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# The neural substrates of verum acupuncture compared to non-penetrating placebo needle: An fMRI study

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ABSTRACT

Acupuncture, an ancient East Asian therapeutic technique, is currently emerging as an important modality in complementary and alternative medicine around the world. Several studies have provided useful information regarding neurophysiological mechanisms of acupuncture in human brain activation. We explored brain activation using functional magnetic resonance imaging (fMRI) and compared verum acupuncture to placebo needles. Two fMRI scans were taken in random order in a block design, one for verum acupuncture and one for non-penetrating placebo needles at the motor function-implicated acupoint LR2, on the left foot, in 10 healthy volunteers. We calculated the contrast that subtracted the blood oxygen level-dependent (BOLD) responses between the verum and sham acupuncture. Verum acupuncture stimulation elicited significant activation in both motor function-related brain areas, including the caudate, claustrum, and cerebellum, and limbic-related structures, such as the medial frontal gyrus, the cingulate gyrus, and the fusiform gyrus. These findings suggest that acupuncture not only elicited acupoint-implicated brain activation, but also modulated the affective components of the pain matrix. The current investigation of the specific pattern of the brain activation related to genuine acupuncture provides new information regarding the neurobiological basis of acupuncture.



Acupuncture (from the Latin *acus*, "needle," and *pungere*, "to prick") is a technique of inserting and manipulating fine needles at specific points (acupoints) on the body. Many neuroimaging studies have revealed that acupuncture stimulation modulates the central nervous system in humans [1,3,11]. Subsequent functional magnetic resonance imaging (fMRI) investigations regarding several acupoints have demonstrated a correlation between acupoint stimulation and corresponding cortical response, suggesting that acupuncture at disease-implicated acupoints modulates the activity of the disease-related neuromatrix [12,18]. Additionally, several studies have documented that acupuncture, via different kinds of acupuncture stimulation at acupoints with analgesic effects, modulates the pain network, including the hypothalamus and limbic system [5,16,21]. However, many of the studies were not performed with appropriate control groups, so whether the changes were genuinely acupuncture-specific or a general phenomenon that could be elicited as a placebo response or by non-specific effects of mechanical stimulation has not been clearly demonstrated.

To provide an effective and credible placebo (defined as a physiologically inert procedure), the control must be convincing and should mimic, apart from the physiological effect, all aspects of the real active treatment. As a newly developed placebo sham needle is pushed against the skin, it causes a pricking sensation, but as increased pressure is applied, the shaft of the needle disappears into the handle, mimicking a 'stage dagger' [17,19]. Although this 'placebo' needle has been used in clinical trials, few studies have examined the specific effects of verum acupuncture compared to non-penetrating placebo acupuncture. Interfering factors, such as pain or emotion during acupuncture, are considered to contribute, at least in part, to the pattern of brain activity in the field of neuroimaging studies. To provide specific patterns implicated with the therapeutic effect of acupuncture, it is necessary to subtract fMRI brain images evoked by stimulating with sham acupuncture from those evoked by stimulating with verum acupuncture.

The present study was thus performed using fMRI to examine changes in blood oxygen level-dependent (BOLD) responses with verum acupuncture at acupoint LR2, as compared with the response to sham acupuncture.

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This study was carried out in 10 healthy, right-handed subjects (6 men, 4 women; age range 20–34 years). After screening, those with psychiatric or neurological disorders were excluded. They were told that they would experience acupuncture stimulation, but they were not told whether it would be verum or sham acupuncture. All participants received a detailed explanation of the study and written, informed consent was provided. This study was conducted in accordance with the guidelines of the human subjects committee of Kyunghee University, Seoul, Republic of Korea.

Acupuncture was performed by an experienced Korean medical doctor. Each subject received verum or sham acupuncture in random order at acupoint LR2 between the first and second toes on the dorsum of the foot (Fig. 1). The verum acupuncture needle (sterile, disposable, stainless steel, 40 mm long, and 0.25 mm in diameter) was inserted to a depth of 0.8 cm perpendicular to the skin surface. The needle was rotated manually, clockwise and counterclockwise, once per second (1 Hz) for 60 s (ON phase). The needle was then withdrawn for 120 s (OFF phase). The sham procedure was performed using a blunt, telescopic, non-penetrating Park Sham needle (DongBang Acupuncture Inc., Boryeoung, Korea) in an attempt to exclude the placebo phenomenon [17].

After each session, subjects were questioned using the short-form of the needle sensation questionnaire, leading to ratings of both *deqi* and acute pain. The *deqi* scale consists of sore, numb, heavy, and distended sensations, and the acute pain scale consists of hurting and aching sensations. Participants rated the intensity of each sensation using a 6-point Likert scale. They also answered the question "Did you think the acupuncture stimulation you just received was real or sham?"

Subjects were asked to lie in a supine position on the scanner bed with their eyes closed. fMRI scans were conducted over two 9-min periods; one scan involved verum acupuncture and the other scan involved sham acupuncture. The total scan time for each session was 9 min (Fig. 1). Scanning commenced with a rest period (2 min) and was followed by three identical active blocks of needle stimulation (1 min), separated by a rest period (2 min).

All MRI experiments were performed using a 3 T MR scanner (ISOL Tech, Daejeon, Republic of Korea). It is well known that BOLD contrast depends upon the total amount of deoxygenated hemoglobin present in a brain region, which in turn depends upon the balance between oxygen consumption and oxygen supply. These differential signals could enable measurement of functional changes in brain activity. BOLD functional imaging was carried out using a gradient echo planar imaging (EPI) T2*-weighted sequence (TR 3000 ms, TE 25 ms, flip angle 90°, acquisition matrix $64 \times 64$, FOV 220 mm, slice thick 4 mm without gap, voxel size 3.43 mm × 3.43 mm × 4 mm). Image collection was preceded by four dummy scans to allow for equilibration of the MRI signal. For anatomical images, a 3D gradient-echo T1-weighted sequence (TR 2800 ms, TE 16 ms, flip angle 60°, FOV $192 \times 220$, slice thickness 5 mm) was acquired after the functional scans.

The fMRI data were processed using the Statistical Parametric Mapping software (SPM5, http://fil.ion.ac.uk). For motion correction, all functional images were realigned to the first volume of the first scan session. All subjects satisfied our excessive motion threshold of less than 2 mm spatial displacement in any direction. Subsequently, each image volume was normalized to the Montreal Neurological Institute (MNI) space based on Talairach coordinates, and then smoothed spatially using a 5-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel to decrease spatial noise. Low-frequency noise was removed with a high-pass filter, which was applied with default values to the fMRI time series at each voxel. We constructed a design matrix for each subject that included regressors representing the blocks of acupuncture application separately for the verum and sham conditions. Contrast maps were generated between the verum and sham acupuncture regressors for each subject, and the resulting individual contrast maps were used in random-effects group analyses such as one sample *t*-tests and multiple regression analyses. A statistical threshold of $p < 0.005$ (uncorrected), combined with spatial extent threshold (>10 contiguous voxels), was used to detect any significant signal difference between the verum and sham conditions.

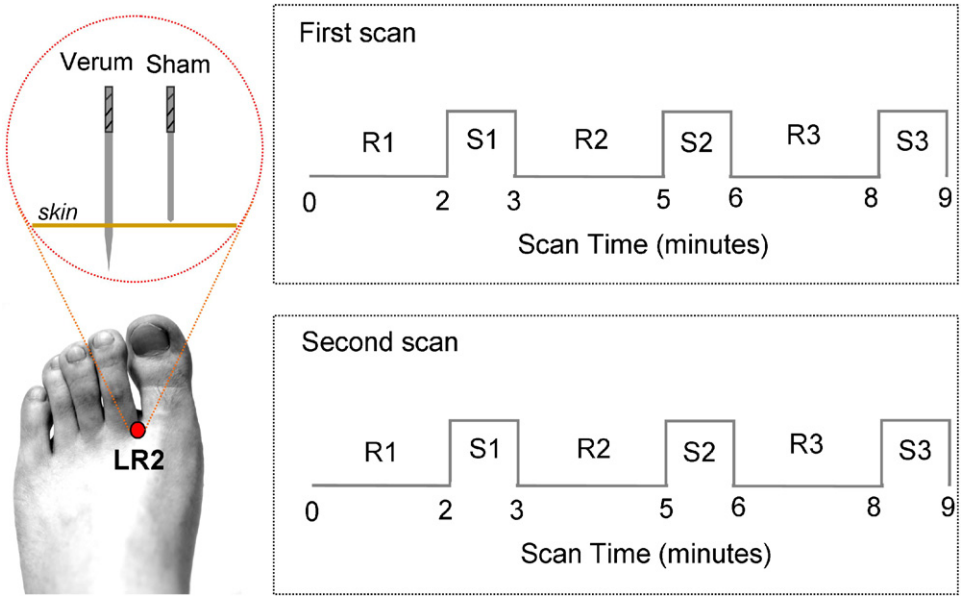


**Fig. 1.** Diagram of verum and sham acupuncture and location of acupoint LR2 are presented in the left panel. The sham acupuncture was performed using a new, blunt, telescopic, non-penetrating Park Sham needle. The total scan time for each scan session was 9 min in the right panel. Scanning commenced with a rest period (R1) and was followed by three identical active blocks of needle stimulation (S1, S2, S3), separated by a rest period (R2, R3). For each participant, two fMRI scans were performed using the above block design, one with three consecutive verum acupuncture stimulations and one with three consecutive sham acupuncture stimulations. The order of the two sessions was randomly allocated.