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Investigation of the large-scale functional brain networks modulated by acupuncture

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Abstract

Previous neuroimaging studies have primarily focused on the neural activities involving the acute effects of acupuncture. Considering that acupuncture can induce long-lasting effects, several researchers have begun to pay attention to the sustained effects of acupuncture on the resting brain. Most of these researchers adopted functional connectivity analysis based on one or a few preselected brain regions and demonstrated various function-guided brain networks underlying the specific effect of acupuncture. Few have investigated how these brain networks interacted at the whole-brain level. In this study, we sought to investigate the functional correlations throughout the entire brain following acupuncture at acupoint ST36 (ACUP) in comparison with acupuncture at nearby nonacupoint (SHAM). We divided the whole brain into 90 regions and constructed functional brain network for each condition. Then we examined the network hubs and identified statistically significant differences in functional correlations between the two conditions. Following ACUP, but not SHAM, the limbic/paralimbic regions such as the amygdala, hippocampus and anterior cingulate gyrus emerged as network hubs. For direct comparisons, increased correlations for ACUP compared to SHAM were primarily related with the limbic/paralimbic and subcortical regions such as the insula, amygdala, anterior cingulate gyrus, and thalamus, whereas decreased correlations were mainly related with the sensory and frontal cortex. The heterogeneous modulation patterns between the two conditions may relate to the functional specific modulatory effects of acupuncture. The preliminary findings may help us to better understand the long-lasting effects of acupuncture on the entire resting brain, as well as the neurophysiological mechanisms underlying acupuncture.

Keywords: Acupuncture specificity; Functional correlations; Functional magnetic resonance imaging (fMRI); Sustained effects

1. Introduction

Acupuncture is an ancient Chinese healing technique that has been used to treat various illnesses for thousands of years [1]. In recent years, it has gained great popularity as an alternative and complementary therapeutic intervention in the Western medicine [2–11]. However, the neural mechanism underlying acupuncture is still unknown, and various controversies remain [12]. In the past decades, noninvasive functional magnetic resonance imaging (fMRI) techniques have provided new insights into the anatomy and physiological function underlying acupuncture [2–11].

Previous neuroimaging studies have primarily focused on the neural activities involving the acute effects of acupuncture [6,7,9,13]. According to the theory of the Traditional Chinese Medicine, acupuncture can induce long-lasting effects even after the needling manipulation being terminated [14]. In addition, one recent study reported time-variability and long-lasting effects during the course of multiple-block acupuncture [3]. Other studies have also demonstrated that neural responses induced by acupuncture have the saliently

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time-varying characteristics [11,15]. Therefore, the sustained effects should be taken into account for which the actual effect of acupuncture can be appropriately studied [16]. Recently, several researchers have begun to pay attention to the sustained effect of the acupuncture and its influence on the resting brain [2–5,10,11,15]. Dhond et al. revealed that acupuncture can influence intrinsic connectivity of the default mode network and sensorimotor network in the poststimulus resting brain [5]. Our group also reported that acupuncture could exert modulatory effect on the insula-anchored brain network during the poststimulus resting period [2]. Evidence from another report suggested that a set of brain regions activated by acupuncture stimulation exhibited high temporal coherences in the poststimulus resting state [4]. Collectively, these studies demonstrated the existence of various function-guided brain networks underlying the prolonged effect of acupuncture.

Most of the previous studies on acupuncture focused on the functional connectivity associated with one or a few preselected seed regions of interest (ROIs). Although ROI-based analysis can identify brain regions functionally connected to the initially selected brain regions, it is unable to completely characterize the joint interactions among multiple brain regions in the entire resting brain networks. Recently, several researchers have brought a fresh perspective to investigate the functional correlations in the resting brain networks at the whole-brain level [17–20]. This allows us to quantitatively characterize the global organization and also provides new insight into the topological reconfiguration of the whole brain in response to external task modulations [18]. To our knowledge, few studies have investigated the functional correlations in the entire brain modulated by acupuncture. As a peripheral input to transduce signals into the brain, acupuncture may induce the reorganization of the functional connectivity across different functional brain subsystems. Considering that the acupuncture may exert modulatory effects in the entire brain, we think it will be helpful to investigate the functional correlations from the perspective of whole brain for a better understanding of the basic neurophysiological mechanisms underlying acupuncture.

In this study, we sought to investigate the functional correlations throughout the entire brain during the poststimulus resting period following acupuncture at acupoint ST36 (ACUP) in comparison with acupuncture at nearby nonacupoint (SHAM). To this end, we divided the whole brain into 90 cortical and subcortical regions and constructed functional brain network for each condition. The network hubs were examined, and statistically significant differences were identified by comparing the correlation coefficients of each pair between two conditions [17,19,20]. This allowed us to explore how the large-scale resting brain networks are modulated by acupuncture during the poststimulus period and to test whether the modulatory effects of acupuncture on the whole resting brain networks were functional specific.

2. Materials and methods

2.1. Subjects

In order to reduce intersubject variabilities, all participants were recruited from a homogeneous group of 14 college students (seven males, ages of 24.3±1.8 years). All subjects were right handed and acupuncture naive. Exclusion criteria were any neurological disorder, any medical disorder that would impact the central nervous system, any contraindications to a high magnetic field, as well as any past or current history of psychiatric disorder, substance abuse or treatment with psychiatric medications. After a complete description of the study was given to all subjects, written informed consent was obtained, as approved by a local institutional review board for human studies.

2.2. Experimental paradigm

A newly experimental paradigm, namely, the nonrepeated event-related fMRI design, was adopted to explore the neural responses induced by acupuncture [8]. Both ACUP and SHAM experiments incorporated 1.5-min needling manipulations, preceded by a 1-min rest and followed by another 12.5-min rest scanning (without acupuncture manipulation). The presentation sequence of these two runs was randomized and balanced throughout the subject population, and every subject performed only one run each day, 24 h apart. During the experiment, the subjects were instructed to keep their eyes closed and remain relaxed without engaging in any mental tasks.

Acupuncture was performed at acupoint ST 36 on the right leg (Zusanli, located four finger breadths below the lower margin of the patella and one finger breadth laterally from the anterior crest of the tibia) [8]. A sterile disposable 38-gauge stainless steel acupuncture needle (0.2 mm in diameter and 40 mm in length) was used to deliver acupuncture stimulation. During acupuncture, the needle was rotated manually clockwise and counterclockwise for 1 min at a rate of 60 times/min by a balanced “tonifying and reducing” technique [7]. The precise locations of needling, the presumed acupuncture effects and the stimulation paradigm were not divulged to the subjects. The procedure was performed by the same experienced and licensed acupuncturist on all subjects. Sham acupuncture was initially devised with needling at nonmeridian points (2–3 cm away from ST 36) with needle depth, stimulation intensity and a manipulation method identical to those used in verum acupuncture [8]. For the picture of ST36 and SHAM, please refer to Fig. 1 (top right) in Ref. [8].

2.3. Psychophysical response

At the end of each run, the participant was questioned about aching, soreness, fullness, numbness, dull or sharp pain and any other sensations felt during the stimulation. The intensity of each sensation was measured on a scale from 0 to 10 (0=*no sensation*, 1–3=*mild*, 4–6=*moderate*, 7–8=*strong*, 9=*severe* and 10=*unbearable sensation*). Because sharp pain was considered an inadvertent noxious stimulation, we excluded the subjects from further analysis if they experienced the sharp pain [11]. Among the 14 participants, none experienced the sharp pain. Although sensations such as soreness, numbness and fullness occurred at higher rates among subjects undergoing acupuncture stimulation than among those undergoing sham intervention, no significant differences in the overall frequency of experience were found between acupuncture and sham stimulation control conditions (Fisher's Exact Test, P>.05). The level of sensation was kept low (mild to moderate) throughout these two conditions. Average ratings of the reported five elements of Deqi sensations fell between 0 and 4.0 on the 10.0-point scale for both ACUP and SHAM. The highest scores in individual cases were mainly distributed in the range of 3 to 8.

2.4. Data acquisition and analysis

Images were acquired using a 3-T GE Signa scanner. Head movements were minimized by a custom-built head holder. Thirty-two axial slices (field of view=240 mm×240 mm, 64×64 matrix, 5 mm thickness), parallel to the AC-PC line and covering the whole brain, were obtained using a T2*-weighted single-shot, gradient-recalled echo planar imaging sequence (repetition time=1500 ms, echo time=30 ms, 90° flip angle). After the functional run, high-resolution structural information on each subject was also acquired using three-dimensional MRI sequences with a voxel size of 1 mm^3 for anatomical localization.

All images were preprocessed using SPM5 software. Firstly, the image data underwent slice-timing correction and realignment for head motions using least squares minimization. None of the subjects had head movements exceeding 1 mm on any axis and head rotation greater than 1°. Then, the image data were further processed with spatial normalization based on the Montreal Neurological Institute space and resampled at 2×2×2 mm^3 [21]. After that, the functional images were spatially smoothed with a 6-mm full width half maximum Gaussian kernel. Several procedures were adopted to remove possible spurious variances from the data through linear regression [22,23]: (a) six motion parameters, (b) whole-brain signal averaged over the entire brain, (c) signal from a region in cerebrospinal fluid, (d) signal from a region centered in the white matter, and (e) linear drift. Finally, the fMRI waveform of each voxel was temporally band-pass filtered (0.01 Hz<f<0.08 Hz).

2.5. Interregional correlations computation

The preprocessed data sets were firstly parcellated into 90 cortical and subcortical regions using anatomical templates defined by Tzourio-Mazoyer et al. [24]. For each subject, the time series corresponding to the post-stimulus period of BOLD signal intensities from these brain regions were averaged across voxels within each region, respectively, for each condition. Then the time series were correlated region by region with Pearson's correlation coefficient in each data set, creating two square correlation matrices (90×90) [19,20].

2.6. Functional brain networks construction

Fischer's r to z transformation was applied to improve the normality of the correlation coefficients. The individual z values were entered into a random effect one-sample two-tailed t test (P<.05, multiple comparisons corrected) to determine brain regions showing significant correlations within each condition. To account for multiple comparisons, the Benjamini and Hochberg false discovery rate was applied [25]. The significant correlations within each condition were represented as networks for further analysis.

2.7. Nodal characteristics

We investigated nodal characteristics of the brain networks by exploring "betweenness centrality." According to a previous study, the betweenness B_i of a node i is defined as the number of shortest paths between any two nodes that run through node i [26]. The normalized betweenness were calculated as b_i=B_i/<B>, where B was the average betweenness of the network [27]. b_i is a global centrality measure that captures the influence of a node over information flow between other nodes in the network. The hubs of the functional brain network are the brain regions with the value of b_i greater than 1 standard deviation away from the averaged b_i per network [28].

2.8. Direct comparisons between ACUP and SHAM

For direct comparisons, we performed paired t test (P<.05, multiple comparisons corrected) on all 4005 possible connections represented in the two 90×90 correlation matrices related to ACUP and SHAM to determine the brain regions showing differences in functional correlations between two conditions [17,19,20]. To account for multiple comparisons, the Benjamini and Hochberg false discovery rate was applied [25]. Connections significantly different between ACUP and SHAM were displayed for further analysis. In addition, the parcellation scheme of Mesulam was adopted to examine changes in the functional connectivity of five major functional divisions of the human brain [29].

3. Results

3.1. Network hubs

The significant correlations within each condition were visualized as functional brain networks (shown in Fig. 1). To identify the network hubs, we examined normalized nodal betweenness centrality, b_i, of each cortical region in both networks (listed in Table 1). In the case of ACUP, 11 brain regions including four association regions [middle frontal gyrus, cuneus, superior frontal gyrus (medial)], four paralimbic regions [anterior cingulate gyrus, middle cingulate gyrus, posterior cingulate gyrus, middle temporal gyrus

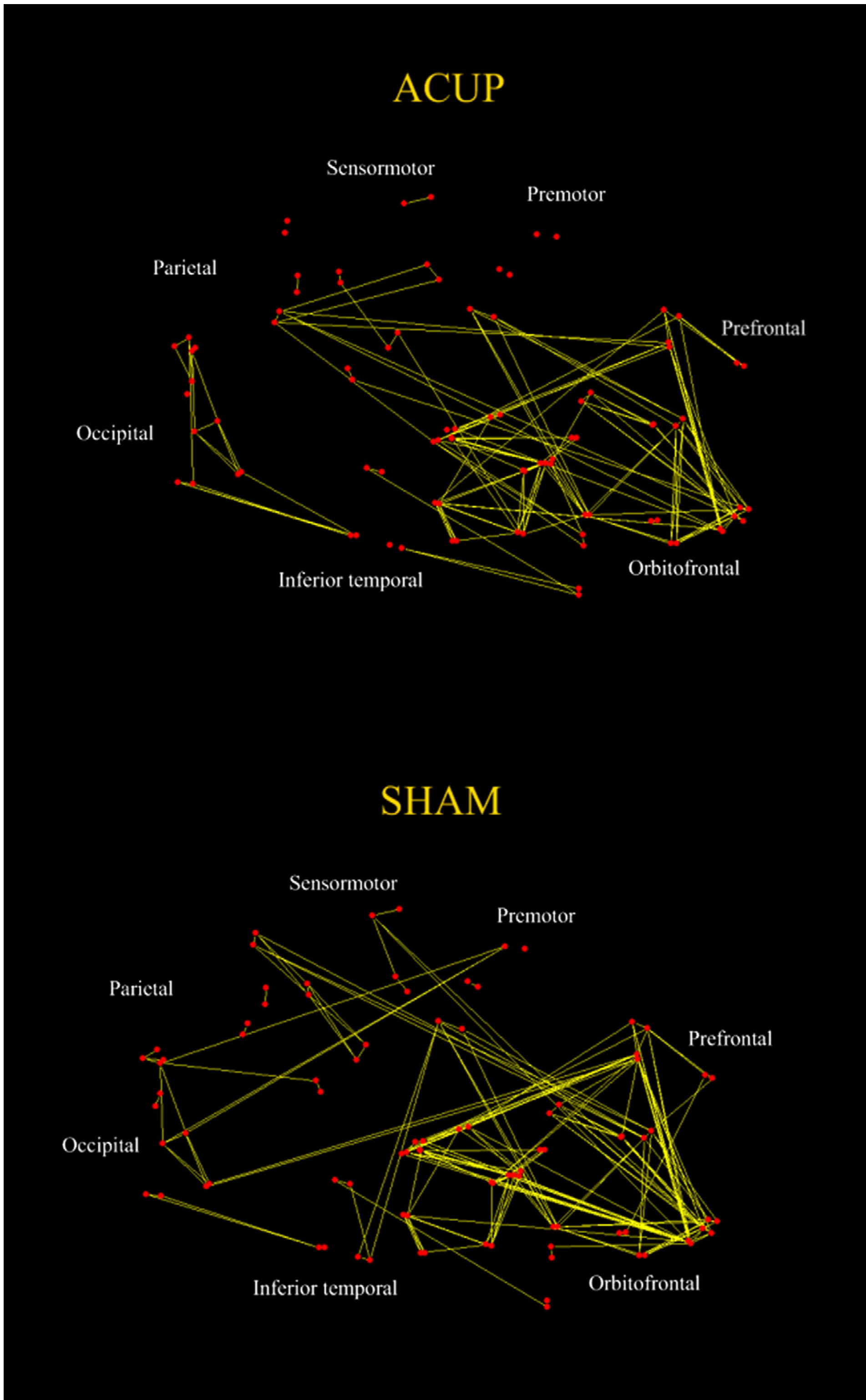

Fig. 1. Graph visualization of the functional brain networks following acupuncture at acupoint ST36 (ACUP) and acupuncture at a nonacupoint (SHAM) represented in a sagittal view of the right side of the brain. Nodes are located according to the *y* and *z* coordinates of the regional centroids in Talairach space (all lines meet $P<.05$, multiple comparisons corrected). Graphs were visualized using Pajek software (vlado.fmf.uni-lj.si/pub/networks/pajek).

Table 1
The hubs of the resting brain networks following acupuncture at acupoint ST36 (ACUP) and acupuncture at nearby nonacupoint (SHAM)

Region	Hem	Classification	b_i	Region	Hem	Classification	b_i
ACUP				SHAM			
OLF	L	Limbic	6.22	OLF	L	Limbic	12.31
MFG	R	Association	5.57	ITG	L	Association	5.70
AMYG	L	Limbic	4.29	MFGorb	R	Paralimbic	4.90
HIPP	R	Limbic	3.67	MFG	R	Association	3.75
MFG	L	Association	3.40	MFG	L	Association	3.11
CUN	L	Association	3.13				
SFGmed	L	Association	2.86				
PCC	L	Paralimbic	2.58				
MTGp	R	Paralimbic	2.31				
ACC	L	Paralimbic	2.26				
MCC	L	Paralimbic	2.21				

The hubs of the functional brain network are the brain regions with the value of the normalized betweenness b_i greater than 1 standard deviation away from the averaged b_i per network [27]. The regions were classified as primary, association, limbic and paralimbic systems as described by Mesulam (1998) [29]. Abbreviations: OLF, olfactory cortex; MFG, middle frontal gyrus; AMYG, amygdala; HIPP, hippocampus; CUN, cuneus; SFGmed, superior frontal gyrus (medial); PCC, posterior cingulate gyrus; MTGp, middle temporal gyrus (temporal pole); ACC, anterior cingulate gyrus; MCC, middle cingulate gyrus; ITG, inferior temporal gyrus; MFGorb, middle frontal gyrus (orbital); L, left; R, right.

(temporal pole)] and three limbic regions (olfactory cortex, amygdala, hippocampus) were identified as the network hubs (listed in Table 1). In the case of SHAM, five brain regions including three association regions (middle frontal gyrus, inferior temporal gyrus), one paralimbic region [middle frontal gyrus (orbital)] and one limbic region (olfactory cortex) were identified as the network hubs (listed in Table 1).

3.2. Direct comparisons between ACUP and SHAM

For directly comparing the connectivity difference between two conditions, paired t test was performed on all 4005 potential connections included in the 90×90 correlation matrices. Compared to SHAM, more increased correlations were found in the poststimulus resting brain network following ACUP. As shown in Table 2 and Fig. 2A, increased positive correlations following ACUP compared with SHAM were mainly related with the limbic and subcortical regions such as the right amygdala (R_AMYG), the right thalamus (R_THA), the right pallidum (R_PAL) and the right olfactory cortex (R_OLF). In contrast, decreased correlations between ACUP and SHAM were primarily related with the association and primary regions such as the left posterior cingulate gyrus (L_PCC) and the frontal cortex. As presented in Table 3 and Fig. 2B, increased negative correlations were mainly related with the limbic/paralimbic and subcortical regions such as the left insula (L_INS), the left anterior cingulate gyrus (L_ACC), R_THA and the R_OLF. In contrast, only one connection related with the frontal cortex was found to be decreased and to have a negative correlation in ACUP compared with SHAM.

4. Discussion

In this article, we investigated the functional brain organizations in the poststimulus resting state following ACUP in comparison with SHAM. Considering that acupuncture can induce long-lasting effects beyond the time it is being administrated, imaging its sustained effect on the entire brain may further help elucidate the neurophysiological mechanisms underlying acupuncture. In comparison with conventional functional connectivity analysis, we examined the distributions of functional correlations throughout the entire brain. We identified network hubs in the poststimulus resting brain following ACUP and SHAM.

Table 2
The significantly different positive interregional correlations between acupuncture at acupoint ST36 (ACUP) and acupuncture at nearby nonacupoint (SHAM) (P<.05, multiple comparisons corrected)

Region 1	Classification	Region 2	Classification	P value
ACUP>SHAM				
R_AMYG	Limbic	R_IFGtri	Association	.0062
R_THA	Subcortical	R_ANG	Association	.0041
R_PAL	Subcortical	L_IOG	Association	.0058
R_OLF	Limbic	R_SFG	Association	.0029
R_OLF	Limbic	R_MFG	Association	.0062
R_HES	Primary	L_FG	Association	.0059
R_FG	Association	L_IOG	Association	.0038
R_FG	Association	L_FG	Association	.0058
L_SFGmed	Association	R_SFG	Association	.0061
L_ITG	Association	L_SFGmed	Association	.0095
ACUP<SHAM				
L_PCC	Paralimbic	R_SFGorb	Paralimbic	.0005
R_HIPP	Limbic	R_HES	Primary	.0027
L_PreCG	Primary	R_IFGoper	Association	.0063
L_SPG	Association	L_SMG	Association	.0076
R_IFGoper	Association	L_IFGtri	Association	.0057

The regions were classified as primary, association, limbic, paralimbic and subcortical systems as described by Mesulam (1998) [29]. Abbreviations: AMYG, amygdala; IFGtri, inferior frontal gyrus (triangular); THA, thalamus; ANG, angular gyrus; PAL, pallidum; IOG, inferior occipital gyrus; OLF, olfactory cortex; SFG, superior frontal gyrus; MFG, middle frontal gyrus; HES, Heschl gyrus; FG, fusiform gyrus; SFGmed, superior frontal gyrus (medial); ITG, inferior temporal gyrus; PCC, posterior cingulate gyrus; SFGorb, superior frontal gyrus (orbital); HIPP, hippocampus; PreCG, precentral gyrus; IFGoper, inferior frontal gyrus (opercular); SPG, superior parietal gyrus; SMG, supramarginal gyrus; L, left; R, right.

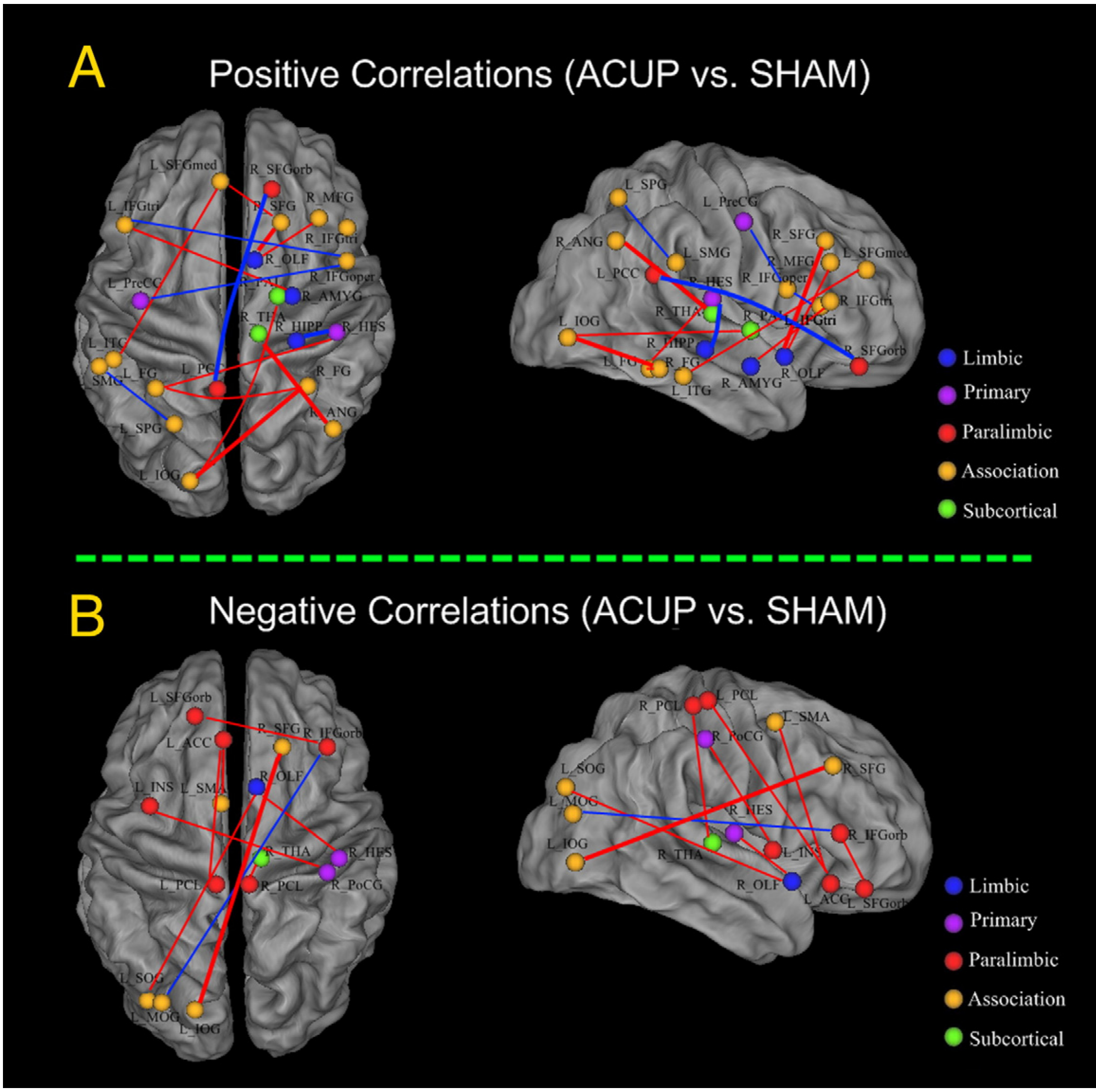

Fig. 2. Graph visualization of the significant differences in correlations between acupuncture at acupoint ST36 (ACUP) and acupuncture at a nonacupoint (SHAM) using Caret software [40]. (A) Positive correlations between ACUP and SHAM. (B) Negative correlations between ACUP and SHAM. The regions were classified as primary, association, limbic, paralimbic and subcortical systems as described by Mesulam (1998) [29]. The red and blue lines indicate the significantly increased and decreased interregional correlations between the corresponding regions, respectively; for the direct comparison, line width is proportional to the significance level (all lines meet $P<.05$, multiple comparisons corrected). Abbreviations: AMYG, amygdala; IFGtri, inferior frontal gyrus (triangular); THA, thalamus; ANG, angular gyrus; PAL, pallidum; IOG, inferior occipital gyrus; OLF, olfactory cortex; SFG, superior frontal gyrus; MFG, middle frontal gyrus; HES, Heschl gyrus; FG, fusiform gyrus; SFGmed, superior frontal gyrus (medial); ITG, inferior temporal gyrus; PCC, posterior cingulate gyrus; SFGorb, superior frontal gyrus (orbital); HIPP, hippocampus; PreCG, precentral gyrus; IFGoper, inferior frontal gyrus (opercular); SPG, superior parietal gyrus; SMG, supramarginal gyrus; INS, insula; PoCG, postcentral gyrus; ACC, anterior cingulate gyrus; SMA, supplementary motor area; PCL, paracentral lobule; SOG, superior occipital gyrus; IFGorb, inferior frontal gyrus (orbital); MOG, middle occipital gyrus; L, left; R, right.

For direct comparisons, statistically significant differences were identified by comparing the correlation coefficients of each pair between two conditions. Since there have been few previous studies reporting the modulation patterns exerted by acupuncture on the entire functional brain networks, identifying functional correlations at the whole-brain level may shed further light on how such peripheral inputs are conducted and mediated through the central nervous system.

The results presented that the network hubs were located in the limbic/paralimbic and association regions and that more network hubs were identified underlying ACUP than SHAM. Network hubs indicated stronger interactions with other brain regions and were considered to be important nodes in this network. This may indicate that more extensive brain regions were involved in the resting brain networks following ACUP than SHAM to achieve its functional specific modulatory effects. In the case of ACUP, the limbic/paralimbic regions such as the amygdala, hippocampus and ACC emerged as the network hubs, suggesting their roles in the functional specific modulatory effects of acupuncture on

Table 3
The significantly different negative interregional correlations between acupuncture at acupoint ST36 (ACUP) and acupuncture at nearby nonacupoint (SHAM) (P<.05, multiple comparisons corrected)

Region 1	Classification	Region 2	Classification	P value
ACUP>SHAM				
L_INS	Paralimbic	R_PoCG	Primary	.0082
L_ACC	Paralimbic	L_SMA	Primary	.0088
L_ACC	Paralimbic	L_PCL	Association	.0056
R_THA	Subcortical	R_PCL	Association	.0068
R_OLF	limbic	L_SOG	Association	.0053
R_OLF	limbic	R_HES	Paralimbic	.0058
L_SFGorb	Paralimbic	R_IFGorb	Paralimbic	.0069
R_SFG	Association	L_IOG	Association	.0003
ACUP<SHAM				
R_IFGorb	Paralimbic	L_MOG	Association	.0050

The regions were classified as primary, association, limbic, paralimbic and subcortical systems as described by Mesulam (1998) [29]. Abbreviations: INS, insula; PoCG, postcentral gyrus; ACC, anterior cingulate gyrus; SMA, supplementary motor area; PCL, paracentral lobule; THA, thalamus; SOG, superior occipital gyrus; OLF, olfactory cortex; HES, Heschl gyrus; SFGorb, superior frontal gyrus (orbital); IFGorb, inferior frontal gyrus (orbital); SFG, superior frontal gyrus; IOG, inferior occipital gyrus; MOG, middle occipital gyrus; L, left; R, right.

the entire resting brain networks. This is consistent with previous study that has suggested the much more frequent involvement of these brain regions in acupuncture [30]. With abundant afferent and efferent nerve fibers between the limbic system and the cortical and subcortical structures, the amygdala appears to play an important role in acupuncture analgesia by emotion modulation [31–33]. Moreover, one recent study has demonstrated the existence of on an amygdala-associated brain network modulated by acupuncture [8]. According to previous studies, hippocampus activity can be strongly modulated by means of both pain and acupuncture stimulation [34,35]. In addition, the ACC contains a high concentration of opioid receptors and has been regarded as a key modulator of the internal emotional response to pain [36]. Taken together, these brain regions (the amygdala, hippocampus, ACC) are largely overlapped with the neural networks for pain perception. Acupuncture may recruit distributed cortical and subcortical brain networks that are also implicated in both inhibitory and facilitating effects in the pain modulation system for both sensation and affective pain perception [8]. These brain regions emerged as network hubs following ACUP, indicating that verum acupuncture may modulate the pain perception by suppressing the action in pain-affective areas. This finding may relate to the functional specific modulatory effects of acupuncture at acupoint ST36. In the case of SHAM, the network hubs included the olfactory cortex, inferior temporal gyrus, middle frontal gyrus (orbital) and middle frontal gyrus. This result is consistent with previous studies that have suggested that acupuncture at a nonacupoint primarily modulate the frontal association cortices [13]. Collectively, the results suggested that a long-lasting effect of acupuncture could modulate intrinsic functional correlations in the entire resting brain networks.

For direct comparisons between the two conditions, more increased correlations were found in the resting brain network following ACUP compared to SHAM. This may be attributed to more varied and stronger sustained effects evoked by verum acupuncture. Notably, increased correlations between ACUP and SHAM were mainly related with the limbic/paralimbic and subcortical regions such as the insula, amygdala, ACC and thalamus. The result is in accordance with previous studies that have demonstrated significant modulatory effects of acupuncture on wide limbic/paralimbic nuclei, subcortical structures and the neocortical system of the brain [7]. The insula has abundant connections and a functional interface between the limbic system and the neocortex, making it a unique position to assign significance to the sensory information it receives [37]. Considering that acupuncture mediates the neurophysiological system with more voluntary components of self-control and self-regulation to achieve homoeostasis, we speculated that the insula may engage in monitoring the ongoing modulation of acupuncture effects on the internal states of the organism [3]. The increase in the connectivity related with the insula suggests acupuncture sustained effects reflecting its specific modulation on the central nervous system [8]. Apart from these, one recent study has demonstrated that there is an insula-anchored brain network modulated by acupuncture [2]. Other brain regions are overlapped with the pain neuromatrix such as pain sensory (the thalamus) and pain affective (the ACC, amygdala). Therefore, the increased connectivity in these brain regions following ACUP may contribute to the specific effect of acupuncture by shifting autonomic nervous system balance and altering the affective and cognitive dimensions of pain processing [38,39]. In contrast, decreased correlations between ACUP and SHAM were mainly related with the association and primary regions such as the sensory and the frontal cortex. The enhanced correlations associated with these brain regions following SHAM compared to ACUP suggested that the postsham modulatory effects on the resting brain networks may primarily be represented in modulating neuron interactions associated with the sensory and frontal cortices [13]. From these observations, we inferred that acupuncture and sham may exert heterogeneous sustained effects on the whole functional brain network.

In conclusion, we investigated the whole functional brain networks in the poststimulus period following ACUP compared to SHAM. The result showed that the limbic/paralimbic regions such as the amygdala, hippocampus and anterior cingulate gyrus emerged as network hubs following ACUP but not SHAM. For direct comparisons, increased correlations for ACUP compared to SHAM were primarily related with the limbic/paralimbic and subcortical regions such as the insula, amygdala, anterior cingulate gyrus and thalamus, whereas decreased correlations were mainly related with the sensory and frontal cortices. These results demonstrated that acupuncture and sham may exert heterogeneous modulation patterns on the whole functional brain network during the poststimulus period. This may relate to the functional specific modulatory effects of acupuncture. The preliminary findings may help us to better understand the long-lasting effects of acupuncture on the entire resting brain, as well as the neurophysiological mechanisms underlying acupuncture.

Acknowledgments

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