# Visual cortical activations on fMRI upon stimulation of the vision-implicated acupoints

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We used fMRI to reveal the visual cortical activations during conventional or electro-acupuncture over four vision-implicated acupoints in 18 healthy volunteers and compared the results with those obtained during direct visual stimulation. Positive activations were seen over the visual cortex during visual stimulation in all subjects, and similar activations were observed in 10 subjects during conventional acupuncture as well as in eight and seven subjects during electro-acupuncture at 2 and 20 Hz, respectively. Negative activations were also seen over the occipital lobes, temporal gyri and frontal gyri bilaterally in 13 subjects during conventional acupuncture. Thus, acupuncture may modulate the activity of relevant brain sites. Our results also suggest that electro-acupuncture is useful in future studies. *NeuroReport* 14:669–673 © 2003 Lippincott Williams & Wilkins.

**Key words**: Acupoint; Acupuncture; Chinese medicine; Electro-acupuncture; fMRI; Neuroimaging; Vision; Visual cortex

## INTRODUCTION

Acupuncture, a key component of traditional Chinese medicine, has been widely practiced in China and neighboring countries for over 3000 years. Acupuncture has become popular in the West as an alternative or complementary medicine, and has aroused much interest in the scientific and medical communities [1,2]. The National Institutes of Heath Consensus Development Panel has concluded that acupuncture is efficacious in adult postoperative and chemotherapy-induced nausea and vomiting, as well as in postoperative dental pain, and that acupuncture may be helpful in drug addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain, osteoarthritis, low back pain, carpal tunnel syndrome, and asthma [3]. Nevertheless, its mechanisms remain elusive.

MRI can measure the tiny regional change in the blood oxygenation level dependent (BOLD) effects from increased neuronal activity during a specific task. Thus, fMRI permits non-invasive mapping of brain activity during various specific tasks [4]. Recently, fMRI has been used to map the sites of brain activation during acupuncture [5–12]. While most studies reported an increase (positive activation) in BOLD effects, some revealed both activations and deactivations (negative activations) [5,6,8,12]. As acupoint stimulations can generate time-logged modulation of activities of specific brain sites, therapeutic benefits of acupuncture may be related to a central neural mechanism. In this study, we used fMRI to reveal any visual cortical activations during conventional or electro-acupuncture over four vision-implicated acupoints [5,11] in 18 healthy volunteers and compared the results with that obtained during direct visual stimulation with light-emitting diodes (LED) in the same cohort.

## MATERIALS AND METHODS

Twenty healthy Chinese volunteers (eight males; mean age 42 years) gave their written consents and participated in the present study. The protocol was approved by the Ethics Committee of the University of Hong Kong, Hong Kong. A 1.5 T scanner (Signa Horizon Echo Speed with version 8.2 software, General Electric Medical Systems, Milwaukee, WI, USA) with a maximum gradient strength of 23 mT/m and a quadrature head coil was used. The subject was first familiarized with the experimental procedures and environmental conditions to minimize anxiety and enhance task performance. After acquiring the sagittal spin echo (TR 500 ms; TE 8 ms) localizer images, fMRI was performed using a single-shot, gradient-echo version of echo planar pulse sequence under the following scan parameters: TR 2000 ms; TE 60 ms; flip angle 90°; matrix $64 \times 128$; field of view $24 \times 24$ cm; slice thickness 6 mm; inter-slice gap 1 mm; receiver bandwidth ± 133 kHz; multi-phase and single excitation. The same block design of RARARARA was adopted for direct visual stimulation as well as each type of acupuncture stimulations with R representing rest and A representing one kind of stimulation; each period lasted

20 s, and each run lasted 160 s. fMRI data was first collected during direct visual stimulation with LED (L150NWC, American Opto Plus LED Corp. La Puente, CA, USA) flashing at 8 Hz. Next, fMRI was repeated during conventional acupuncture over four vision-implicated acupoints (bladder (BL) 60, BL65, BL66, and BL67) [5,11] located in the lateral aspect of right foot (Fig. 1). This was followed by fMRI during electro-acupuncture at 2 Hz and finally during electro-acupuncture at 20 Hz over the same acupoints. Bipolar electro-acupuncture was conducted with the positive electrodes over BL65 and BL67 and negative ones over BL60 and BL66. Intensity of electrical stimulation was set at the mid-level between the barely perceptible and maximally tolerable levels. Subjects kept their eyes open during the entire period of direct visual stimulation and closed their eyes during the periods of acupuncture. Anatomical whole brain MRI was acquired using a $T_1$-weighted, spin-echo sequence.

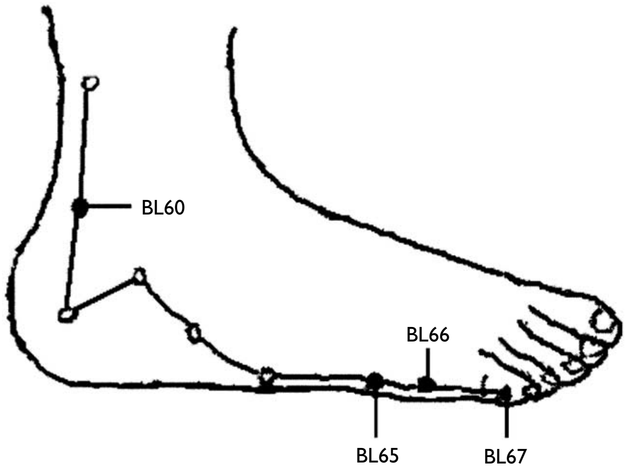

**Fig. 1.** A schematic drawing of the right foot showing the four vision-implicated acupoints.

Post-processing of fMRI data was done using the Matlab software (Version 6.1; Math Works Inc., Natick, MA, USA) and the Statistical Parametric Map (SPM) software package (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, UK). Each of the 80 fMRI images for each kind of stimulation was automatically realigned to the first image of the time series to correct for head movements between scans before normalized and transformed into the Talairach space [13]. Spatial and temporal smoothing was done with a $6 \times 6 \times 12$ mm full width at half maximum Gaussian kernel. The first level SPM t-contrast map was generated for each subject under each type of task states using a box-car function convolved with an empirically derived hemodynamic impulse response function at a threshold of $p=0.001$ (uncorrected). The second level analysis of random effects was used for comparisons within the group of subjects who had significant activations in the first level analysis during each type of task states at a threshold of $p=0.001$ (uncorrected), $p=0.001$ (uncorrected), $p=0.005$ (uncorrected), $p=0.005$ (uncorrected), $p=0.002$ (uncorrected) for LED stimulation, positive as well as negative activations during conventional acupuncture, electro-acupuncture at 2 Hz, and electro-acupuncture at 20 Hz, respectively [14]. Uncorrectable head motions were seen in two subjects, precluding analysis of the fMRI data.

## RESULTS

Table 1 summarizes the regions with significant activations during each type of task states. During LED stimulation, positive activations were seen in all 18 subjects over the right cuneus of the occipital lobe (Brodmann area (BA) 18) and left lingual gyrus of the occipital lobe (BA18; Fig. 2a). Stimulation of the four vision-implicated acupoints on the right foot without LED stimulation produced positively

**Table 1.** Regions with significant activation during LED stimulation, conventional acupuncture (CA), or electro-acupuncture (EA).

| No. of subjects | Method of stimulation | Activated regions | Coordinates | | | | Volume (mm$^3$) | Nature of activation | T | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | BA | X | Y | Z | | | | |
| 18 | LED | Right cuneus of occipital lobe | 18 | 8 | −78 | 6 | 40 | Positive | 4.80 | 0.001 |
| 18 | LED | Left lingual gyrus of occipital lobe | 18 | −2 | −80 | 0 | 464 | Positive | 4.80 | 0.001 |
| 10 | CA | Left cuneus of occipital lobe | 18 | −4 | −85 | 16 | 168 | Positive | 4.80 | 0.001 |
| 10 | CA | Right cuneus of occipital lobe | 18 | 4 | −80 | 16 | 112 | Positive | 4.80 | 0.001 |
| 10 | CA | Right posterior cingulate of limbic lobe | 30 | 18 | −64 | 10 | 112 | Positive | 4.80 | 0.001 |
| 10 | CA | Right inferior frontal gyrus | 45 | 50 | 20 | 10 | 112 | Positive | 4.80 | 0.001 |
| 13 | CA | Right cuneus of occipital lobe | 18 | 3 | −82 | 16 | 56 | Negative | 8.05 | 0.005 |
| 13 | CA | Left cuneus of occipital lobe | 18 | −2 | −75 | 14 | 56 | Negative | 8.05 | 0.005 |
| 13 | CA | Right transverse temporal gyrus | 41 | 52 | −18 | 12 | 88 | Negative | 8.05 | 0.005 |
| 13 | CA | Left transverse temporal gyrus | 41 | −52 | −15 | 12 | 104 | Negative | 8.05 | 0.005 |
| 13 | CA | Left middle frontal gyrus | 46 | −50 | 40 | 16 | 56 | Negative | 8.05 | 0.005 |
| 13 | CA | Right middle frontal gyrus | 46 | 50 | 40 | 12 | 56 | Negative | 8.05 | 0.005 |
| 8 | EA at 2 Hz | Right ceneus of occipital lobe | 18 | 4 | −80 | 18 | 48 | Positive | 8.50 | 0.005 |
| 8 | EA at 2 Hz | Left cuneus of occipital lobe | 18 | −5 | −70 | 16 | 40 | Positive | 8.50 | 0.005 |
| 8 | EA at 2 Hz | Left occipital lobe and middle temporal gyrus | 19 | −60 | −65 | 16 | 56 | Positive | 8.50 | 0.005 |
| 8 | EA at 2 Hz | Right inferior frontal gyrus | 45 | 55 | 20 | 16 | 40 | Positive | 8.50 | 0.005 |
| 7 | EA at 20 Hz | Left cuneus of occipital lobe | 17 | −10 | −80 | 10 | 48 | Positive | 4.52 | 0.002 |
| 7 | EA at 20 Hz | Left cuneus of occipital lobe | 18 | −4 | −90 | 10 | 56 | Positive | 4.52 | 0.002 |
| 7 | EA at 20 Hz | Left middle occipital lobe | 18 | −10 | −92 | 16 | 56 | Positive | 4.52 | 0.002 |
| 7 | EA at 20 Hz | Right cuneus of occipital lobe | 18 | 4 | −90 | 10 | 48 | Positive | 4.52 | 0.002 |

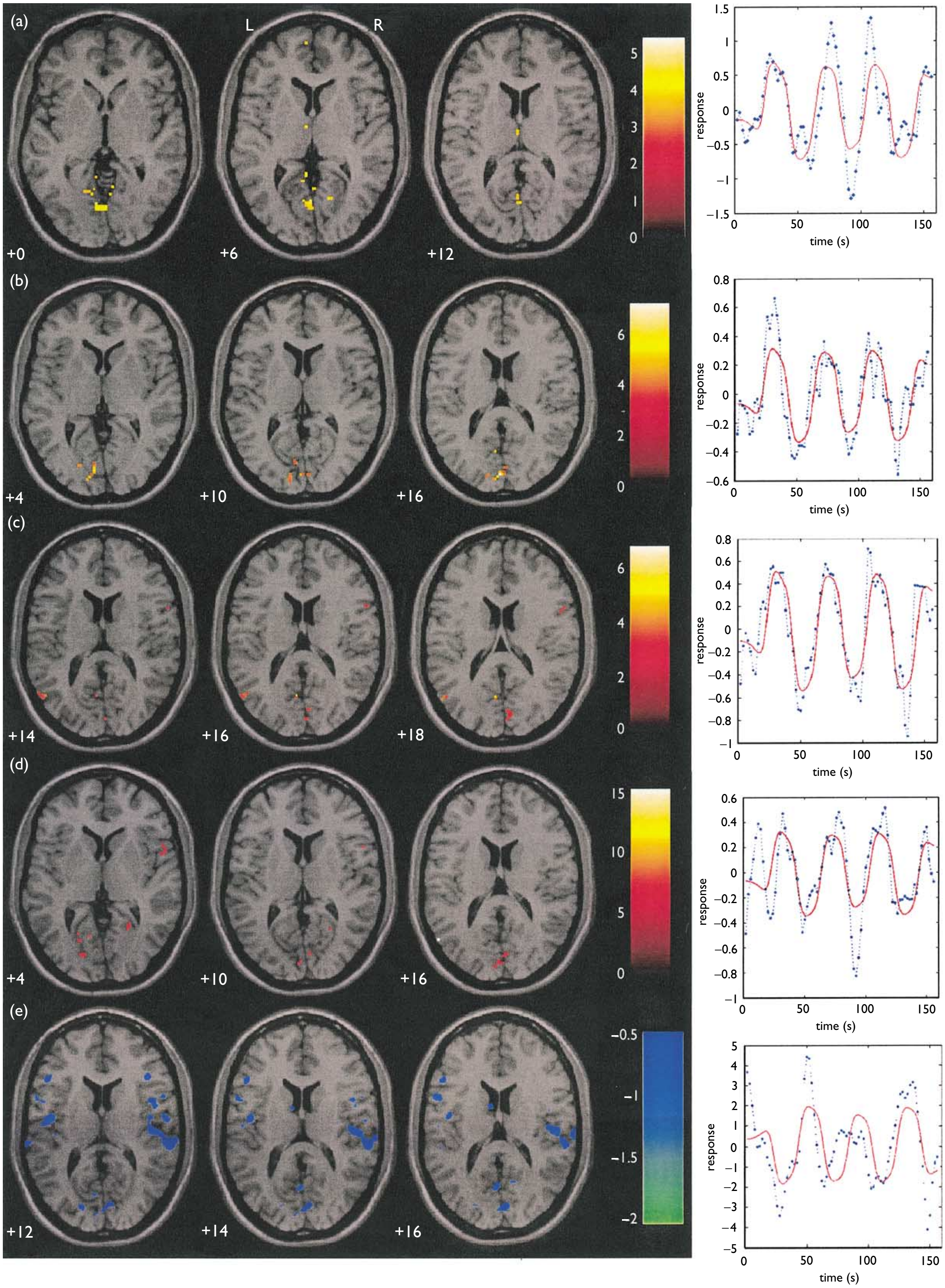

**Fig. 2.** Normalized second level group SPM t-contrast maps (in color) overlaid on the corresponding axial $T_1$-weighted images (in gray scale labeled with the height in mm relative to the bicommissural line) showing significant positive activations (left-hand side) and the average time-courses of all activations in the same slice (right-hand side) during LED stimulation (**a**), conventional acupuncture (**b**), and electro-acupuncture at 2 Hz (**c**) or 20 Hz (**d**) as well as negative activations and the average time-course of all deactivations in the same slice (right-hand side) during conventional acupuncture (**e**). Adjusted and fitted responses of the average time-courses were depicted in blue and red, respectively, with the horizontal time scale in seconds. L = left; R = right.

activated pixels over the right and left cuneus of the occipital lobe (BA17, BA18) in 10, 8, and 7 subjects during conventional acupuncture (Fig. 2b), electro-acupuncture at 2 Hz (Fig. 2c), and electro-acupuncture at 20 Hz (Fig. 2d), respectively. In addition, negatively activated pixels were obtained bilaterally over the cuneus of the occipital lobe (BA18), the transverse temporal gyrus (BA41), and the middle frontal gyrus (BA46) during conventional acupuncture in 13 subjects (Fig. 2e).

## DISCUSSION

Visual stimulation using LED produced positive activation over the visual cortex bilaterally in all the subjects [4,15]. Electro-acupuncture permits stimulation of acupoints in an objective manner [7,12]. Similar to previous fMRI studies of acupuncture [5–12], time-logged increase (positive activation) or decrease (negative activation) in BOLD signals was observed over distinctive brain sites. Previous studies have shown that analgesic points such as gallbladder 34, large intestine 4 and stomach 36 modulate the activity of the hypothalamic–limbic system [6,8,9,16]. Activations of the corresponding cerebral sites were also reported for the vision-implicated acupoints (BL60–BL67) and the hearing-implicated acupoints (Sanjiao 5) [5,7,11]. In this study, the visual cortex was activated bilaterally in some subjects during conventional or electro-acupuncture over four vision-implicated acupoints on the right foot. Our results are in general agreement with previous fMRI studies on the same acupoints [5,11]. Although non-specific activations during acupuncture stimulation are possible, our results support the notion that stimulation of peripheral acupoints can somehow modulate the activities of specific brain sites. Such an ability of acupuncture applied over certain disease-implicated acupoints may mediate the therapeutic benefit of acupuncture.

Nevertheless, brain activations on fMRI during conventional or electro-acupuncture are somewhat different from that during LED stimulation. First, the total volume of activated brain sites is smaller during acupuncture than LED stimulation, suggesting that physiological stimulation is more effective in increasing the BOLD signal over the visual cortex [5]. Second, the activated sites were different when conventional or electro-acupuncture was applied, as well as when electro-acupuncture was applied at different frequencies over the same acupoints. It is possible that peripheral stimulation of acupoints would activate the brain via multi-synaptic pathways and that the nature and pattern of stimulation may affect the recruitment of the pathways. Previous studies reported that the frequency of peripheral nerve stimulation affected the response [1,17]. Third, negative and positive activations were seen during conventional acupuncture while positive activations only were observed during LED stimulation and electro-acupuncture. Similar findings of positive and negative activations were also observed in the original fMRI study on vision-implicated acupoints BL60–BL67 using conventional acupuncture [5] but not in a recent study in which laser acupuncture was applied only to BL67 of the left foot [11]. It is possible that negative activation represents a suppression of background neuronal activity [18]. In this study, negative BOLD signals were seen around the positively activated regions within the visual cortex. The authors of a different study proposed a steal phenomenon for the negative BOLD signals [19]. Nevertheless, bilateral negative activations were rather extensively seen in the frontal and temporal cortices. We speculate that manual twisting and other movements of the acupuncture needle may produce a non-specific suppression of activities over multiple brain sites. Fourth, bilateral cortical activations were seen with unilateral stimulation of the acupoints on the right foot [5]. Callosal fibers, which provide inter-hemispheric visual–visual transmission, may be responsible for the bilateral activations [20,21]. Fifth, activations were seen in non-visual cortices during acupuncture. A possible explanation is that some neurons in the parietal and temporal lobes receive inputs from both visual cortices [22]. Another possibility is non-specific activations [10,12].

One major drawback of fMRI studies on acupoint stimulation is that not all subjects undergoing acupuncture will have significant activations according to the standard SPM analysis. In this study, only 39–72% of the subjects had significant activations during conventional or electro-acupuncture; the reasons are not known. According to the theory of traditional Chinese medicine theory, effective acupuncture is accompanied by a specific sensation of *deqi* [10]. It is plausible that presence of *deqi* is correlated with significant activations on fMRI [16].

The lack of an appropriate sham acupuncture condition is a limitation of the present study. We recently reported the brain activation on fMRI during word generation or electro-acupuncture over two language-implicated acupoints in 17 healthy Mandarin-speaking male Chinese volunteers [23]. Electrical stimulation of the sham acupoints located 1 cm lateral to the true acupoints failed to produce any significant activation. Including similar sham acupoints for BL65, BL66, and BL67 is technically difficult.

## CONCLUSION

The present fMRI results obtained during the application of conventional or electro-acupuncture over four vision-implicated acupoints support the proposition that acupoint stimulation can somehow modulate the activity of specific brain sites and the hypothesis that modulation of the brain activity may underlie the benefit of acupuncture treatment. Nevertheless, further studies are required to clarify the clinical relevance of the positive and negative activations over different brain sites during acupuncture. Electro-acupuncture at 2 Hz may be preferred in future studies of vision-implicated acupoints because the resulting brain activations on fMRI closely resemble that of direct visual stimulation.

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