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Neuroscience Letters 354 (2004) 50–53

Neuroscience Letters

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Evidence from brain imaging with fMRI supporting functional specificity of acupoints in humans

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Received 14 August 2003; received in revised form 25 September 2003; accepted 26 September 2003

Abstract

We tested whether the stimulation of acupoints in the same spinal segments could induce different central responses with functional magnetic resonance imaging (fMRI) study. Stimulation of acupoints ST36/SP6 (Zusanli/Sanyinjiao) or GB34/BL57 (Yanglingquan/Chengshan) both activated primary and secondary somatosensory area, insula, ventral thalamus, parietal Brodmann Area 40, temporal lobe, putamen, and cerebellum, while de-activated amygdala. Nevertheless, ST36/SP6 stimulation specifically activated orbital frontal cortex and de-activated hippocampus. Alternatively, stimulation of GB34/BL57 activated dorsal thalamus and inhibited those of primary motor area and premotor cortex. Thus, stimulation of acupoints in the same spinal segments induced distinct though overlapped cerebral response patterns, which indicated the existence of acupoint specificity.

Keywords: fMRI; Transcutaneous nerve stimulation; Electroacupuncture; Acupuncture; Acupoint specificity; Brain imaging

Acupuncture has recently been recognized in the Western world as a useful procedure of complementary medicine, especially in the treatment of chronic pain syndromes, as proposed by NIH Consensus [11]. It is well known that acupoints (specific points in the body surface with high sensitivity to acupuncture treatment) should be carefully selected for different disorders, according to the Chinese acupuncture theory as well as clinical practices. Nonetheless, it remains to be understood why stimulation of neighboring areas should produce entirely different effects.

Non-invasive brain imaging techniques, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), provided the possibility to address these problems in human beings [1–3,5,7,8,12,15,16]. For example, Cho et al. [2] first reported that bilateral visual cortex could be activated by acupuncture stimulation of acupoints correlated with eye disorders in the feet. The same group also demonstrated that needle stimulation of the auricular acupoint for the hand leads to selective fMRI changes in the somatosensory region of the postcentral gyrus corresponding to the actual hand [3]. Studies on acupuncture at points with strong analgesic effect (such as Zusanli and Hegu) implied that the limbic system was involved during the stimulation [7,15,16]. However, acupoint specificity is not fully supported by other fMRI studies. For instance, Siedentopf et al. [12] reproduced Cho's results that laser acupuncture at eye-related acupoint could activate the visual cortex, while Gareus et al. [5] did not.

In the present study, we tried to find whether different but close acupoints (in the same spinal segments) could induce different fMRI responses. If no acupoint specificity exists, they should produce virtually similar responses. Conversely, if significantly different responses were derived from these stimulations, we should have better reason to believe that acupoints may bear some specificity.

Twelve healthy and right-handed subjects (six males and six females), aged 29.1 ± 6.5 (mean ± SD) were volunteered in the experiment. In compliance with guidelines of human experiments from local ethical committee of Peking University, each of the subjects had provided informed consent with the adequate understanding of the purpose and procedure of the study. All subjects were free to withdraw

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doi:10.1016/j.neulet.2003.09.080

from the experiment at any time. None had a history of psychiatric or neurological disorders. None was in pain or distress at the time of the study.

Since electrical acupoint stimulation (EAS) has been widely used as a substitute for classical acupuncture [6,8,16], it was also adopted in this study. This led to the benefit that stimulation parameters applied to all subjects were generally similar, thus the only difference will be where the stimulus was applied. In the present study, two pairs of acupoints on the left leg were selected for comparison, i.e. ST36 (or Zusanli, located 5 cm below the lateral flank of the knee joint) and SP6 (or Sanyinjiao, 5 cm above the medial tarsal of the ankle joint) as one case, and GB34 (or Yanglingquan, located in the foveola anterio-inferior to the fibula capitulum) and BL57 (or Chengshan, located in the inferior apex of the belly of Gastrocnemius muscle) as the other. Anatomically, ST36 and GB34 are both innervated by L5 spinal nerve, while SP6 and BL57 both belong to L4 spinal segment (see Fig. 1). A pair of skin electrodes was placed on the selected acupoint pairs. Han's acupoint nerve stimulator (LH-202H, Huawei Co. Ltd., Beijing) was used to deliver the stimulation. The proper intensities of EAS (constant current output) for each of the individual volunteers were tested before the start of formal experiments. The intensity was adjusted to a maximal but comfortable level, ranging from 8 to 15 mA (averaged at 10.92 mA). No noxious or any unpleasant feeling was allowed. The frequency of stimulation was set at 100 Hz (square wave with width of 0.2 msec).

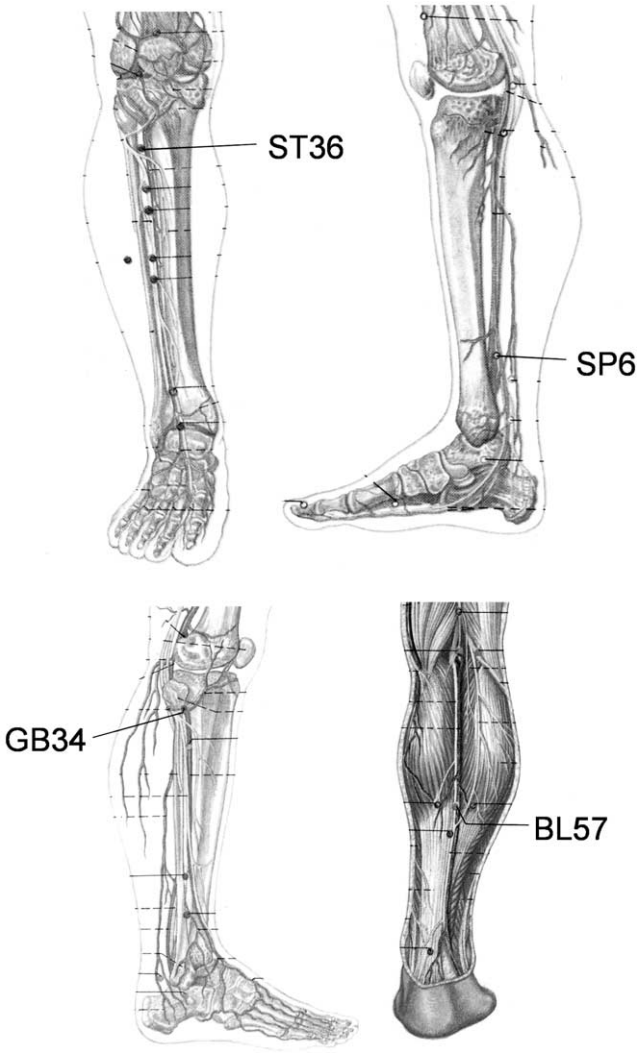

Fig. 1. Anatomical positions of the acupoints. ST36, Zusanli; SP6, Sanyinjiao; GB34, Yanglingquan; and BL57, Chengshan.

All MRI experiments were performed on a 1.9 T whole body MRI scanner (Prestige, GE/Elscint Ltd., Haifa, Israel) with a standard head coil. For the fMRI images, a gradient echo planar imaging (EPI) T2*-weighted sequence based on blood oxygenation level dependent (BOLD) effect was employed. The slice thickness/space (THK) was set at 6.0/0.0 mm, in-plane resolution at 2.9×2.9 mm, and TR/TE/flip angle at 3000 ms/45 ms/90°. The field of view (FOV) was 373×212 mm^2, and the acquisition matrix was 128×72. A complete set of 20 continuous axial sections covering the whole brain including cerebellum was obtained repeatedly every 3 s to fill 120 time points during 6 min. For anatomical images, a 3D gradient-echo T1-weighted sequence (TR/TE 25/4 ms; FOV 220×220 mm^2; THK 2.0/0.0 mm, Matrix 220×220; resolution: 1×1 mm^2) was selected and the images were used for Talairach transformation and functional mapping during data analysis later. Another set of 20 spin-echo T1-Weighted images (TR/TE 750/12 ms, FOV 220×220 mm^2; THK 6.0/0.0 mm; Matrix 220×220; resolution 1×1 mm^2) with same position of fMRI acquisition was obtained for image registration.

Each subject received two 6-min EPI scanning, separated by 15 min. During each of the fMRI scanning, the EAS was delivered on either acupoints ST36/SP6 or GB34/BL57 with the order balanced across all subjects. In the 6-min fMRI scanning, EAS was given within the 2nd, 4th and 6th min, each lasting 1 min. The 1st, 3rd, and 5th min served as the control or resting phases without any stimulation.

Data from one subject was excluded in our further analysis due to his relatively severe head motion during imaging. Analysis of functional neuroimaging (AFNI) Software [4] was applied in the data processing. For each of the remaining 24 subjects, we first made motion correction, and then calculated the mean value at each time-point across voxels of all brain regions to obtain a time-course of the averaged signal. There we performed a detrending process with the algorithms of linear least squares to achieve a sensible signal-to-noise ratio [10]. Afterwards, functional images were registered with the anatomical MR images. These image loci were then transformed into Talairach space [13]. Functional images were resampled and blurred into $3 \times 3 \times 3$ mm^3 voxels. The first three of the 120 time points were discarded due to a problem of the T1 equilibrium (stability) of the image system. Finally, smoothed functional data from eleven subjects were averaged. Then the averaged time series were

cross-correlated with the ideal stimulation curve adjusted for the hemodynamic delay effects. The threshold for activated voxel was set to $P < 10^{-5}$ and clustered at the threshold of four voxels so that the corrected significance in whole brain is less than 0.05, as estimated by a Monte Carlo simulation. Functional MR Imaging data were visually inspected to ensure that each reserved activation was actually within the brain, and the localization of the activated brain regions was confirmed by an experienced neuro-radiologist.

All subjects experienced soreness and numbness (so called 'De-Qi' sensation of acupuncture) of different extent around the stimulation sites, which are normal responses both in transcutaneous electric acupoint stimulation (TEAS) and the traditional maneuver acupuncture treatment. No pain and other discomfort were reported during the EAS treatment.

Areas activated by EAS on ST36/SP6 and GB34/BL57 were demonstrated in Figs. 2A,B, respectively, and summarized in Table 1. EAS on ST36/SP6 activated bilateral primary somatosensory area (SI), secondary somatosensory area and insula (SII/Ins), bilateral ventral thalamus, parietal Brodmann Area 40 (BA40), temporal lobe, orbital frontal lobe, and cerebellum, as well as contralateral putamen and ipsilateral parietal BA7. It also de-activated bilateral amygdala and hippocampus. The extent and intensity of contralateral SI and SII were stronger than ipsilateral, while those of ipsilateral cerebellum were more robust than contralateral. Alternatively, EAS on GB34/BL57 activated contralateral SI, bilateral SII/Ins, ventral thalamus, parietal BA40, temporal lobe, pons, and cerebellum, as well as contralateral putamen and dorsal thalamus. The de-activation happened in bilateral amygdala, primary motor area (MI), and premotor cortex (PMC).

According to the theory of Traditional Chinese Medicine, acupoints were functionally related either to certain visceral organs, or to some global function such as pain sensory or skeletal muscle movement. These relationships have been partially proved by clinical application of acupuncture therapy. However, it remains a mystery how a point at the body surface should have these functional correlations. The study of Cho et al. [2] tried to locate this relationship within the brain. One limitation of this study is that only non-acupoints were used as control. Hence it is still unclear whether other acupoints, especially those within the same spinal segment, may produce similar or different responses.

In the current study, with stimulation of acupoints innervated by the same spinal segments, we demonstrated that although these two pairs of location shared some brain activation and de-activation in common, they do have distinct response patterns. For example, stimulation of ST36/SP6 was related with the activation in orbital frontal cortex and ventral thalamus, and deactivation in hippocampus and parietal BA7. Most of these areas were regarded to be involved in visceral modulation. It is very interesting that acupoints ST36 and SP6 were also very effective for

Table 1
Brain areas activated by EA at different acupoints

Brain areas	ST36/SP6	GB34/BL57
R-SI	+	+
L-SI	+	
B-MI/PMC		−
B-SII/Insula	+	+
B-Parietal BA40	+	+
L-Parietal BA7	−	
Thalamus		
B-Ventral anterior	+	
B-Ventral posterior		+
R-Dorsal		+
B-Orbital Frontal	+	
B-Temporal	+	+
B-Cerebellum	+	+
R-Putamen	+	+
B-Amygdala	−	−
B-Hippocampus	−	
B-Pons		+

+/−, activation/de-activation. Blank, no significant change of BOLD signal was found. Abbreviations: B, bilateral; R, right (contralateral); L, left (ipsilateral); SI, primary somatosensory area; SII, secondary somatosensory area; MI, primary motor area; and PMC, premotor cortex.

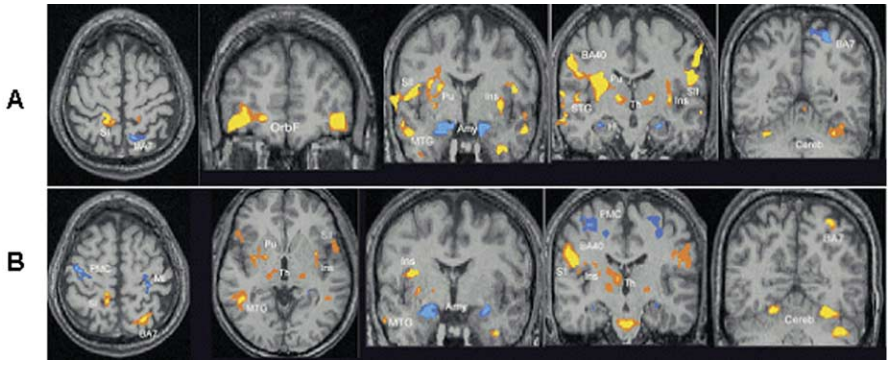

Fig. 2. Averaged result from 11 subjects of 100 Hz group. (A) Activations by EAS on ST36/SP6. (B) Activations by EAS on GB34/BL57. Amy, amygdala; BA, Brodmman area; Cereb, cerebellum; Hi, hippocampus; Ins, insula; MI, primary motor cortex; MTG, middle temporal gyrus; OrbF, orbital frontal; PMC, premotor cortex; Pu, putamen; SI, primary somatosensory area; SII, secondary somatosensory area; STG, superior temporal gyrus; Th, thalamus.

visceral disorders [9], such as stomach, intestine, etc. On the other hand, GB34 and BL57 were important acupoints for functional modulation of muscles and tendons [14]. Consistently, stimulation of these acupoints induced de-activation in MI/PMC, as well as the activation in dorsal thalamus, which were known to be involved in motor functions. Therefore, the activation/de-activation pattern observed in this study may reflect a possible mechanism underlying these clinic phenomenons.

In summary, our results indicated that stimuli of different acupoints in the same spinal segment could induce different fMRI activation patterns in the brain, which is somehow consistent with its empirical application in practice. Nonetheless, it is still not sure whether those specific responses detected were the basis for or the result of their clinic effect. At least but not at last, the current results provide a neurobiological evidence for the existence of acupoint specificity, though further proofs are still necessary to elucidate this phenomenon.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (grant number 30170307), the National Basic Research Program of China (G1999054000), the 211 Neuroscience Project from the Ministry of Education of China, and a startup grant for young scientists from the 985 project of Peking University.

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