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Acupoint-specific fMRI patterns in human brain

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Abstract

Specific central nervous system (CNS) responses to acupuncture have recently attracted attention. It is important to understand the differences in fMRI images of the brain evoked by acupuncture at an acupoint and at a nearby "sham" point. Here, we report analyses of fMRI images of the brains of 37 healthy volunteers in response to acupuncture at Liv3 (Taichong) and LI4 (Hegu) versus their sham points. We found common activation areas in response to Liv3 or LI4 acupuncture in the middle temporal gyrus and cerebellum, along with deactivation areas in the middle frontal gyrus and inferior parietal lobule, compared with the effects of acupuncture at sham points. Acupuncture at Liv3 evoked specific activation at the postcentral gyrus, posterior cingulate, parahippocampal gyrus, BA 7, 19 and 41, but deactivation at the inferior frontal gyrus, anterior cingulate, BA 17 and 18, compared with acupuncture at its sham point. Acupuncture at LI4 evoked specific activation at the temporal pole, but deactivation at the precentral gyrus, superior temporal gyrus, pulvinar and BA 8, 9 and 45, compared with acupuncture at its sham point. These observations reveal that acupuncture at acupoints induces specific patterns of brain activity, and these patterns may relate to the therapeutic effects of acupuncture.

Keywords: fMRI; Brain imaging; Acupuncture; Acupoint specificity

Acupuncture originated in ancient China and has been used by Chinese and other eastern peoples to restore, promote and maintain health [18]. Today, the value of acupuncture is recognized in the Western world. It has been approved as an alternative treatment or a beneficial adjunct for treating drug addiction, asthma, and chronic pain, as well as in stroke rehabilitation [12].

Unfortunately, the underlying mechanisms of acupuncture remain unclear. Since the 1970s, many studies of acupuncture on experimental animals have shown that it modulates the neuro-endocrine and circulatory systems, among others [7]. Studies on human beings were limited by the lack of noninvasive methods, but neuroimaging techniques such as functional MRI (fMRI) and positron emission tomography (PET) provide new tools for such studies. Cho et al. reported that acupuncture at vision-related acupoints in the foot, which are used to treat eye diseases in Traditional Chinese Medicine (TCM), activate the visual cortex bilaterally [2]. Similar results were reported by Siedentopf et al. [13]. Stimulation of the acupoints at LI4 (Hegu), ST36 (Zusanli) and GB36 (Waiqiu) regulates the hypothalamus and limbic system [1,8,9,15,16]. These studies provide primary evidence for the mechanisms underlying acupuncture therapy.

According to TCM, acupuncture at specific acupoints is able to treat certain types of diseases. Zhang et al. have demonstrated that electroacupuncture stimulation (EAS) at two pairs of acupoints in the same spinal segment evokes specific responses in brain images obtained with fMRI [19]. However, it is possible that interfering factors such as pain

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or emotion during acupuncture may also contribute, at least partially, to the pattern of brain activity revealed by fMRI imaging, but they won't contribute to the specific effect of acupoint. So, subtracting fMRI brain images evoked by stimulating the "real" acupoint from those evoked by stimulating a nearby "sham" acupoint, may provide precise and specific patterns related to the therapeutic effect of acupuncture [15]. In this study, we report the patterns of fMRI brain images evoked by stimulating real versus sham acupoints at and near Liv3 and LI4.

The study population comprised 37 healthy right-handed volunteers (23 males and 14 females), aged 26.8 ± 3.6 (mean $\pm$ S.D.) years. No subject had a history of psychiatric or neurological disorders. Volunteers were told they would experience acupuncture stimulation, but they were not told whether it was at a real or a sham acupoint. Each volunteer gave written consent, and the study protocol was approved by the local Ethics Committee of the Chinese Academy of Sciences.

The experiments were carried out with a 1.5 T whole body scanner (Sonata, Siemens, Germany), with a standard head coil. The images covered the whole brain and were parallel to the AC-PC line. Functional images were obtained using a blood oxygenation (BOLD) T2*-weighted gradient-echo EPI sequence with in-plane resolution of 3.44 mm (TR 3000 ms, TE 50 ms, flip angle 90°, field of view 220 mm × 220 mm, matrix 64 × 64, 6 mm slice thickness and 1.2 mm gap).

Each subject only received once acupuncture at one of the four points in a random order: Liv3 (Taichong) on the dorsum of the foot; LI4 (Hegu) on the dorsum of the hand; one sham acupoint near Liv3, approximately 10 mm anterior to Liv3; and the sham acupoint near LI4, approximately 10 mm anterior to acupoint LI4 (Fig. 1). Anatomically, both Liv3 and its related sham acupoint are innervated by the L5 spinal nerve, while both LI4 and its related sham acupoint belong to the C7 spinal segment. And the sham acupoints are not located in the meridian.

The therapeutic effect of acupuncture is known to last several minutes to several hours; this is termed the post-effect. Consequently, the experimental design for therapeutic acupuncture should differ from those for visual or auditory studies [10]. Some researchers have recognized this and thus left a long recovery time between sessions in their fMRI experiments [1,5]. Since the exact duration of the post-effect is unknown, a single block experimental design was adopted in the present study to avoid its influence. Subjects were instructed to remain relaxed, their eyes were covered with blinders (Aearo Co., USA) and their ears were plugged with earplugs (Aearo Co.). The lights in the magnet room were dimmed and there were no sounds other than scanner noise during the measurements. After 62 baseline scans, a silver needle 0.30 mm in diameter and 25 mm long was inserted and twirled for 60 scans; then the needle was withdrawn while fMRI scanning continued, until a total of 402 scans was acquired. All of the acupuncture manipulations were performed by the same expert. During acupuncture, the needle was twirled manually clockwise and anticlockwise at 1 Hz with "even reinforcing and reducing" needle manipulation. The depth of needle insertion at the sham acupoint was approximately 15 mm, the same as at the real acupoint. All the points in this study were on the right hand or foot.

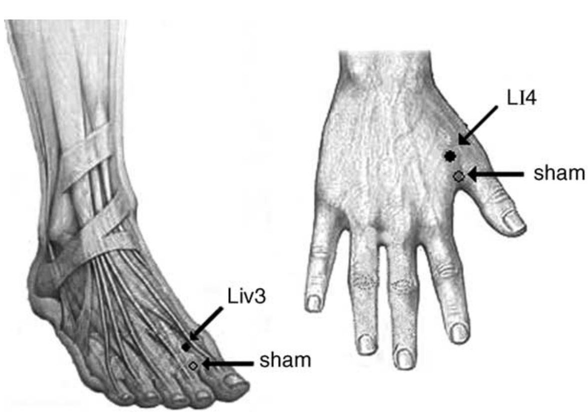

Fig. 1. Anatomical locations of the stimulation points: Liv3, LI4 and nearby sham acupoints (non-acupoints).

The fMRI data were processed with Statistical Parametric Mapping software (SPM99, http://www.fil.ion.ac.uk). The first two volumes were discarded, so every subject had 400 volumes. After realignment, the images were normalized to the Montreal Neurological Institute (MNI) space and then smoothed spatially using a 9 mm × 9 mm × 9 mm Gaussian kernel. The smoothed data were analyzed voxel by voxel at two levels. The first level, for each individual subject, was fixed effects analysis based on the general linear model with a box-car response function as the reference waveform convolved with the Poisson HRF. The cerebral areas activated or deactivated during acupuncture at the real acupoint and the sham acupoint relative to the baseline were obtained. To acquire the specific active areas induced by the stimulating at the real acupoint relative to at the sham acupoint, the second level was performed using random effects analysis based on the two-sample *t*-test model with the results of fixed effects analysis [6]. The results were reported using the coordinates of Talairach space.

Data from three subjects were discarded because of significant head movements, so data from 34 subjects were included in the analysis. The results of random effects analysis between the two real acupoints and the corresponding sham acupoints are illustrated in Fig. 2 and summarized in Table 1 (height threshold, $p = 0.01$ uncorrected, spatial extent threshold, 10 voxels). By using random effects analysis, discrepancies in the activation areas between Liv3 and the corresponding sham acupoint were obtained. Acupuncture at Liv3 significantly activated Brodmann area 19 (BA 19) bilaterally, middle temporal gyrus, cerebellum, ipsilateral posterior cingulate, parahippocampal gyrus, contralateral postcentral gyrus, and BA 7, 20 and 21. However, bilateral inferior frontal gyrus and BA 10, the ipsilateral anterior cingulate, BA 17, 18 and 42, and the contralateral supramarginal gyrus were deactivated.

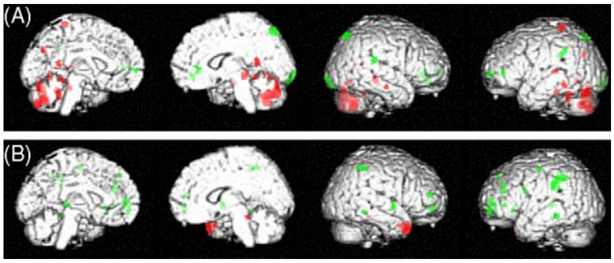

Fig. 2. (A) Activation areas of the real acupoint Liv3 in contrast to the nearby sham acupoint, and (B) LI4 in contrast to a nearby sham acupoint. Red denotes activated areas and green denotes deactivated (decrease of signal intensity change) areas.

Alternatively, acupuncture at LI4, compared with the corresponding sham point, activated ipsilateral middle temporal gyrus, temporal pole and cerebellum. Deactivation occurred in the bilateral middle frontal gyrus and inferior parietal lobule, ipsilateral superior temporal gyrus, as well as contralateral precentral gyrus, BA 8, 9, 45 and 46, the middle temporal gyrus and pulvinar.

The results of random effects analysis showed that stimulation of real acupoints activated and deactivated specific brain areas compared with the responses to stimulation at sham acupoints innervated by the same spinal segments. Clearly, there were more activation areas than deactivation areas induced by stimulation at Liv3 while there were more deactivation areas than activation areas induced by stimulation at LI4, which is consistent with previous reports

Table 1
Brain areas responding to acupuncture of real acupoint vs. sham acupoint

Brain areas	Side	BA	Sign	Liv3 vs. sham				Sign	LI4 vs. sham			
				Talairach (mm)					Talairach (mm)			
				X	*Y*	*Z*	*T*		*X*	*Y*	*Z*	*T*
Superior frontal gyrus	L	8						↓	−26	45	38	3.25
Middle frontal gyrus	L	10	↓	−8	58	−1	2.80	↓	−30	56	−6	3.19
	R	10	↓	16	33	−3	2.90	↓	46	50	−8	3.23
Inferior frontal gyrus	L	44	↓	−50	43	2	3.07	↓	−59	9	22	2.95
Precentral gyrus	L	4						↓	−50	−7	50	3.05
Superior parietal lobule	R	7	↓	18	−69	55	5.86					
Inferior parietal lobule	L	40	↓	−61	−41	35	4.32	↓	−63	−33	35	3.84
	R	40						↓	55	−38	48	3.39
Superior temporal gyrus	L	42	↑	−53	−31	9	2.92					
	R	42	↓	65	−32	20	4.31					
	R	22						↓	53	−4	−3	3.12
Middle temporal gyrus	L	21						↓	−59	−35	−8	3.8
	R	21	↑	65	−16	−14	3.37	↑	50	12	−33	3.3
Temporal pole	R	38						↑	36	20	−28	3.04
Occipital lobe	R	17	↓	20	−95	−2	3.44					
	R	18	↓	16	−101	3	3.35					
	L	19	↑	−40	−74	−13	4.20					
	R	19	↑	30	−66	−5	3.04					
Anterior cingulate	R	24	↓	6	37	4	2.70					
Posterior cingulate	R	29	↑	2	−46	10	3.82					
Parahippocampal gyrus	R		↑	24	−31	−5	3.35					
Thalamus (pulvinar)	L							↓	−12	−31	5	3.17
Cerebellum												
Dentate	L		↑	−14	−48	−26	3.69					
Culmen	L		↑	−32	−48	−18	3.34					
	R		↑	2	−43	−6	3.25	↑	16	−38	−13	2.97
Declive	R		↑	8	−75	−16	3.71					
Pyramis	L		↑	−16	−69	−28	3.69					
	R		↑	18	−60	−29	3.35					
Uvula	R		↑	12	−81	−23	3.16					
Inferior semi-lunar lobule	L		↑	−12	−77	−35	2.98					

(↑/↓) Activation/deactivation. Blank, no change. Abbreviations: B, bilateral; R, right; L, left; BA, Brodmann area.

[2,3,8,13,15]. We demonstrated that stimulation at Liv3 and LI4 induced distinct response patterns, which is consistent with the theory of TCM that activating different acupoints can treat different disorders.

In addition to the specific activation or deactivation areas of acupoints, it may also be interesting to report the areas that are activated or deactivated by both real and sham acupoints. This will help to define any contribution of those interfering factors such as pain or emotion during acupuncture to the pattern of brain activity. The results of comparing acupuncture versus resting state both at real and sham point were got using one sample *t*-test at the second level with the threshold $p < 0.001$ uncorrected. The common activation area of Liv3 and the corresponding sham point is contralateral postcentral gyrus, and the common deactivation areas include bilateral hippocampus/parahippocampus. These areas are related to somatosensory and emotion. The common activation areas of LI4 and the corresponding sham point include contralateral insula, superior parietal lobule, middle temporal gyrus and ipsilateral postcentral gyrus, superior temporal gyrus. In these areas, insula is related to pain and emotion, postcentral gyrus is somatosensory area, superior parietal lobule is related to tactile and the temporal cortex is related to emotion. Most of them have also been reported in previous studies [1,5,15].

One limitation for acupuncture studies is the design of controlled experiments, because few attempts have satisfied Western scientific standards and it is difficult to find a true “sham acupoint” [5,9,14]. In this study, sham acupoint innervated by the same spinal nerve with real acupoint while 10 mm afar from the meridian was used. Because the size of an acupoint is unknown, great caution was practiced by the acupuncturist (Dr. Xu) in determining that site.

The cerebellum was markedly activated in our experiments. Recent fMRI investigations have reported cerebellar activity in studies of electroacupuncture and manual acupuncture [16,17]. The cerebellum is related to motor function. Liv3 is often used to treat motor-related disorders in TCM. It is interesting that more areas were specifically activated by Liv3 than by LI4.

Stimulation of Liv3 activates the visual cortex bilaterally—BA 19, and deactivates ipsilateral BA 17 and 18. Cho et al. [2] reported that visual cortex is activated by acupuncture stimulation of acupoints in the feet, which are correlated with eye disorders. Further, in a recent study, Siedentopf et al. [13] confirmed Cho’s results and found that laser acupuncture at eye-related acupoints also activate the visual cortex. Liv3 is also one of the important acupoints for the treatment of eye disorders suggested by TCM. The present finding supports the view that the therapeutic effects of acupuncture may depend on specific activation patterns in the CNS.

The main effects of acupuncture at LI4 were the deactivation of frontal areas, which are known to be related to pain [4]. LI4 is known as a major analgesia acupoint. The deactivation of frontal areas induced by LI4 might relate to this effect. According to TCM, frontal cortex is known to be related to many other functions in addition to pain, such as anxiety. The deactivation in fMRI is found to correspond to the reduction of anxiety [11]. In clinic, LI4 is often used to treat disorders involving affective states, such as anxiety and depression. This may be related to the deactivation of prefrontal cortex.

In summary, our results show that stimuli at different acupoints elicit different fMRI activation patterns in the human brain. The present results provide neuroimaging evidence for the specificity of real versus sham acupoints that may underly the mechanisms by which acupuncture acts in treating certain types of diseases.

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