

Critical Review

Inserting Needles Into the Body: A Meta-Analysis of Brain Activity Associated With Acupuncture Needle Stimulation

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Abstract: Acupuncture is a therapeutic treatment that is defined as the insertion of needles into the body at specific points (ie, acupoints). Advances in functional neuroimaging have made it possible to study brain responses to acupuncture; however, previous studies have mainly concentrated on acupoint specificity. We wanted to focus on the functional brain responses that occur because of needle insertion into the body. An activation likelihood estimation meta-analysis was carried out to investigate common characteristics of brain responses to acupuncture needle stimulation compared to tactile stimulation. A total of 28 functional magnetic resonance imaging studies, which consisted of 51 acupuncture and 10 tactile stimulation experiments, were selected for the meta-analysis. Following acupuncture needle stimulation, activation in the sensorimotor cortical network, including the insula, thalamus, anterior cingulate cortex, and primary and secondary somatosensory cortices, and deactivation in the limbic-paralimbic neocortical network, including the medial prefrontal cortex, caudate, amygdala, posterior cingulate cortex, and parahippocampus, were detected and assessed. Following control tactile stimulation, weaker patterns of brain responses were detected in areas similar to those stated above. The activation and deactivation patterns following acupuncture stimulation suggest that the hemodynamic responses in the brain simultaneously reflect the sensory, cognitive, and affective dimensions of pain.

Perspective: This article facilitates a better understanding of acupuncture needle stimulation and its effects on specific activity changes in different brain regions as well as its relationship to the multiple dimensions of pain. Future studies can build on this meta-analysis and will help to elucidate the clinically relevant therapeutic effects of acupuncture.

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What happens to a person if a needle is inserted into the body? The first intuitive answer is that it will evoke pain, or more accurately, a painful sensation. Interestingly, that exact type of treatment, consisting of “inserting needles into the body at specifically defined points and manipulating them,” is called acupuncture. The word acupuncture comes from the Latin words *acus*, meaning needle, and *pungere*, meaning to prick, and it has been used for pain-relieving therapeutic purposes in the East Asian medical system for more than 2,000 years.^{21,56,60} The clinical effects of

acupuncture have been generally accepted and used worldwide for the treatment of particular symptoms, especially pain.^{3,7,26,59,60}

Acupuncture and its underlying effects have attracted much scientific interest in the past few decades. In particular, most research has focused on “specifically defined points” rather than “inserting needles into the body”. The “specifically defined points” (ie, acupoints) are considered to be important because the classical theory of traditional Chinese, Eastern, and Oriental medicine claims that “acupoint specificity,” or the specific stimulation of well-defined acupoints, results in a clinical effect and that the stimulation of different acupoints results in different effects.^{10,15,54,57} Recently, methods for imaging brain functions, such as functional magnetic resonance imaging (fMRI), have been increasingly used to assess the dynamic response patterns of the brain to acupuncture stimuli, and a number of studies have attempted to confirm this “acupoint specificity” hypothesis.^{14,16,39-41,46,63,64} However, the results are largely heterogeneous, and thus there is a great amount of discrepancy throughout the literature, which results in a lack of convincing evidence to validate this hypothesis.^{6,23,25,32,58} One main reason for this heterogeneity is the choice of a control for these experiments. In particular, these studies compare the stimulation of 1 point of the body to the stimulation of another point of the body (ie, acupoint versus nonacupoint) to prove “acupoint specificity,” which is not an appropriate control in functional neuroimaging experiments.^{10,43}

When assessing common brain responses reported in various functional neuroimaging studies of acupuncture, brain areas such as the somatosensory and association cortices (SI and SII), cingulate cortex, amygdala, hippocampus, thalamus, and insula have typically been evaluated regardless of whether an acupoint or nonacupoint was stimulated.^{5,23,27-29,31,34,48,61,62} These distributed brain areas seem to largely overlap with a network of brain structures called the pain matrix, which refers to a pain-specific network in the brain that exhibits specific patterns of brain responses elicited by nociceptive stimuli.³⁰ Pain has been described as “a multitude of different, unique experiences,”⁴⁵ and according to Melzack et al,³⁰ pain sensation is a result of the multidimensional interaction between the sensory-discriminative, cognitive, and affective-motivational components of pain. With advances in functional neuroimaging, each of these pain-related components has been ascribed to different structures of the pain matrix in the brain; for example, the lateral pain system, which projects through a specific set of lateral thalamic nuclei to the primary somatosensory cortex, is thought to represent the sensory-discriminatory aspects of pain, while the medial pain system, which projects through the various medial thalamic nuclei to the anterior cingulate cortex (ACC) and the insula, is known to represent the affective components of pain.^{2,33,55}

In the present study, we examined brain responses to acupuncture stimulation with a main focus on inserting needles into the body; furthermore, we performed a meta-analysis of acupuncture studies, where acupunc-

ture stimulation was defined as a mechanical needle stimulation that penetrated the skin. We did not focus on specifically defined points, which means that we did not limit the site of needle penetration to a particular set of acupoints. From a physiological point of view, it is assumed that the experience of having needles inserted into the body mainly consists of the following 3 components: 1) pain; 2) somatosensory/tactile sensation; and 3) cognitive factors, including expectation, placebo effects, and sociocultural context.³⁷ We focused on determining the cortical regions that were consistently activated due to acupuncture needle penetration and compared those regions to commonly activated and deactivated brain networks that are associated with pain or somatosensory/tactile sensation. Thus, we assessed studies that implemented different types of nonpenetrating tactile stimulation as a control. Cognitive factors are also known to considerably contribute to the ascribed clinical effects of acupuncture; however, it was difficult to specify them in this study, and as other reviews have already focused on these factors, we decided not to address this question in the present study.¹ To date, very few systematic reviews of brain activation in response to acupuncture stimulation have been performed^{13,17,38}; on the basis of previous brain imaging studies, our goal was to provide an overview of the literature that describes the brain’s responses to acupuncture needle penetration.

Methods

Study Selection

Studies that were published prior to September 2011 were selected for inclusion in our meta-analysis from the BrainMap (www.brainmap.org^{24,35}) and Pubmed (www.pubmed.org; search strings: “acupuncture AND fMRI”) databases. The selection criteria for “acupuncture stimulation” studies included the following: 1) the use of fMRI to study brain activity in healthy adults during acupuncture stimulation; 2) the inclusion of needle-acupuncture penetrating the skin and the exclusion of other types of acupuncture, such as electric or laser acupuncture; 3) the inclusion of a contrast of tactile stimulation against the general task baseline in their data analyses (eg, von Frey filaments or nonpenetrating placebo needles); 4) the reporting of results as 3-dimensional coordinates in stereotactic space; and 5) the use of English as the written language. On the basis of these criteria, 28 articles were deemed suitable for the meta-analysis.

Among these 28 publications, the results of 51 “acupuncture stimulation” experiments defined as above were selected for further analysis, which varied in the number of participants (9–67), the duration of needle stimulation (30–120 seconds), and the number of described foci (2–28) used. The type of controls also varied among these 28 publications, and the results of 10 “tactile stimulation” experiments were selected for further analysis, which utilized control tasks that provided contact with the skin, but did not penetrate the skin, and included a tactile

sensation, such as a superficial pricking with von Frey filaments or nonpenetrating placebo needles. All stimulation foci were acupoints. The results of these experiments were then analyzed separately to reveal the neural correlates of acupuncture stimulation, and contrast and conjunction analyses (ie, acupuncture versus tactile stimulation) were performed to make comparisons between the results of the studies that were included.

Activation Likelihood Estimation (ALE) Meta-Analysis

All analyses were performed using the 2.1 version of the GingerALE (www.brainmap.org/ale) application, which was based on the revised version¹⁹ of the ALE approach to coordinate-based meta-analysis of neuroimaging data.³⁵ The algorithm aims to identify the brain areas that are related to a convergence of activations across a series of experiments; it also aims to determine whether the clustering of activity is greater than would be expected from the null distribution of a random spatial association between the results that were obtained in the analyzed experiments. The coordinates reported in 2 of the studies that were included in the meta-analysis were determined according to the standard space of the Montreal Neurological Institute, and these coordinates were converted to Talairach space coordinates using formulas that were provided by Matthew Brett (<http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>). The space for the analysis was divided into 2- × 2- × 2-mm voxels, and a Gaussian filter with a full-width at half-maximum of 15 mm was used to generate the ALE map. Each ALE map was reported with a corrected *P* value of < .05. ALE values were overlaid onto the Colin brain anatomical template (available at <http://brainmap.org/ale/colin1.1.nii>), which had been normalized to the Talairach space using the Multi-image Analysis GUI (Mango) image processing system (<http://ric.uthsca.edu/mango>). The resulting brain areas were anatomically labeled by referencing them to probabilistic cytoarchitectonic maps of the human brain using the SPM Anatomy Toolbox.²⁰

Results

ALE Meta-Analysis for Acupuncture Stimulation

The results of the ALE analysis for all of the studies that used acupuncture stimulation can be found in Fig 1, and specific cluster details are reported in Table 1. The analysis indicated that common activation patterns occurred in response to acupunctural stimulation in various brain regions, such as the insula, thalamus, ACC, SII, primary visual cortex, inferior frontal cortex, superior temporal cortex, superior temporal gyrus, amygdala, and cerebellum. The analysis also demonstrated that common deactivation patterns occurred in response to acupunctural stimulation in various brain regions, such as the medial prefrontal cortex (mPFC), subgenual ACC, caudate, amygdala, posterior cingulate cortex (PCC), thalamus, parahippocampus, and cerebellum.

ALE Meta-Analysis for Tactile Stimulation

The results of the ALE analysis for all of the studies that used nonpenetrating tactile stimulation can be found in Fig 2, and specific cluster details are reported in Table 2. The analysis indicated that common activation patterns in response to tactile stimulation occurred in brain regions such as the insula, SI, SII, inferior frontal cortex, putamen, and cerebellum. It also demonstrated that common deactivation patterns in response to tactile stimulation occurred in brain regions such as the ACC, parahippocampus, and precuneus.

Discussion

The main objective of this study was to characterize the brain's response pattern to inserting needles into the body using an ALE meta-analysis, and we found common patterns of activation and deactivation in the brain that were associated with acupuncture needle stimulation.

Activation Patterns Following Acupuncture Stimulation

The current meta-analysis showed that penetrating acupuncture needle stimulation evoked brain activation in the insula, thalamus, ACC, SII, primary visual cortex, inferior frontal cortex, superior temporal cortex, superior temporal gyrus, and cerebellum (Fig 1). These results suggest the activation of the sensorimotor cortical network, which includes brain areas such as the insula, thalamus, SI and SII, also described as parts of the lateral pain system, representing the sensory-discriminatory dimensions of pain.^{18,49} Many fMRI studies have described the activation of these sensorimotor brain areas as a common feature of acupunctural stimulation.^{23,27,31,34,47,61,62} Various sorts of pain sensations such as soreness, aching, or dull pain seem to be closely linked with the activation of these brain areas, as has been reported by previous studies using the techniques of percept-related fMRI.⁴⁹ Moreover, stronger activations of these areas seem to reflect pain-associated components of acupunctural needle stimulation, as it often correlates with stronger psychophysical ratings of pain, especially when compared to controls such as tactile stimulation.^{23,27,31,34,47,49,61,62} Thus, activation in sensorimotor brain areas such as the insula, thalamus, SI, and SII presumably reflects involvement of the sensory pain-associated components of acupunctural needle stimulation.

Deactivation Patterns Following Acupuncture Stimulation

The current meta-analysis revealed that penetrating acupuncture needle stimulation is associated with the widespread deactivation of brain regions, such as the mPFC, subgenual ACC, caudate, amygdala, PCC, thalamus, parahippocampus, and cerebellum (Fig 1). These results were consistent with findings from previous studies, which indicated that acupuncture stimulation results in

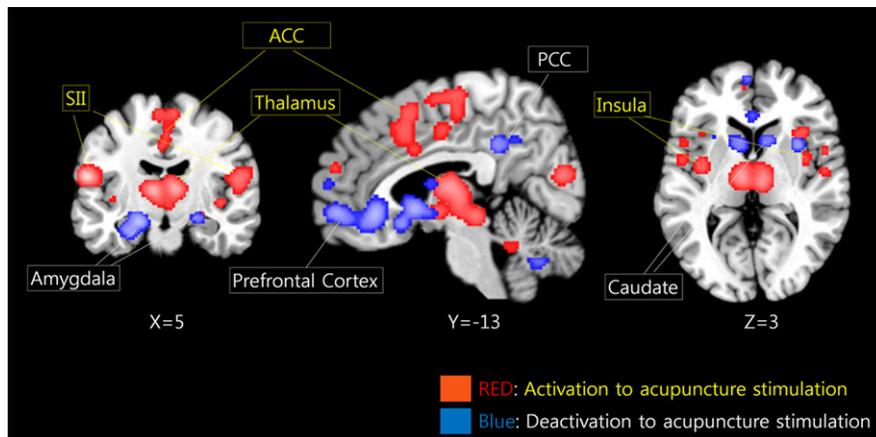


Figure 1. Brain areas associated with acupuncture stimulation that exhibited increased (red) and decreased (blue) activity. ALE maps were computed using GingerALE v.2.1 at a false discovery rate corrected threshold of $P < .05$ with a minimum cluster size of $K > 200$ mm^3 . ALE values were overlaid onto the Colin brain anatomical template and normalized to the Talairach space using the Mango image processing system.

the extensive deactivation of the limbic-paralimbic neocortical network, including the mPFC, subgenual ACC, PCC, caudate, amygdala, hippocampus and parahippocampus.²³ These brain areas have also been suggested

to modulate the cognitive and affective dimensions of pain, and it has been postulated that the anti-pain and anti-anxiety effects of acupuncture, including other regulatory effects, are mediated through the deactivation of these limbic-paralimbic-neocortical circuits.²³ Some behavioral data might support this hypothesis, as it has been shown that the same areas are activated by exposure to painful stimuli^{4,8} and that deactivation of these regions was significantly attenuated when psychophysical response of sharp pain was recorded.^{28,29} Furthermore, it has been reported that stronger deactivation of these regions is related to a greater subjective rating of relaxation.⁴⁹

The regions in the limbic-paralimbic neocortical network that are deactivated during acupuncture stimulation seem to have similar spatio-temporal characteristics to the core regions in the default-mode network.²⁹ This network, also known as the task-negative network, consists of brain regions that are highly active when an individual is in a resting state but shows patterns of deactivation when exposed to external stimuli.^{9,51} Several studies have shown that the activity levels in various structures in this network, such as the PCC, inferior parietal cortex, and mPFC, were reduced in response to different types of painful stimuli.^{42,44} In a recent study, Kong et al³³ found that mild heat pain stimulation evoked a widespread fMRI signal decrease in several brain regions of the default-mode network, including the mPFC, PCC/precuneus, and temporal gyrus. Thus, an alternative explanation for the deactivation that is evoked by acupuncture needle stimulation could be a shift in activity that occurs between monitoring internal physical and mental states and monitoring the external environment. Further research is needed to validate these hypotheses.

Activation and Deactivation Patterns Following Tactile Stimulation

Although coherent activation and deactivation patterns associated with tactile stimulation were also observed in the sensorimotor and limbic-paralimbic brain

Table 1. Results of ALE for Acupuncture Stimulation

REGION	SIDE	BA	X	Y	Z	VOLUME (MM ³)	ALE
Positive response							
Thalamus			-8	-14	6	11,888	.040978
ACC	B	24	2	14	42	8,696	.025781
Secondary somatosensory cortex	L	40	-56	-20	18	8,000	.055501
Secondary somatosensory cortex	R	40	60	-20	20	6,168	.045275
Primary visual cortex	B	18	4	-80	16	1,712	.028203
Insula	L	13	-38	-6	0	1,280	.026712
Insula	R	13	38	-2	-4	1,112	.018747
Inferior frontal gyrus	L	22	-50	12	-2	1,032	.02271
Insula	R	13	36	20	2	800	.019462
Superior temporal gyrus	L	44	-50	0	6	696	.018961
Cerebellum			0	-50	-28	632	.020992
Amygdala	R		24	-6	-14	560	.017999
Superior temporal gyrus	R	22	54	6	0	416	.015901
Middle frontal gyrus	R	46	44	34	14	240	.017808
Superior frontal gyrus	L	9	-26	56	26	224	.019147
Superior temporal gyrus	L	22	-44	-58	16	216	.019465
Negative response							
Medial frontal gyrus	B	32	0	34	-10	13,520	.031677
Subgenual ACC	B	25	4	8	-6		.022789
Caudate	B		-8	10	0		.017922
Amygdala	L		-20	-8	-20	4,896	.031945
PCC	R	31	4	-40	34	1,808	.01836
Clastrum	R		34	10	0	816	.021148
Thalamus			0	-2	10	512	.0204
Amygdala	R		24	-10	-16	496	.01728
PCC	R	30	12	-50	12	400	.016869
Cerebellum (culmen)	R		36	-38	-28	288	.017411
Parahippocampus	R		28	-40	-6	272	.016638
Cerebellum (tonsil)	R		6	-64	-38	200	.013661

Abbreviations: B, bilateral; L, left; R, right; BA, Brodmann area.

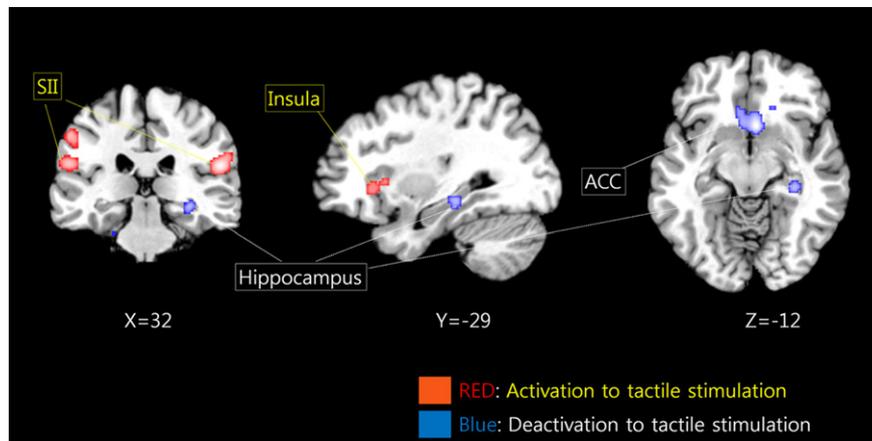


Figure 2. Brain areas associated with tactile stimulation that exhibited increased (red) and decreased (blue) activity. ALE maps were computed using GingerALE v.2.1 at a false discovery rate corrected threshold of $P < .05$ with a minimum cluster size of $K > 200 \text{ mm}^3$. ALE values were overlaid onto the Colin brain anatomical template and normalized to the Talairach space using the Mango image processing system.

networks, the changes in the activity levels of various brain regions were markedly weaker, and they were limited to such an extent that the observed changes in activation were not statistically significant (Fig 2).

Pain-Specific Overlapping Activation and Deactivation Patterns

According to the results of the present study, the brain areas activated and deactivated by acupuncture needle stimulation largely overlap with the brain regions that constitute the so-called pain matrix.^{2,33,55} Pain encompasses a multitude of stimuli. In the current analysis, we only included acupuncture studies that consisted of mechanical acupuncture needle stimulation that penetrated the skin. It is natural to assume that penetration of the skin is painful. This could explain the common brain responses to acupuncture needle stimulation. However, the more essential question is whether the main clinical effect of acupuncture is due to

noxious stimulation through diffuse noxious inhibitory controls.⁵² The existence of different acupuncture stimulation methods, such as laser or electric acupuncture, that use other types of stimuli that are not painful refutes this view. However, it would be interesting to test whether other sorts of painful stimuli, such as heat, cold, or pressure, can produce similar analgesic effects comparable to acupuncture.^{18,50} The existence of different alternative and complementary medical treatments, such as moxibustion or acupressure, supports this idea. Further studies and analyses are needed to find more definite answers to these questions.

Potential Limitations

Basic Limitations of Meta-Analyses

The present study is an ALE meta-analysis of existing fMRI data, which is basically a localization technique that provides information about where the most consistent patterns of activation are located in the brain; this technique does not provide information about the magnitude of the effects.²² Although this is a powerful technique that provides considerable neuroanatomical insights into the human brain, it cannot provide a definite account of the role and functions of each brain structure or offer a complete explanation of the resulting clinical effects. Moreover, it should be noted that the process of converting fMRI data into standard coordinates across various studies can sometimes result in misidentifications of brain regions in the meta-analysis.³⁶ Finally, a meta-analysis is limited by the number of published studies available. While there are a number of questions that deserve further analysis, these questions cannot be investigated if there are not enough studies that can be categorized and labeled together, which is often the case in the field of acupuncture research.

Limitations Due to the Experimental Condition

Most of the acupuncture experiments included in our study were carried out in an experimental environment,

Table 2. Results of ALE for Tactile Stimulation

REGION	SIDE	BA	X	Y	Z	VOLUME (MM ³)	ALE
Positive response							
Secondary somatosensory cortex	L	40	-58	-30	22	2,112	.015106
Cerebellum (vermis)			0	-70	-24	2,040	.016876
Secondary somatosensory cortex	R	40	56	-30	20	2,016	.018983
Primary somatosensory cortex	L	2	-56	-28	42	656	.015758
Insula	R	13	30	26	-4	416	.012891
Putamen	L		-22	6	8	272	.012383
Insula	R	13	34	16	0	240	.011129
Inferior frontal gyrus	R	13	42	26	4	200	.010489
Negative response							
Subgenual ACC	B	25	6	16	-12	1,504	.017362
Precuneus		31	0	-64	30	304	.013042
Parahippocampus	R	36	32	-30	-12	296	.012813

Abbreviations: B, bilateral; L, left; R, right; BA, Brodmann area.

which is partly due to the nature of the design of an fMRI experiment. However, pain experiments have repeatedly shown that the brain network for pain perception partially differs depending upon the condition (ie, experimental versus clinical) and type of pain (ie, acute versus chronic).^{2,12} Thus, the patterns of brain activation and deactivation observed in the studies included in our analysis could be partly due to the experimental condition used, and a different pattern may have resulted with real patients in a clinical environment. Moreover, the long-term analgesic effects of acupuncture are known to persist for quite some time in clinics¹¹; however, it is only possible to evaluate the short-term effects that are visible in the brain using neuroimaging techniques.^{13,17,38} Studies that evaluate the time course of actions in the brain for a longer period of time during clinical acupuncture treatment are still lacking.

The Point-Specificity Problem

Previous fMRI investigations have claimed that there are correlations between the stimulation of specific acupuncture points and the corresponding cortical responses, which suggests that specific acupuncture points have salubrious effects on target organ systems that are located far from the site of needle insertion. Cho et al¹⁴ first reported that the acupunctural stimulation of vision-related acupuncture points, such as BL67, activates the visual cortex. A group of subsequent studies attempted to duplicate this work in various ways^{39,53} but were unable to replicate the results, which leaves the acupuncture point specificity hypothesis open to debate. Gareus et al²⁵ reported that acupuncture at the vision-related acupuncture point GB37 did not produce any activation in the visual cortex or its associated areas. An fMRI study by Kong et al³² indicated that acupunctural stimulation of 2 vision-related acupoints (BL60 and GB37) and a nonacupuncture point resulted in similar widespread deactivation patterns in the occipital lobe. Wesolowski et al⁵⁸ also reported a lack of evidence for the specificity of the ear-specific acupuncture point GB43 in relation to the activation of the primary auditory

cortex. Therefore, at least according to recent literature, it seems that there is a more or less consistent activation and deactivation pattern of brain responses to acupuncture needle stimulation, regardless of specifically defined points. Certainly, the acupoint specificity hypothesis cannot be totally ruled out, as there are more than 360 acupuncture points in the body, each of which may potentially produce different brain activation/deactivation patterns according to the classical acupuncture theory.

In the present study, we evaluated brain responses produced as a result of "inserting needles into the body" and therefore included brain activation patterns that resulted from the activation of more than 20 different acupoints; we did not evaluate specific sets of acupoints and mostly neglected the specific differences between acupoints. Therefore, it is difficult to determine any acupoint-specific patterns of activation or deactivation from our current analysis.

Conclusion

In summary, the results of our ALE meta-analysis of fMRI studies revealed common activation patterns in the sensorimotor cortical network and deactivation patterns in the limbic-paralimbic-neocortical network following acupuncture needle stimulation. A similar but weaker pattern was observed with control tactile stimulation. These results suggest that the hemodynamic responses that occur in the brain in response to acupunctural stimulation reflect not only sensory-discriminative, but also cognitive and affective dimensions of pain. This finding also implies that the clinical effects of acupuncture stimulation can potentially be improved and modulated together with other factors (eg, sociocultural and contextual-environmental factors), which can also influence different aspects of pain.³⁷ Furthermore, future studies should focus on the associations between changes in brain response patterns to acupuncture and the therapeutic effects of acupuncture across different disorders.

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