opioidergic neurochemical modulation, and cortical oscillatory reorganization. The fact that all these studies were performed in different laboratories, by different groups of patients and using different imaging techniques increases the

confidence that the effects observed are not just due to some non-specific mechanism. However, the field is still not mature in the number of participants, standardization of protocols, length of follow-up, and testing of potential mediators in order to make clear and definitive clinical recommendations. The best and most direct route to biological credibility and clinical optimization of acupuncture is continued investment in well-designed acupuncture trials using neuroimaging.

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