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Comparison of visual cortical activations induced by electro-acupuncture at vision and nonvision-related acupoints

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ABSTRACT

In the current study, we investigated whether or not stimulation at vision and nonvision-related acupoints was able to induce similarity in the time domain, although stimulation at different acupoints could produce similar spatial distributions. This phenomenon still remains uncertain and contradictory. We introduced a novel experimental paradigm using a modified non-repeated event-related (NRER) design, and utilized the methods of independent component analysis (ICA) combined with seed correlated functional connectivity analysis to locate visual cortical activations and to study their temporal characteristics during electro-acupuncture (EAS) at vision-related acupoint GB 37 and nonvision-related acupoint KI 8. Results showed that strong activations were present in the visual cortical areas (BA 17/18/19) at both acupoints, but temporal correlation analysis indicated that they were modulated in opposite directions during the resting state after acupuncture. Our results revealed that acupuncture at vision and nonvision-related acupoints can induce similar activations in spatial distribution but different modulation effects temporally.

Acupuncture, an ancient therapeutic technique, is emerging as an important modality of complementary medicine in Western countries [7–9]. The development of imaging techniques, such as positron resonance imaging (PET) and functional magnetic resonance imaging (fMRI) has provided new tools for us to obtain a non-invasive appreciation of the anatomy and physiological function involved during acupuncture in humans.

During the past few years, numerous researchers [14,29–32] have studied the effects of acupuncture using fMRI. Among them, several researchers focused their studies on vision-related acupoints. One of the original studies was conducted by Cho et al. [3]; they reported that acupuncture at vision-related acupoints Zhiyin-Kunlun (BL 67-BL 60) in the foot, which are used to treat eye diseases in Traditional Chinese Medicine (TCM), activated the visual cortex bilaterally. Recently, Cho et al. [4] published a retraction of their earlier results reporting that 'there is no point specificity, at least for pain and analgesia effects, and that we no longer agree with results in our PNAS article'. When Li et al. [18] revealed the visual cortical activations during conventional or electro-acupuncture (EAS) over four vision-implicated acupoints, they obtained similar activations as seen in direct visual stimulation. Siedentopf et al. [26] and Litscher et al. [20] used laser acupuncture on acupoint BL 67, leading to the activation of visual brain areas. However, Gareus et al. [12] and Kong et al. [17] did not discover the blood oxygenation level dependent (BOLD)-response correlation in the visual cortex with acupuncture at BL 60 and Guangming (GB 37) points.

The aforementioned studies used a multiple-block paradigm; however, our group's latest studies [24,33] analyzed the different effects during the course of multiple-block acupuncture, and results have indicated that there exist time-variability and sustainability during acupuncture. Therefore, we think the multiple-block design may not fully disclose acupuncture effects. Kong's [17] results indicated that EAS at BL 60, GB 37 and non-acupoints induced signal decreases in the lateral occipital cortex and there was no significant difference among them. Due to the time-variability during acupuncture, we aimed to investigate whether or not there existed similarity in the time domain, although stimulation at

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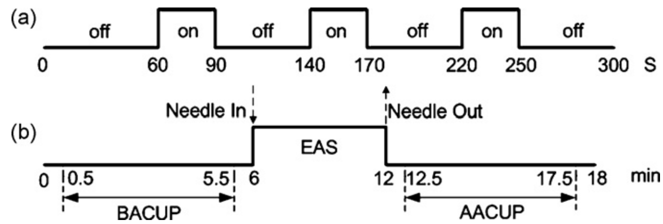

Fig. 1. Experimental paradigm shows (a) the block design of the checkerboard and (b) the stimulation by electro-acupuncture.

different acupoints could induce a similar distribution in certain brain areas. Because of the sustainability achieved during and after acupuncture, we introduced a novel experimental design in this study using a modified non-repeated event-related (NRER) design [24], and chose GB 37 as the vision-related acupoint, it is described as a very effective acupoint influencing multiple vision-related disorders, such as cataracts, night blindness and optic atrophy [21]. We chose Jiaoxin (KI 8) as the nonvision-related acupoint, which is mainly used to treat menoxenia [27]. The data-driven method, independent component analysis (ICA) combined with seed correlated functional connectivity analysis, were also introduced in this study according to our experimental design. ICA is being increasingly applied to fMRI data [1,22] and has many far better advantages as compared to other fMRI analysis methods including correlation and statistical parametric mapping (SPM) [11], in which the time courses and/or spatial extents of the anticipated effects must be modeled explicitly prior to analysis.

The study was performed on 36 right-handed volunteers with normal vision (16 males and 20 females), aged 22.7 ± 2.5 years. All subjects were acupuncture naïve and gave written informed consent as approved by West China University of Medical Science. All subjects were in accordance with the Declaration of Helsinki.

All 36 subjects were randomly divided into three groups and variances across subjects were counterbalanced across groups. The first group was conducted by using a conventional checkerboard 4 Hz light flash stimulation to the eye. The block design consisted of 30 s stimulations (on) separated by 50 s resting scans (off), as shown in Fig. 1(a). In group 2, a 6 min resting scan was performed, after 1.5 min break, then the electrode was connected to the end of the needle and the needle was inserted into the acupoint GB 37, which is located on the lateral aspect of the lower leg on the anterior border of the fibula. EAS was performed at a frequency of 50 Hz and was maintained at 2–3 mA; after a 6 min stimulation, the acupuncturist pulled the needle out and the scan stopped for 1.5 min. Finally, another 6 min resting state scan was performed, as shown in Fig. 1(b). In group 3, stimulation was at the nonvision-related acupoint KI 8, which is located in the area posterior to the medial border of the tibia; manipulation and stimulation were identical to group 2.

The experiments were carried out in a 3T (GE Medical SIGNA EXCITE) scanner. A gradient echo T2*-weighted sequence with in-plane resolution of 3.75 mm × 3.75 mm (TE 30 ms, TR 2 s, matrix 64 × 64, FOV 240 mm, flip angle 90°) and a set of T1-weighted high-resolution structural images (TE 5.7 ms, TR 2.2 ms, matrix 256 × 256, FOV 256 mm, flip angle 12°, in-plane resolution 1 mm × 1 mm, slice thickness 1 mm) were acquired.

All group data were preprocessed and analyzed using Statistical Parametric Mapping 5 (SPM5, http://www.fil.ion.uclac.uk/spm). Images were first corrected for within scan acquisition time differences between slices and then realigned to the first volume

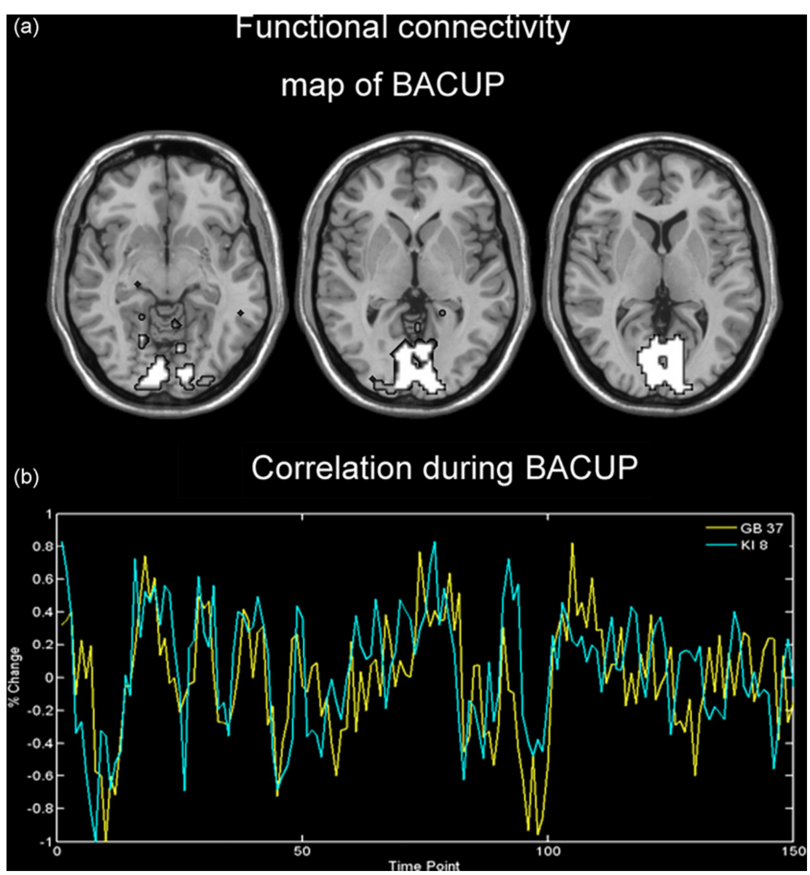

Fig. 2. (a) The brain functional connectivity map of the visual area during the BACUP state. (b) The graph shows a positive correlation between the two acupoints during the resting state before acupuncture (correlation coefficient is 0.5152 (P < 0.05, Bonferroni correction)).

to correct for interscan head motions (one subject in group 3 was excluded because head movement was greater than 1 mm). Next, we spatially normalized the realigned images to the standard EPI template and resampled them to a voxel size of 3 mm × 3 mm × 3 mm. Finally, the functional images were spatially smoothed with a Gaussian kernel of 6 mm × 6 mm × 6 mm FWHM to decrease spatial noise.

Further statistical analysis of smoothed data from group 1 was carried out using SPM5. A random-effect one sample *t*-test ($P < 0.001$) was used to examine the group result of the checkerboard stimulation. The group activation map of the hemisphere contains multiple-functional regions including Brodmann area (BA 17, 18 and 19). Since animal and human studies indicated that the primary visual area (PVA) plays an important role in memory-related visual imagery during resting state and in visual imagery during visual perception [5,15,16,25,28], we chose BA 17 as the region of interest (ROI) for the following study.

During the data analysis of groups 2 and 3, we extracted only 5 min of resting state before acupuncture (BACUP) and 5 min of resting state after acupuncture (AACUP), as shown in Fig. 1(b). First, functional connectivity analysis was carried out using the time course of the ROI to correlate with the BACUP data (both groups 2 and 3) and their correlated networks were defined as a template representing the PVA functional networks during resting state, as shown in Fig. 2(a). The smoothed AACUP data were then arranged into Group ICA of the fMRI Toolbox (GIFT, http://icatb.sourceforge.net/). Using the Informax ICA algorithm, the number of independent components (ICs) was separated by Group ICA, which was estimated to be 40 [19]. The mean ICs of all subjects, the corresponding mean time courses and ICs for each subject were obtained from the Group ICA separation and back-reconstruction [2]. Then, a frequency filter was applied to remove those components in which a high-frequency signal (>0.1 Hz) constituted 50% or more of the total power in the Fourier spectrum [6]. Next, the template defined above was used to select the 'best-fit' of the remaining low-frequency components in each subject [13]. The analysis procedure of group 3 was identical to group 2. One sample *t*-tests were performed to determine the resting state networks (groups 2 and 3) after acupuncture. Finally, we used the mean time series corresponding to the specific ICA components of BACUP and AACUP in group 2 to be individually correlated with those in group 3.

At the group level, the functional network during resting state before acupuncture was located in bilateral visual areas that included the inferior occipital gyrus (IOG, BA 17/18), the middle occipital gyrus (MOG, BA 18), cuneus (BA 17/18) and lingual gyrus (LG, BA 17/18/19), which also extends to the precuneus (BA 31); the pre- and post-central gyri, lateral superior frontal gyrus (SFG, BA 8), middle frontal gyrus (MFG, BA 6) and bilateral inferior frontal gyri (IFG, BA 47); lateral middle temporal gyrus (MTG, BA 21), lateral fusiform gyrus, left parahippocampal gyrus (PHIPP) and the posterior cingulate cortex (PCC, BA 30/31), as well as the thalamus, putamen, culmen and declive.

The functional networks of the resting state after acupuncture (both groups 2 and 3) share some common brain areas that have a different extension or localization, as shown in Fig. 3. These areas are mainly in the visual cortex which include the cuneus (BA 17/18/19), lingual gyrus (BA 17/18), and also the precuneus (BA 31), precentral gyrus, IFG, superior temporal gyrus (STG) (BA 22), MTG (BA 21), inferior temporal gyrus (ITG), PHIPP, PCC and culmen.

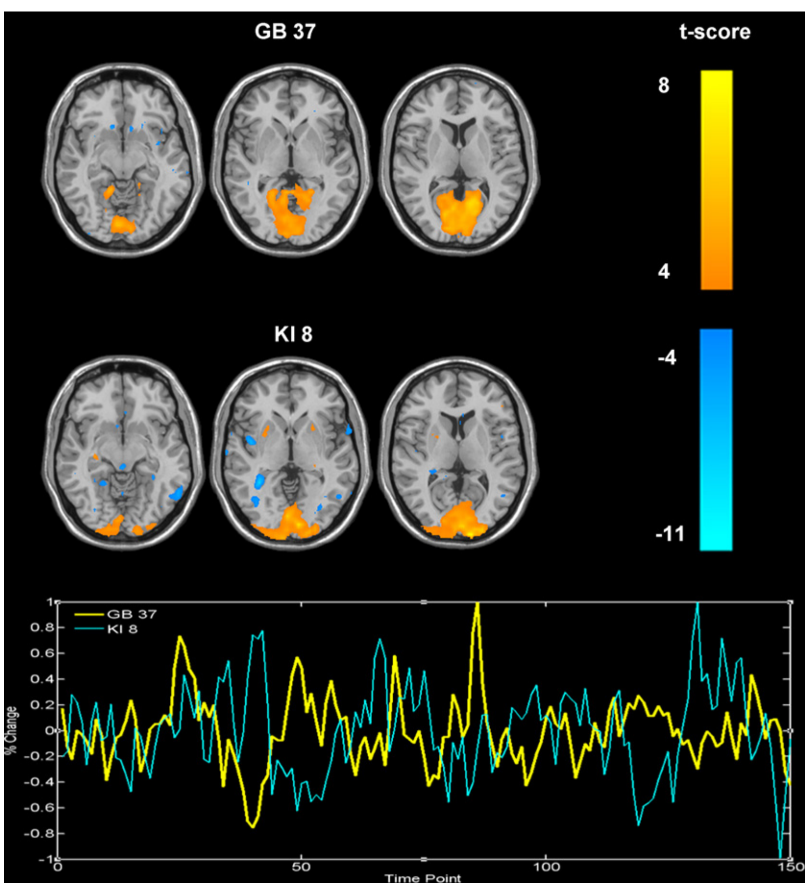

Fig. 3. The random effect analysis results of GB 37 and KI 8. The graph describes the negative correlation between them (correlation coefficient −0.1691 ($P < 0.05$, Bonferroni correction)).

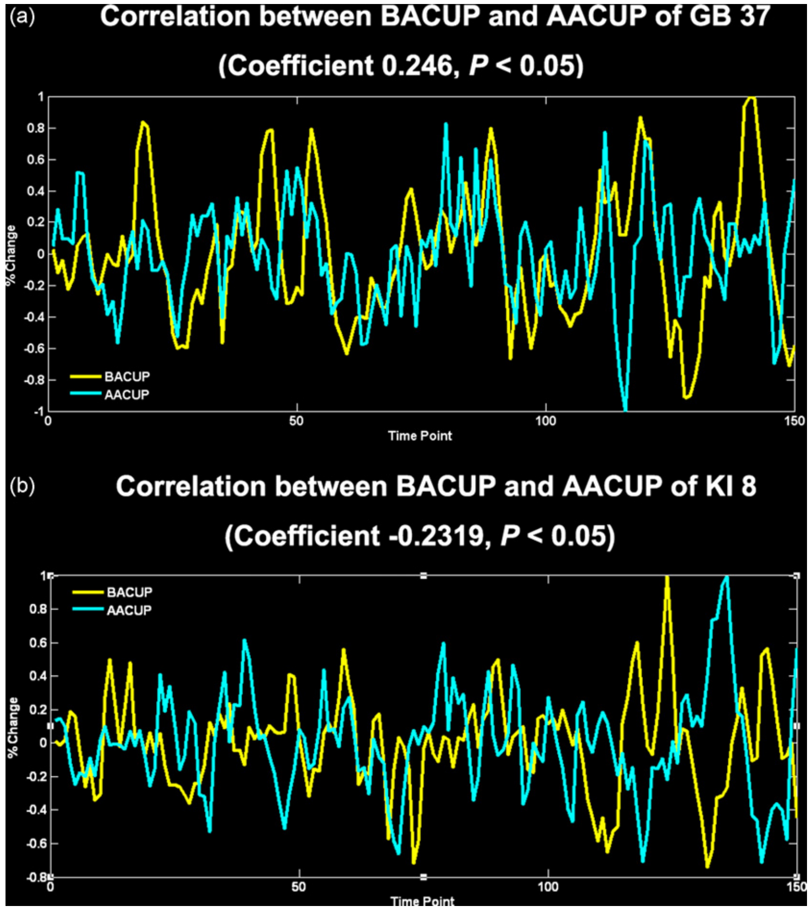

Fig. 4. Intra-subject analysis between BACUP and AACUP states of the two acupoints. (a) The graph shows a positive correlation during stimulation at GB 37 (coefficient 0.246, $P<0.05$, Bonferroni correction). (b) The curve presents anti-correlation when stimulation at KI 8 (coefficient −0.2319, $P<0.05$, Bonferroni correction).

Group 3 also had activated areas in the IOG (BA 17/18), MOG (BA 18), bilateral fusiform gyrus (BA 20/37), lateral insula (BA 13) and superior parietal gyrus (SPG) (BA 7) as compared to the SFG, MFG, cingulate cortex (BA 24/32), hippocampus and amygdala in group 2.

We then extracted the mean time series corresponding to the best-fit ICA components of BACUP and AACUP in group 2 and correlated them with those in group 3. There were no significant differences of BACUP states between the two groups in the spatial and temporal domains, and their time courses showed a positive correlation with a coefficient of 0.5152 ($P<0.05$, Bonferroni correction), as shown in Fig. 2(b). During the intra-subject analysis between BACUP and AACUP, positive correlation (coefficient 0.246, $P<0.05$, Bonferroni correction) was present during stimulation at GB 37, as shown in Fig. 4(a); meanwhile, acupuncture at KI 8 induced anti-correlation (coefficient −0.2319, $P<0.05$, Bonferroni correction), as shown in Fig. 4(b). We also noted that the AACUP sessions of the two groups presented a negative correlation with a coefficient of 0.1691 ($P<0.05$, Bonferroni correction), as shown in Fig. 3.

We compared brain activation changes in the visual cortical areas by stimulating vision and nonvision-related acupoints. The combined analysis methods of seed correlated functional connectivity and ICA, revealed that stimulation of the two acupoints induced similar activations in spatial distribution via EAS, but different modulation of the temporal pattern.

Wang et al.'s [28] study verified the existence of spontaneous activity in the PVA of normal-sighted subjects during resting state, and we discovered that acupuncture modulated the overall brain functional network instead of a specific region [24,33]. Therefore, we used the time course of the ROI obtained from the checkerboard stimulation to correlate with the resting state data before acupuncture. The activated brain areas were then defined as a template representing the brain functional network associated with PVA during resting state, and used it to study the modulation effects on the brain functional network during resting state before and after acupuncture.

The BACUP resting state analysis of the two acupoints showed that there were no significant differences between them in the spatial and temporal domains, and the time course of the two components showed a positive correlation, that is because they share the same level of resting state before needle manipulation. The group analysis of GB 37 and KI 8 during the AACUP states illustrated common areas in the visual cortex which included the cuneus (BA 17/18/19), lingual gyri (BA 17/18), precuneus (BA 31), precentral gyrus, IFG, STG (BA 22), MTG (BA 21), ITG, PHIPP, PCC and culmen. EAS at both vision-related acupoint GB 37 and nonvision-related point KI 8 produced signal changes in the occipital cortex; this result was consistent with Kong's [17] study. Kong [17] only verified the spatial, but not temporal, distribution patterns of these different acupoints, due to the sustained effects of acupuncture in post-stimulus rest, and the BOLD signal does not change as the multiple-block paradigm; therefore, we introduced the correlation analysis of the time series corresponding to the specific ICA components between GB 37 and KI 8. Their individual intra-subject temporal analysis indicated that stimulation at GB 37 induced a signal increase; meanwhile, acupuncture at KI 8 decreased the signal strength. Thus, these phenomena may account for their negative correlation characteristic during the

AACUP state. Although stimulation at these two different acupoints both induced the same activations in the occipital cortical areas in spatial distribution, their temporal characteristics showed a significant difference. Therefore, we concluded that acupuncture stimulation at the two acupoints could induce distinct temporal modulation of the brain functional network by combining the analysis of both of their temporal and spatial properties.

In addition, Kong's [17] study only focused on the signal changes in the occipital cortex, but we believe acupuncture modulates a functional network instead of a specific region. Thus, except for the common activated brain areas in the occipital cortex, acupuncture at KI 8 also induced activity in the HIPP, periaqueductal gray (PAG) and insula. HIPP is associated with the analgesic effects of acupuncture [32]. The PAG belongs to a brain stem area and is related with noxious stimuli and their modulation [10]. It is well known that the insula is consistently activated during the administration of pain [23]. Meanwhile, acupuncture at GB 37 mainly activated the occipital cortical areas. This difference in spatial distribution may reflect the functional discrepancy of the two acupoints.

In this study we compared EAS at vision-related acupoint GB 37 with a nonvision-related acupoint KI 8. Our results support the proposition that acupuncture at vision and nonvision-related acupoints can induce similar activations in the visual cortex spatial domain, but results in a different modulation pattern in the temporal domain. With regards to the mechanism of acupuncture, the properties of both spatial and temporal should be considered. The new experimental paradigm is capable of disclosing the effects produced during acupuncture. More importantly, these preliminary results may lead to further study of acupuncture effects at other acupoints.

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